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THE CHEMISTRY OF CARBAMATES

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1 Introduction

Carbamic acid, H_2NCOOH, the half amide of carbonic acid, does not exist as the free acid. Only some heterocyclic carbamic acids form relatively stable compounds. In contrast to this, carbamates including derivatives resulting from replacement of hydrogen atoms at the nitrogen atom by organic radicals form quite stable compounds. The chemistry of carbamates was first reviewed by Adams and Baron [1] in 1965. Recently it has attracted interest of many chemists, pharmacologists, agriculture specialists and industrial branches producing plastics, which is especially due to the wide range of biological activity and useful protecting properties of the respective compounds in organic synthesis.

The carbamate function as considered in this review is based on the trivalent group –O–CO–N<. On attaching various radicals to three free valences of this group, on can obtain many classes of compounds, including the cyclic carbamates as 1,3-oxazol-2-ones or 1,3-oxazin-2-ones.

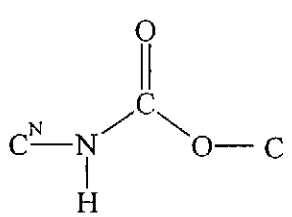
This article is based on the author's original papers and on some other recently published ones.

2 Nomenclature

In the IUPAC nomenclature, carbamic acid esters are referred to as carbamates or (by the trivial name) urethanes. The historical term "urethan" represents ethyl carbamate, and it has been retained in the name of a class of polymers, "polyurethans". The common name "urethylan" is rarely used in reference to methyl carbamate. In Chemical Abstracts, Chemical Substances Index, simple esters are indexed only at the heading Carbamic acid esters, while the other esters are indexed at the other compounds. When a locant is needed in the modification, the "(ester)" term is dropped. For examples $CH_3NHCO_2CH_2CH_2OH$ is 1,2-ethanediol mono(methylcarbamate) (ester) according to Chem. Abstr. and 2-hydroxyethyl-N-methylcarbamate according to IUPAC. A carbamic acid ester in the presence of functions having higher nomenclature priority expressed as suffix is indicated by a (carboxyamino) radical in its prefix. For example $(C_6H_5)_2C{=}NOCONHC_6H_5$ is O-phenylcarbamoylbenzophenone oxime (IUPAC) and Methanone, diphenyl-O-[(phenylamino)carbonyl]- oxime (Chem. Abstr.). Cyclic carbamates are indexed as heterocycles.

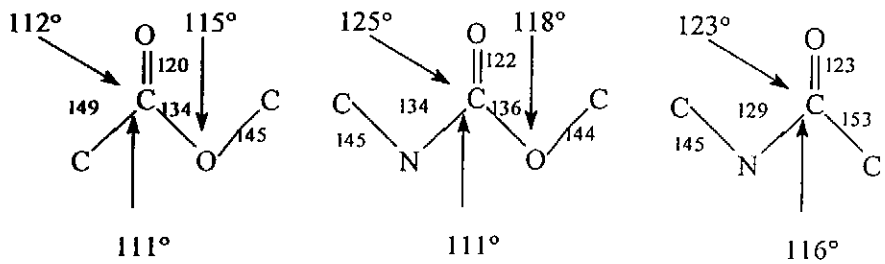
3 Molecular and Electronic Structure of Carbamate Group

Experimental *X*-ray geometry and ab initio calculations of various crystalline carbamates show bond distances and angles for the carbamate group. The basic heavier atoms of carbamate (C, N, O, O^{C-}) are rigid planar. The C^O, C^N and N hydrogen(s) are not in plane of the basic atoms [2,3].



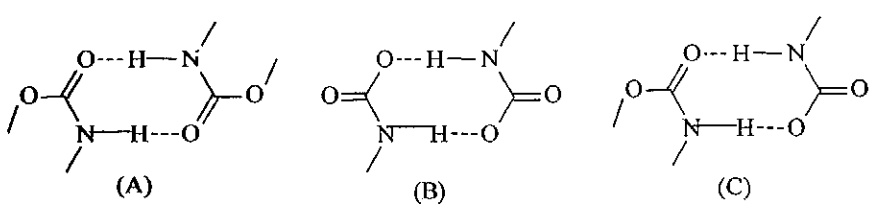
The optimised geometry for representative methyl N-methylcarbamate skeleton has the following values of bond length (pm) and dipole-moment (D): C=O (122, 2.0); C–N (134, 1.0), C^N–N (145, 0.3); C–O (135, 1.5); C–O (144, 1.5); the angles (deg) O–C–N (125); C–N–H (115); C–N–C^N (119); O–C–N (111); C–O–C (118). The rotation barriers (kJ mol^{-1}) were found to be higher than 50.4 for C–O, and 67 for C–N bond [4]. The force constant of C=O bond in carbamates lies between the corresponding values in esters and amides. The dipole-moment of C=O

bond with respect to stretching co-ordinate is closer to the value in amides than to that in esters. The character of individual bonds in N–CO–O structure is essentially different. The bonds N–C and C–O have a partial double character due to n,π conjugation. The order of C–N and C–O bonds in carbamates is lower than that in amides or esters [5]. Electronic absorption spectra of series of aryl and O,N-diaryl carbamates were measured by Hamed *et al.* [6] and confirmed the extent of conjugation across the carbonyl group and the effect of substituent.



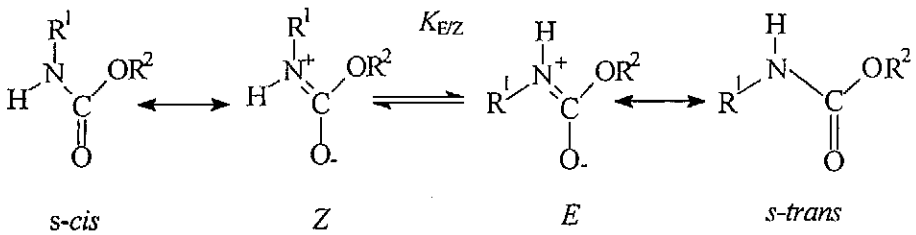
carboxylic acid ester N-methylcarbamate carboxylic acid amide.

The intramolecular hydrogen bond was studied in an experimental study of induced frequency shifts of the N–H, C–O and C=O stretching modes and by normal mode vibrational analysis [7,8]. Three types of intermolecular hydrogen bonds –NH···O=C, (A-structure), NH···O–C (B-structure), and their combination (C-structure) were studied. Out of them, the A- and B-structure bonds were found to be comparably strong. The C-structure bond is only ca 50 – 60% as strong as the former two bonds [4].



In discussing the conformations of carbamate, two conformers (*s*-cis and *s*-trans) may be considered when the nitrogen atom carries two identical substituents (as in primary and tertiary carbamates), whereas it is necessary to take four conformations into account when the nitrogen of carbamate carries non-identical substituents (secondary carbamates). *Z* - *E* (syn - anti) are limiting geometry structures (e.g. rotamers) of the above-mentioned *s*-cis and *s*-trans conformers containing charged nitrogen atom. The *E* rotamer is favoured ($K_{E/Z}$ = 2 – 19), for

steric and electrostatic reasons. The carbamate *E/Z* rotamers can be determined by ^{1}H and ^{13}C NMR spectroscopy. In general, the most diagnostic peak was the carbamate *NH* signal [9]. The *Z* signal decreases as the temperature is increased [10,11]



4 Physical, and Physiological Properties

Carbamates are liquids or solids. Increasing number of carbon atoms in the OR group attached to carbonyl function causes the melting point of the solids to increase, too. Introduction of an aromatic residue into OR leads to a melting point increase, especially when the nucleus is substituted in para-position, see Fig.1. Substitution of hydrogen atoms at nitrogen by alkyl groups decreases the melting point [12]. Aliphatic N,N-dialkylcarbamates are liquids. Their boiling points are high (> 180 °C). Their distillation, except for methyl or ethyl carbamates, must be carried out under vacuum because of their thermal decomposition (see below). Lower aliphatic carbamates are water soluble. Substitution at nitrogen decreases their solubility. The solubility of carbamates in polar organic solvents is high, but their solubility in hydrocarbons is limited.

Lower carbamates are carcinogens. They have narcotic effects, they are toxic, large doses can cause hepatitis or fatal hepatic necrosis. First symptoms are burning in the throat, nausea and vomiting, watery to bloody diarrhoea, and cardiovascular collapse. Acute oral dose for rat is LD_{50} 0.1 – 10 g kg^{-1}. Aromatic N-methyl-carbamates are generally biodegradable and have low to moderate persistence in soil. They are less toxic for men and are effective inhibitors of acetylcholin-esterase [13]. Some of them are used as sedatives (meprobamat) and others as effective herbicides and pesticides [14].

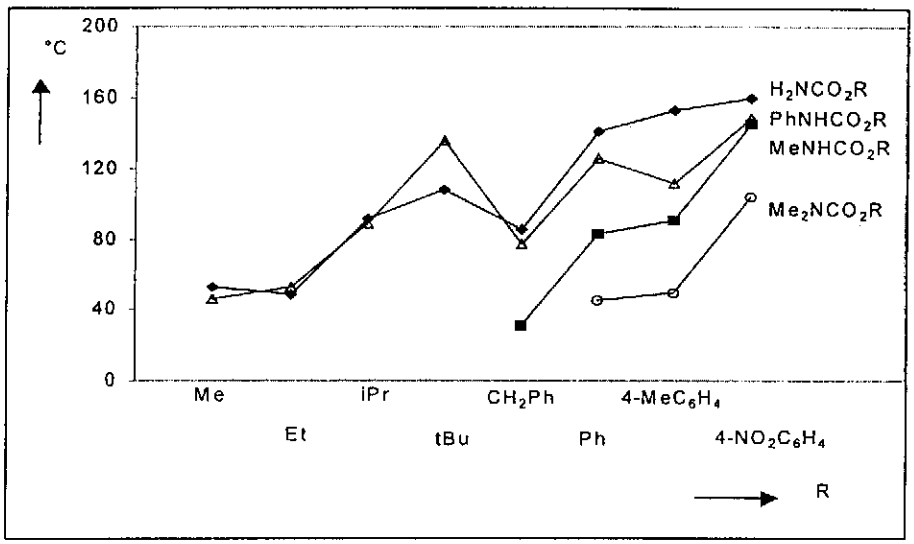


Fig. 1 Dependence of b.p. upon the kind of alkyl- or arylgroup in carbamates (◆), N-phenylcarbamates; (Δ), N-methylcarbamates; (■) and N,N,-dimethylcarbamates (O)

5 Methods of Analysis

N-Arylcarbamates are used as derivatives for characterisation of alcohol. In the past, carbamates were also determined by hydrolysis and subsequent oxidation of the released alcohols or by acidimetric determination of ammonia. At present, the analyses of carbamates (first of all the most biologically active group of N-methylcarbamates) and fragments of their biochemical decomposition are carried out by separation methods. They form undesirable components of food and environment, to which they are emitted as residual compounds from agricultural treatment of soil and plants. Many chromatographic methods are favoured techniques for determination of carbamates, but immunoassay, biosensor, spectrophotometry and electrochemistry were used as well. Average sensitivity for chromatographic determination of carbamates is about 0.01 mg per 1 kg sample [15]. Extensive surveys were published in reviews by McGarvey [16] and Yang et al [17]. The samples of contaminated natural resources containing carbamates are preconcentrated and cleaned. The most common method is the extraction by water-immiscible organic solvents (e.g. dichloromethane, chloroform, petroleum ether, ethyl acetate) with the aid of some physical means (i.e., sonification, shaking, homogenising, Soxhlet process etc.). But direct injection of water samples without any concentration procedure was also applied. Extraction followed by column chromatography on Florisil, Celite-Nuchar, silica gel and alumina or solid phase extraction by cartridges containing silica C18 (for pre-treatment of water or wine

samples) are carried out prior to chromatographic HPLC analysis [18], TLC [19] or GC [20]. Aminopropyl-bonded silica was used to clean grain, fruit and vegetables or remove matrix interferences from samples [21,22]. Increasingly supercritical fluid extraction is being used in analysis with aqueous samples or samples with high moisture content [23] where sample on polymeric column was eluted using supercritical carbon dioxide [24–26].

HPLC is especially suitable since many carbamates lack the thermal stability necessary for GC determination. In general, HPLC analyses were carried out under reversed-phase conditions using C18 columns [27] or C8 cartridges [28,29]. Spectroscopic UV, fluorescence, or mass spectrometric detection methods were used mainly for detection of the fractions [30,31].

Gas chromatography with MS detection has been routinely used in the analysis of ethylcarbamate on two-dimensional GC techniques with NPD detection on PEG-20M column and OV-1 (Ref. [31]), or DB-17 and DB-5, The detection limit was 13 $\mu g\ l^{-1}$ (Ref. [33]). However, the application of GC to the analysis of polar thermally labile carbamates requires cold on-column injection marks and a chemical ionisation ion trap detector [34]. Supercritical fluid chromatography coupled with MS detection provides an alternative tool for the determination of thermally labile samples [35]. Gel permeation chromatography was also used for N-methylcarbamate pesticide residues [36]. TLC is frequently used for determination of carbamates due to its low cost and simplicity. Spraying reagents e.g. phenylhydrazine hydrochloride [37], 7-amino-4-hydroxynaphthalene-2-sulfonic acid [38] and ammonium cerium nitrate [39] were introduced for detection.

For detection of pesticidal active carbamates in vegetables and various matrices acetylcholinesterase-based biosensor [40–42] is used.

6 Synthesis of Carbamates

The syntheses given below were developed for the preparation or production of aliphatic or aromatic carbamates, or carbamoyl oximes. Some of the below-given syntheses are generally used, others are suitable for some specific carbamates. On the other hand, starting compounds and reaction conditions limit the application of the individual methods at laboratory and industrial conditions.

6.1 Alcoholysis of Carbamic Acid Derivatives

$$R^1R^2NCO\text{-}X + R^3OH \xrightarrow{-HX} R^1R^2NCOOR^3$$

X = Cl (*see* 6.1.1), X= NR^1R^2 (*see* 6.1.2), X= OR^4 (see 9.1)

6.1.1 Alcoholysis of Carbamoyl Chlorides

Alcoholysis is most frequently used for preparation of tertiary carbamates, which can be prepared in the most simple way by heating of carbamoyl chloride with the appropriate alcohol under the reflux [43]. The same reaction was carried out in the presence of catalytic amounts of tertiary amine or pyridine [44]. A reliable preparation of N,N-dialkylcarbamates is the heating of carbamoyl chloride with solid alkaline salt of hydroxy compound in an organic solvent [45] or formed one in the reaction mixture using a water solution of sodium hydroxide. These reactions are carried out in two-phase systems water-organic solvent in which the organic product is finally dissolved [46].

6.1.2 Alcoholysis of Urea and its N,N′-Disubstituted Derivatives

Owing to its low price, urea can be favourably used for preparation of primary carbamates. This method is used rather on industrial than on laboratory scale because it requres devices for higher pressures and temperatures. The reaction is carried out in an excess of the alcohol used since the released ammonia (amine) can convert the carbamate to urea in a reverse reaction. The reaction is controlled by removal of ammonia from the reaction mixture. Tin(II) chloride was used for alcoholysis of urea to give 60 – 77% yields of alkylcarbamate or 62 – 65% yields of dicarbamates from dioles [47]. Alcoholysis of urea proceeds also in the presence of alcoholates, which can be prepared in situ from an alkali metal or its hydride. The yields of the reactions catalysed in this way are ca 95% (Ref. [48]). Under similar conditions, the phenolysis of urea using catalytic amounts of sodium phenolate can be realised. The resulting phenyl carbamate can be extracted from the reaction mixture with tetrachloromethane in the yield of 73 %, small quantities of phenyl allophanate and cyanuric acid being the by-products [49].

6.2 Aminolysis of Carbonic Acid Derivatives

$$R^1R^2NH + X\text{-}COOR^3 \xrightarrow{-HX} R^1R^2NCOOR^3$$

X = Cl (see 6.2.1), OR^4 (see 6.2.2).

6.2.1 Aminolysis of Chloroformates

This method is most commonly used for the preparation of primary, secondary and tertiary carbamates. The reaction is heterogeneous, the amine being dissolved in water and the chloroformate in ether, benzene or dichloromethane, and the reaction mixture is cooled to a temperature of 5 – 10 °C. The hydrogen chloride released during the reaction is neutralised with sodium hydrogencarbonate.

The yields of reaction are almost quantitative [50]. The reaction can also be carried out in the presence of tertiary amines, or in excess of starting amine [51,52]. The removal of hydrogen chloride with zinc also appears to be a simple and very general method for synthesis of carbamates; it proceeds fast and leads to high yields of the product (90 – 98%) [53]. The reaction is accelerated by electron-donor substituents in the starting amine and by electron-acceptor substituents in the R^3-group in chloroformate molecule. The reaction mechanism of chloroformate aminolysis was described by Yew *et al.* [54].

6.2.2 Partial Aminolysis of Carbonic Acid Diesters.

Aminolysis is a multi-step reaction where the first step is an equilibrium reaction. The reaction rate is positively influenced by the presence of basic catalysts, by removal of volatile alcohols, or by separation of low soluble carbamate from the reaction mixture. The released alcohol acts as an inert part of the solvent from which the carbamate can be crystallised. Aryl carbonates react faster than alkyl carbonates with amines, but the reaction product is a mixture that is difficult to separate. The separation of phenol from such a reaction mixture by aqueous solution of hydroxide is limited by the low hydrolytic stability of the aryl carbamates formed. An excess of amine can lead to the subsequent conversion of carbamate to urea. That is the reason why aminolysis of carbonates is suitable for synthesis of lower alkyl N-aryl- or N-alkylcarbamates. Common preparation of those compounds is reported by Angeles [55] in reaction of diethyl carbonate and corresponding amine in the presence of sodium hydride in benzene. Zinc hydroxide and carbonate [56] or anhydrous zinc N,N-diethylcarbamate [57] were used for synthesis of methyl N-phenycarbamate from aniline and dimethyl carbonate without solvents by heating at 160 °C, 8 atm, for 5 hr with the yield of 97.5%. An isocyanate is the product of reaction of tert-butyl carbonate with primary amines in the presence of dimethylaminopyridine (DMAP). The subsequent alcoholysis of isocyanate with an alcohol (R′OH) leads to carbamate $RNHCO_2R'$ (Ref. [58]).

$$RNH_2 + (\textit{tert}\text{-BuO})_2CO \xrightarrow[-\,\textit{tert}\text{-BuO}^-]{\text{DMAP}} RNCO \xrightarrow{R'OH} RNHCO_2R'$$

6.3 Carboxylation and Alkylation (or Alkenylation) of Amines

$$R^1R^2NH + CO_2 \xrightarrow{-H^+/base} R^1R^2NCO_2^- \xrightarrow{R^3\text{-hal}/-\text{hal}^-} R^1R^2NCO_2R^3$$

The most obvious and convenient approach involves the addition of a primary or secondary amine to carbon dioxide, followed by alkylation of the intermediate carbamate salt. In general, the first step in the two-step process can easily be accomplished *via* non-assisted addition of the amine to CO_2 in non-aqueous solutions [59] or better in the presence of Cs^+ (Ref. [60]) or Nd^{3+} ions (Ref. [61]).

The direct reaction of carbon dioxide, aliphatic amines and alkyl halide was found to give the corresponding alkyl carbamate. The alkylation of metal carbamates occurs sporadically and is complicated by electrophilic attack at carbamic nitrogen to give N-alkylation product [62]. In the presence of crown-ethers the yields of carbamates obtained under mild conditions [63] are better (35 – 55%). Also reported was a two-step direct electrochemical process of carbonylation-alkylation carried out in the solution of acetonitrile using cathodic process and electrolytically generated base $O_2^{-\cdot}$. The reaction proceeds at room temperature in an electrolyser with the yields of organic carbamate [64,65] ranging about 73 – 98%.

Bruneau a Dixneuf [66] used acetylene or terminal alkines for a pot synthesis of alkenylcarbamates under the catalysis by ruthenium(II) complexes

$$RC{\equiv}CH + CO_2 + HNR^2_2 \xrightarrow{\text{[Ru-complex]}} \underset{E,\ Z}{RCH{=}CHOCO_2NR^2_2}$$

Vinyl pyrrolidine-1-carboxylate in the presence of $[(\text{norbornadiene})RuCl_2]_n$ was obtained from pyrrolidine, CO_2 and acetylene in 63% yield.

6.4 Reactions of Alcohols, Phenols or Oximes with Isocyanates

$$R^1NCO + R^2OH \longrightarrow R^1NHCOOR^2$$

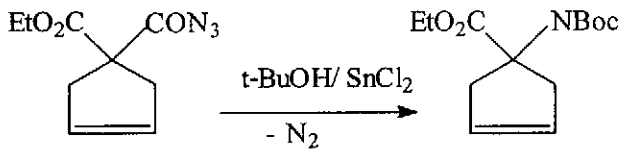
Isocyanic acid, HNCO, can be used for the preparation of primary carbamates. The acid itself is prepared from its salt often in the presence of an acid at room temperature [67]. Alkyl or aryl isocyanates are most frequetly used for the

preparation of secondary carbamates because the reaction proceeds almost quantitatively with the minimum occurrence of by-products. Reaction is carried out by refluxing an equimolecular mixture of isocyanate and alcohol [68], phenol or oxime in benzene, THF or other aprotic solvent. Lewis bases, such as triethylamine [69], and Lewis acids, such as dibutyltin dilaurate, are useful catalysts [70]. The presence of phenolates or carboxylates in the reaction mixture accelerates formation of allophanates and isocyanurate as side products [68]. The order of the reactivity of isocyanates is following: prim-alkyl > sec-alkyl > tert-alkyl > phenyl. An addition of 10 mol % of SmI_2 in a solution of HMPA and THF proved to be very convenient. The reaction proceeds at the temperature of −78 °C within a few minutes [71]. Tarasov et al. studied the kinetics of addition of alcohols to aromatic isocyanates in various solvents [72].

The starting isocyanate can be prepared in situ in the reaction mixture. One of the methods is the reaction of alkyl halide with alkali isocyanate. The reaction is catalysed by a quaternary ammonium salt and proceeds in a polar aprotic solvent (MeCN). The yields usually are high (65 – 95%) [73].

The Hofmann degradation of amides represents another preparation method of isocyanates in a reaction mixture. The classical Hofmann rearrangement was improved using oxidative reagents. When an alcohol is used as the solvent, the corresponding alkylcarbamate is produced. Primary aliphatic and aromatic carboxamides with $Hg(OAc)_2$–NBS in the presence of alcohols and DMF give the corresponding carbamates almost quantitatively [74,75]. Oxidation of amides by a mixture of NBS and octahydropyrimido[1,2-a]azepin (DBU) also gives very good yields [76]. The rearrangement of benzamide to methyl N-phenylcarbamate was realised with NBS and NaOMe, Ref. [77]; methyl N-(4-methoxyphenyl)carbamate was prepared in a similar way [78]. The yields were almost quantitative in both reactions. Principal disadvantageous method with NaOMe is not capable of effecting the rearrangement of either 4-dimethylaminobenzamide or 4-nitro-benzamide.

Curtius-Staudinger degradation uses carboxylic acids as the starting material and proceeds *via* acyl azide and isocyanate. Boc_2O and tributylphosphine are the reagents for the preparation of tert-butylcarbamates [79]. The reaction was also carried out in solid phase on a polymeric support (Wang resins). A series of fluorenyl methylcarbamates were prepared using diphenylphosphoryl azide (DPPA) and subsequent heating of the acyl azide formed (an intermediate in the presence of fluorenylmethanol), with the yield of 49 – 86% (Ref .[80]). The conversion of α-azidocarbonyl alkenoates *via* the Curtius rearrangement [81] was used for preparation of unsaturated α-NBoc carboxylic acid esters



6.5 Oxidative Amination of Carbon Monoxide

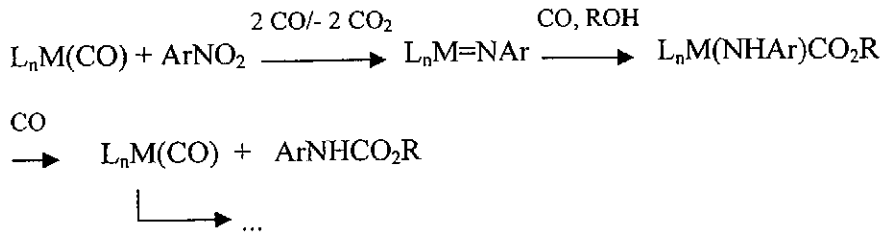
$$R^1NH_2 + CO + R^2OH + 1/2\ O_2 \xrightarrow{\text{cat.}} R^1NHCOOR^2 + H_2O$$

These types of reactions were elaborated for the conversion of aromatic amines to alkyl N-arylcarbamates. They can be carried out in the presence of palladium as a catalyst [82]. The catalytic system Pd/C was modified by the presence of NaI and $Mn(CO)_5Br$ in alcoholic solution [83]. Similar products were also produced by the electro-oxidation of a mixture of amines and carbon monoxide on palladium in methanolic solutions in the presence of $Pd(OAc)_2$ and $Cu(OAc)_2$ (Ref. [84]).

6.6 Reductive Carbonylation of Organic Nitro Compounds

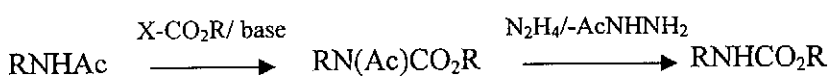
$$R^1NO_2 + 3\ CO + R^2OH \longrightarrow R^1NHCOOR^2 + 2\ CO_2$$

Aromatic nitro compounds undergo reductive carbonylation in the presence of alcohols, giving mainly alkyl N-arylcarbamates. Arylureas, N-alkyl-N′-arylureas, N,N-dialkyl-N′-arylureas and aromatic amines are side products [85]. In most cases, reductive carbonylation is catalysed by palladium, ruthenium, and to a lesser extent by rhodium, platinum and iron [86]. Silver salts, 1,10-phenanthroline and *p*-toluenesulfonic acid are also highly active and give 90 – 96% yield of carbamate [87]. In the case of $Ru_3(CO)_{12}$ and NEt_4Cl as co-catalyst the alcohol should participate in the catalytic cycle [88].



The ligand L with Ru (or Pd or Rh) can form complexes $[Ru(saloph)Cl_2]Cl$, $[Pd(TMphen)_2][PF_6]_2$, $[Pd(phen)_2(OTf)_2]$, $[Rh(py_3Cl_3)]$ and others. Butyl formate or toluene were used as solvents. It is common to use pressures of 1.5 – 5.0 MPa and temperatures of 150 – 200 °C (Refs [89,90]). The substrates with electron-donating substituents at the para position decrease the yield of conversion. Electron-withdraving substituents lead to azobenzenes as side products [91]. Reductive carbonylation is used for industrial production of carbamates.

6.7 Transacylation of Amides to Carbamates

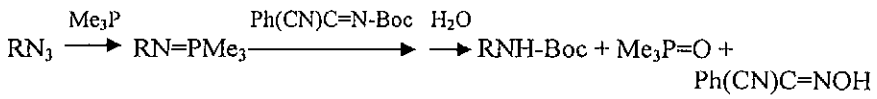


The selective amide to carbamate transformation is an indirec method for changing amine protective groups. This method was optimised in two steps: (1) introduction of an alkoxycarbonyl group and (2) cleavage of the acetate. The two steps were then combined in an efficient standard one-pot procedure. Thus N-acetyl-L-valine methyl ester was acylated with di-tert-butyl dicarbonate (Boc_2O) in the presence of 4-dimethylaminopyridine (DMAP) in THF to give N-acetyl-N-(tert-butoxycarbonyl)-L-valine methyl ester (85%). The subsequent hydrazinolysis step with hydrazine hydrate in methanol gives N-(tert-butoxycarbonyl)-L-valine methyl ester in 100% yields [92].

6.8 Conversion of Azides to Carbamates

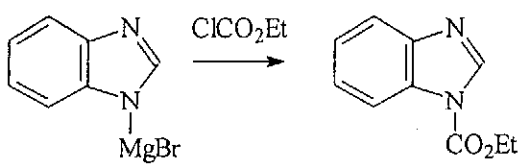
Reduction of several azides with hydrogen-presaturated Pd/C in the presence of Boc_2O gave tert-butyl-carbamates in yields of 71 – 93%. In the presence of substrates with double or triple bonds or Cbz and related protecting groups, this method is generally incompatible [93,94]. The primary and secondary azides with these reducible groups can be converted to carbamates in a one-pot conversion by reaction with trimethylphosphine folloved by addition of 2-(tert-butoxycarbonyl-

imino)-2-phenylacetonitrile (Boc-ON) in 87 – 100% yields [95]

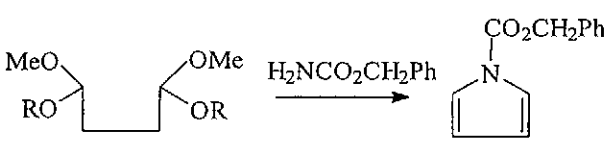


6.9 Synthesis of N-Heterocyclic Carboxylates

The reports concerning the N-carboxylic acids esters were reviewed by Katritzky [96]. The pyrrole, indole, pyrazole, or benzimidazole N-anions prepared by the treatment with potassium hydroxide, sodium ethoxide, methylmagnesium iodide, butyllithium in the presence of chloroformate thus afforded the corresponding N-heterocyclic carbamates. For instance, ethyl benzimidazole-1-carboxylate can be prepared by the reaction of benzimidazole magnesium bromide with ethyl chloroformate [97]



Another way for preparation of N-heterocyclic carboxylates is cyclization of aliphatic diacetals (prepared by anodic oxidation of the alkenyl alkyl ethers) with alkyl carbamates [98]



6.10 Synthesis of N-Substituted Carbamates, Thio- and Dithiocarbamates

The preparation of N-halogeno, N-nitro, N-nitroso, N-arylsulfonyl, N-chlorosulfonyl and N-acylkarbamates will be described in Section 11. N-Hydroxycarbamates [99,100] and N-methoxycarbamates [99] were prepared by similar

routes as those described in Section 6.2. Aldoximes are starting compounds in preparation of N-hydroxycarbamates by a reductive method given by Wu [101].

$$RCH{=}NOH + Et_3SiH + ClCO_2Ar \longrightarrow RCH_2N(OH)CO_2Ar$$

The synthesis of N-aminocarbamates (e.g. carbazates) by hydrazinolysis of carbamic acid diesters by a common method given in Section 6.2.2 was optimised by Vlasák [102]. The reaction of chloroformate with hydrazine gives a mixture of carbazate and hydrazine-1,2-dicarboxylate [103]. The reaction conditions for preparation of aromatic thio- and dithiocarbamates from phenols or thiophenols and isothiocyanates were similar to those given in Section 6.4 , Refs [104,105].

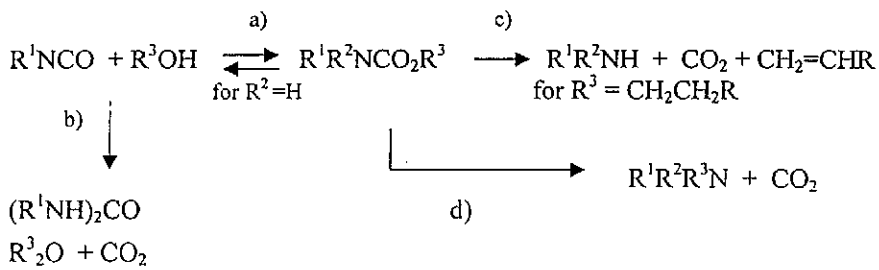
7 Acidity of Carbamates

The acidity of acyclic carbamates and their cyclic form (2-oxazolones) is very low and was measured in DMSO solutions against standard acid. Values of pK_a of carbamates are high, e.g. ethylcarbamate 24.6 (in DMF 25.1), 2-oxazolidone 20.9, 2-oxazolone 15.0, benzoxazol-2-one 12.1 (Ref. [106]). The large increase in acidity is due to the stabilisation of the heteroaromatic anions. Conjugated bases of benzoxazol-2-ones are stable systems, which can ionise without decomposition in hydroxide solutions in contrast to other carbamates [107]. Electron-attracting groups connected to oxygen and especially to nitrogen increase the acidity of 2-benzoxazolones, 2-benzoxazolinones and aryl N-arylcarbamates. The hydrolytic stability of conjugated bases of the last two groups and structurally similar O-(phenylcarbamoyl)benzaldehyde oximes are low and will be described below. pK_a values of such substrates can be determined in an indirect way by kinetic measurements. Electron withdrawing substituents in any of the nuclei increase the acidity, e.g. their effect from nucleus Ar^1 is characterised by $\rho = 1.0$ (Ref. [108]). A similar but more distant substituent in Ar^2 affects the acidity to a smaller extent, $\rho = 0.2$ (Ref. [69]).

$$Ar^1NHCO_2Ar^2 \underset{}{\overset{K_a\,/\text{-}H^+}{\rightleftharpoons}} Ar^1N^-CO_2Ar^2$$

8 Thermal Decomposition of Carbamates

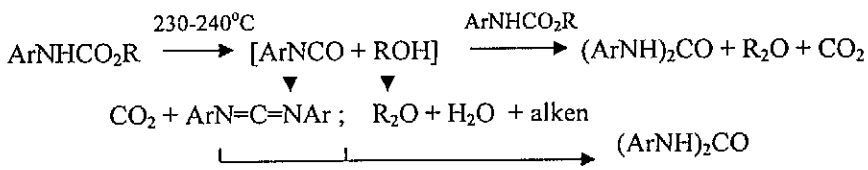
Heating of alkyl- or arylcarbamates can lead to isocyanates, amines, alcohols or phenols, ethers, alkenes and sym. ureas. The proportion of these products in the reaction mixture depends mainly on the nitrogen substitution [109,110], on the decomposition temperature and the time of thermal exposure. According to the particular given conditions, the decomposition can be described in the following ways a – d



The formation of isocyanates *via* (a) was observed when heating secondary carbamates at the temperature of 370 °C in the presence of zinc or calcium oxide. Thus methyl N-ethylcarbamate gave 80% ethyl isocyanate [111]. Similar thermal decomposition also occurs with dialkyl N,N′-polyalkylenedicarbamates in the presence of inert solvents, giving diisocyanates [112]. Catalysts such as dibutyltin dilaurate, tin oleate or some non-volatile diisocyanates (e.g. 1,3-diisocyanato-4-methylbenzene) in reaction mixture make it possible to decrease the temperature of pyrolytic decomposition to 140 – 145 °C (Ref. [113]). Addition of urea or methylurea, which form complexes with carbamates in 1:1 ratio, facilitate the thermal decomposition [114]. Aromatic N-alkylcarbamates are decomposed to isocyanates at temperatures lower than those needed for similar aliphatic carbamates [115], the yields being 50 – 88% (Ref. [110]). Thermal decomposition of non-toxic phenyl N-methylcarbamate at 220 °C is a suitable industrial production method of methyl isocyanate [116,117]. Hexamethylene diisocyanate can be produced in a similar way by the thermal decomposition of diphenyl N,N′-hexamethylene-dicarbamate (95%) [118] as well as toluenediisocyanate by heating of dimethyl 4-methyl-1,3-N,N′-phenylenedicarbamate [119].

Dorofeeva *et al.*[120] observed the formation of sym. diarylureas *via* (b), and they explained it by a two-step reaction where the alcohol formed together with isocyanate in the first step is dehydrated to ether. The water released by the reaction with isocyanate gives urea and carbon dioxide. Hassan and Mourad [121] explain the reaction by thermal decarboxylation of isocyanate to N,N′-diarylcarbodiimide and carbon dioxide and dehydration of alcohol to alkene or ether. N,N′-Diarylurea

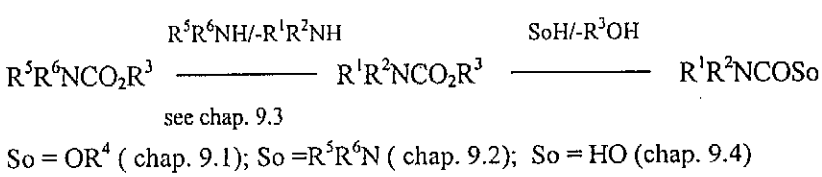
is produced by a mutual combination of the secondary products.



Alkyl N,N-disubstituted carbamates are decarboxylated by heating *via* (c) to sec. amines and alkenes. Blades [122] was the first to describe the thermal elimination of ethyl carbazole-9-carboxylate to carbazole. The exchange of ethyl group at oxygen for 2-(trimethylsilyl)ethyl group leads to the elimination of trimethyl-silylethene even at the room temperature in the presence of tetra-butylammonium fluoride in THF [123]. Remko and Schneider published a theoretical study of the calculation of reaction energy for the decarboxylation of alkyl-carbamates [124] to amines *via* (d). In spite of the fact that a similar elimination is spontaneous for free carbamic acid and its N-substituted derivatives, literature does not give any practical example of such thermal decomposition of carbamate without preliminary hydrolysis.

During heating phenyl N-phenylcarbamate at the temperature of 250 °C for 20 hr, Badr et al. observed formation of reaction products that were different from the previous ones (a – d). A free radical mechanism was suggested for this thermolysis, involving a preliminary homolysis of different bonds in the carbamate molecule, which resulted in formation of biphenyl, aniline, phenol, benzoic acid and diphenylurea [125].

9 Solvolytic Reactions of Carbamates



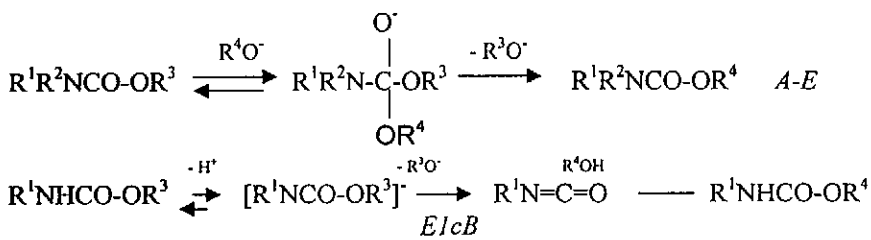
So = OR^4 (chap. 9.1); So =R^5R^6N (chap. 9.2); So = HO (chap. 9.4)

9.1 Transesterification of Carbamates

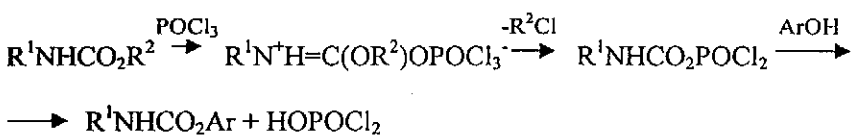
Carbamates in the presence of alkoxylate ions undergo transesterification in a solution of the corresponding alcohol. N-Acylcarbamates can be transesterified by

the alcohol itself at room temperature [126]. Transesterification is an equilibrium reaction in which a higher alkyl carbamate can be produced from a lower one *via* continuous elimination of the lower-boiling alcohol. Titanium(IV) isopropoxide mediated ethyl or tert-butyl carbamate transesterification with allyl or benzyl alcohol at 120 °C with 60 – 85% yield [127].

On the other hand, the rate of transesterification also depends on the acid-base properties of the leaving alkoxy group. Aryl carbamates [128], or O-carbamoyloximes, are transformed by methoxide ion in methanolic solution into methyl carbamates at room temperature. Kožený *et al.* [45] have studied the mechanism of this transesterification. N,N-Disubstituted carbamates and most alkyl carbamates undergo methanolysis by A-E mechanism whereas aryl carbamates with a hydrogen at nitrogen react by E1cB route



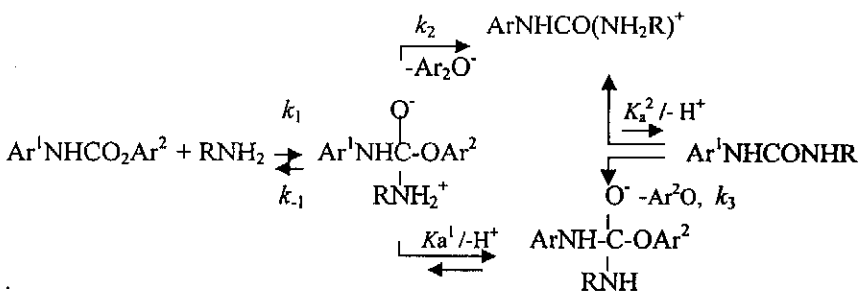
Transesterification of alkyl carbamates into aryl carbamates is not possible under the above-given conditions. In spite of this fact, such transformation can proceed by addition of phosphorus oxychloride to the reaction mixture. This chloride reacts selectively with the alcohol formed during the equilibrium reaction and transforms it to an alkyl chloride which does not take part in the reaction. The reaction intermediate can react only with the phenol [129,130].



A similar re-esterification in the presence of $POCl_3$ can be carried out even in the case of sterically hindered phenols [131]. A conversion of alkyl to aryl carbamate was realised by refluxing of a mixture of the alkyl carbamate with phenol in the presence of *p*-toluenesulphonic acid [132].

9.2 Aminolysis of Carbamates

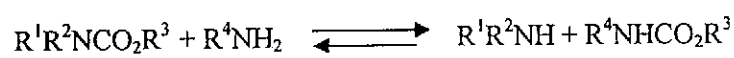
Aminolysis of carbamates can proceed in similar way as transesterification, i.e. by A-E or E1cB mechanism [133,134]. The A-E mechanism is characteristic of N,N-disubstituted carbamates. In this case the aminolysis proceeds slowly or does not at all proceed even at drastic conditions (190 °C for 3 hr) [135]. Carbamates with a hydrogen atom at nitrogen are much more reactive than the above-mentioned ones. The addition-elimination path was observed in a reaction of substituted *p*-nitrophenyl N-phenylcarbamates with benzylamines in acetonitrile media. The reaction course is controlled by formation and splitting of the tetrahedral intermediate in a system of consecutive competitive reactions and equilibria. The decomposition of zwiterionic tetrahedral intermediate (k_2) is rate limiting [136]



Sec. carbamates in the presence of strong bases, such as DMAP or alkali methoxides, are rather ionised to the corresponding conjugated bases which subsequently undergo elimination to give the corresponding isocyanate (E1cB). The latter can react with an amine to give the corresponding urea [45,137].

The reactivity of carbamate is mainly given by the character of the leaving group. Aromatic carbamates are usually more reactive than the aliphatic ones and can react even at room temperature [138]. In the case of carbamates which can react with amines at more reaction centres it is possible to use a little reactive carbamate group (N–Boc) for the aminolysis to proceeds at the other part of the molecule. Seto *et al.* [139] realised a selective substitution of chlorine for neopentylamino group in a model molecule of tert.butyl N-[2-(4-chloro-1,3,5-triazol-2-yl)]-N-phenyl-carbamate.

9.3 Transamination of Carbamates



$$R^1R^2NCO_2R^3 + R^4NH_2 \rightleftharpoons R^1R^2NH + R^4NHCO_2R^3$$

In contrast to aminolysis, transamination of carbamates leads to formation of C–N bond and to splitting of another C–N bond, while the C–O bond does not change. In order to be able to carry out such a reaction, the structure of atoms at a nitrogen should form a better leaving group than that at oxygen. On the other hand, this equilibrium reaction can be supported at suitable conditions by elimination of starting amino group in the form of a volatile amine and, at the same time, by suppressing the splitting of C–O bond kinetically (e.g. by increased concentration of alcohol or phenol in the reaction mixture). That is the reason why we give the published examples of transamination.

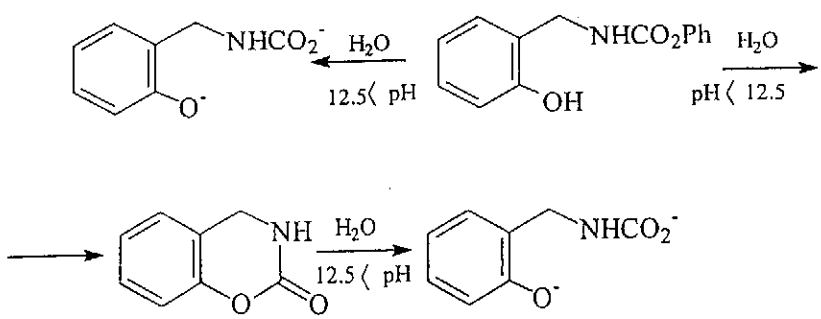
Syntheses of N-(tert-butoxycarbonyl)amino acids and N-(4-methoxybenzoyloxycarbonyl)amino acids for preparation of peptides were realised with model compounds of 1-(tert-butoxycarbonyl)benzotriazole or 1-(4-methoxybenzyloxycarbonyl)benzotriazole and some α-amino acids (phenylglycine and phenylalanine) in aqueous solution of sodium hydroxide in the presence of dioxane at room temperature. The starting carbamates are shown to be effective as α-amino group protectants [140].

Other way of transamination was realised from phenyl carbamate using hexamethylenediamine in the presence of phenol yielding diphenyl hexamethylenedicarbamate [141].

9.4 Hydrolytic Reactions of Carbamates

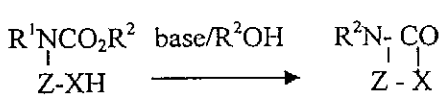
Reactions of this type were studied in context of the research into stability of biologically active carbamates in living organisms [142]. Salts of carbamic acids are formed by hydrolysis in alkaline media. In neutral or acidic media, carbamic acids are produced which subsequently decarboxylate to give the final products — amines or aminium salts [143]. The hydrolysis mechanism depends on the presence of hydrogen atom at the nitrogen atom and on the character of the leaving group. Three possible pathways were studied. (a) Nucleophilic attack of the carbonyl carbon by hydroxide ion giving a tetrahedral complex, followed by its breakdown to carbamic acid salt ($B_{ac}2$). (b) Proton abstraction by hydroxide ion at the nitrogen atom followed by elimination of alkoxide ion to form isocyanate (E1cB) [144]. (c) 'Concerted' S_N2 pathway involving simultaneous cleavage of H–N and RO–C bonds and formation of C–OH. Terc. carbamates and some of alkyl prim. and sec. carbamates hydrolyse *via* ($B_{ac}2$). Aryl prim. and sec. carbamates and similar O-

carbamoyloximes hydrolyse *via* E1cB [145]. The rate of hydrolysis increases with decreasing pK_a of the involved phenol [146,147]. Park et al. theoretically studied the 'concerted' mechanism in the solvolyses of carbamates [138]. The application of 'concerted' mechanism was verified on carbamate models containing an aliphatic [149] or aromatic hydroxy group [150]. Increasing concentration of hydroxide ions increases the rate of C–O bond cleaving (for prim. and sec. carbamates) at pH < pK_a, but it can also influence both the change of the products and mechanism. For example, phenyl N-(2-hydroxybenzyl)carbamate in aqueous buffers at pH < 12.5 cyclizes to 3,4-dihydro-3H benzo-1,3-oxazin-2-one ('concerted'). The same carbamate at pH > 12.5 hydrolyzes to sodium N-(2-hydroxybenzyl)-carbamate (E1cB). The cyclic carbamate formed at lower pH hydrolyzes in solutions of alkali hydroxides to give sodium N-(2-hydroxybenzyl)-carbamate (E1cB) [150].

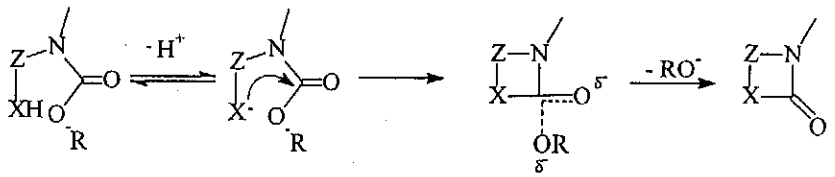


10 Cyclization of Carbamates

10.1 Base Catalyzed Cyclization



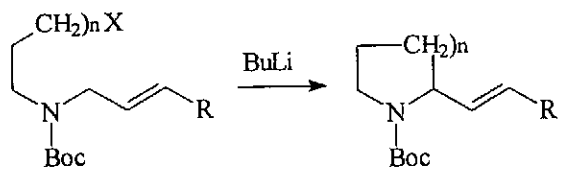
The cyclization can proceed as a substitution of alkoxy or aryloxy group of carbamate with an ionised amino or hydroxyl group of the same molecule. It is a base catalysed reaction which can be facilitated by the favourable topology of reacting groups. Literature gives examples of formation of oxazolidinones [151], benzoxazoles [152], cyclic ureas [153] and benzo-1,3-diazine-2,4-diones [154] and N-aryl-1,3-oxazin-2-ones [155]. Hrabík *et al.* [150] suggested a cyclization path of phenyl N-(2-hydroxybenzyl)carbamates by 'concerted' mechanism.



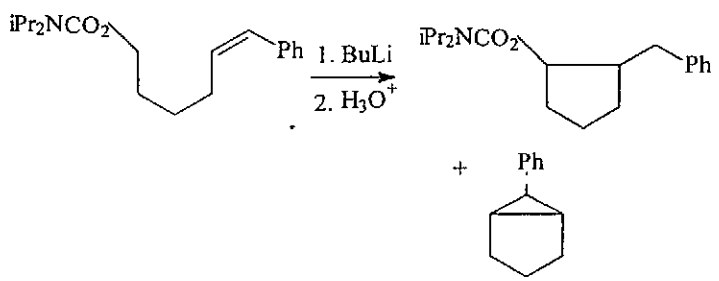
Z = -CH_2CH_2-, -$CH_2CH_2CH_2$-, -C_6H_4-, -$CH_2C_6H_5$-

X = O, S, NH, $CONH_2$

The cyclization of terc.carbamates can proceed even in the absence of ionisable group provided that a C-anion can be formed near the nitrogen or oxygen, for example by the effect of BuLi. The following cyclic compound can be formed from the carbanion by subsequent S_N2i or A_N reaction [156]



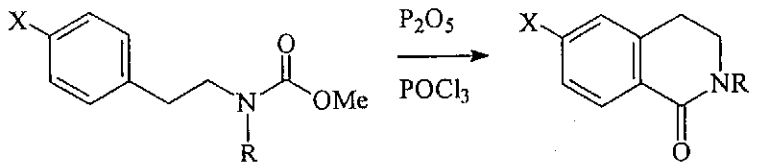
X = Cl, Br
R = H, Me, Ph
n = 1, 2



Tert.carbamate was treated with a solution of butyllithium pre-mixed with (s) sparteine in ether at - 78 °C (Ref. [157]).

10.2 Cyclization in Acidic Media

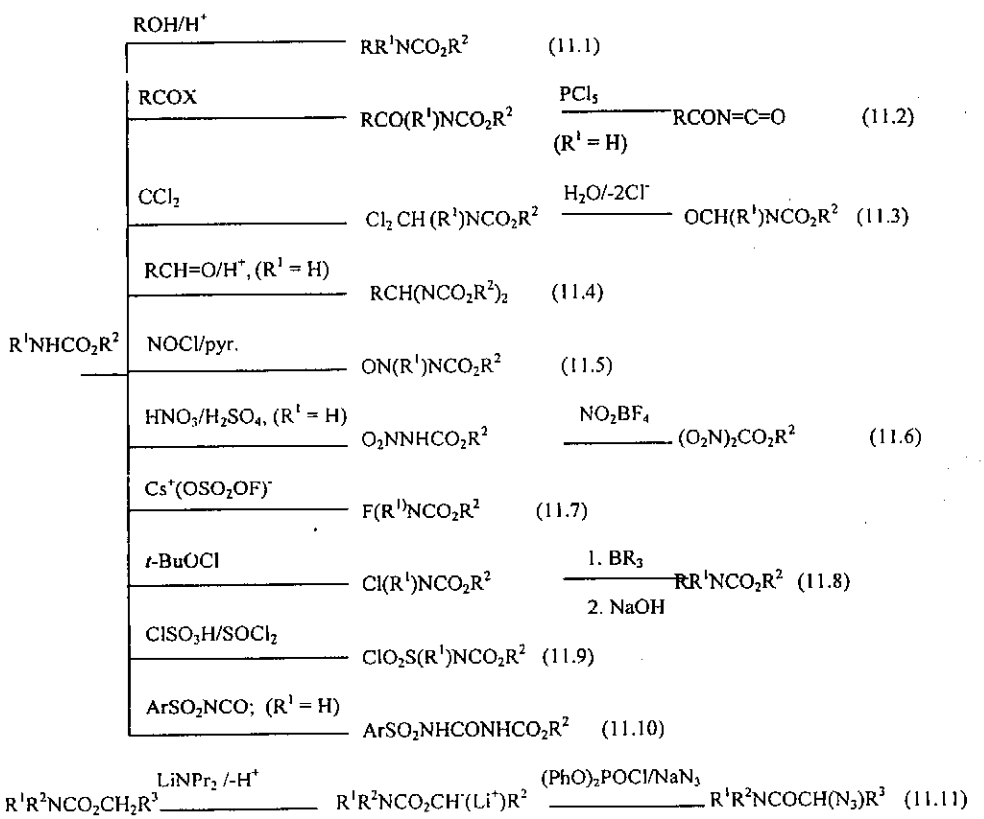
N-Alkyl-N-phenylethylcarbamates in the presence of $P_2O_5/POCl_3$ undergo Bischler–Napieralski cyclization to afford N-alkylated-3,4-dihydroisoquinolones in the yields of 67– 98% (Ref. [158]).



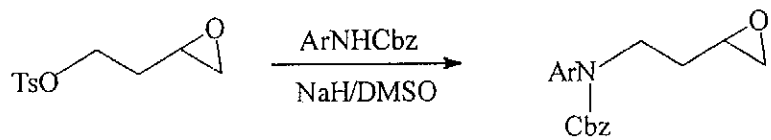
R = Me, Et; X = Cl, F, OMe, Me

11 Reactions at Nitrogen

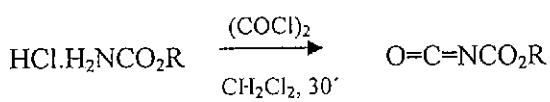
Substitution reactions of one or two hydrogen atoms by an electron-withdrawing group or reactions following such an exchange at the given reaction conditions are given in the chart below



(11.1) The alkylation at nitrogen atom of carbamates proceeds by a reaction of the carbonium ion produced from alcohol in mineral acid medium [159,160] or from alkene in acid medium [161,162]. Conjugated dienes in the presence of acids react with carbamates to give diurethanes [163]. The catalytic system of $Pd(diacac)_2$-phosphorous ligand-acid can give the adduct with one molecule of ethylcarbamate and two molecules of isoprene and 2,3-dimethylbutadiene diolefine, in the form of dimer of diolefin [164]. Alkylation of sec.carbamates can be carried out using hydroxides of alkali metals in aprotic media. An example of such reaction is the below-given regioselective splitting of TsO–C bond in 1-(3,4-epoxy)butyl tosylate by N-anion of benzyl-N-(3-fluorophenyl)carbamate) [165]



(11.2) Anhydrides [166] or acyl chlorides [167,168] were used for acylation in aprotic solutions. Hydrochlorides or hydrogensulphates of alkyl esters of primary carbamates react with oxalyl chloride yielding alkyl isocyanato-formates [169,170].



Ethyl N-trifluoracetylcarbamate prepared by the reaction of ethyl carbamate with trifluoroacetanhydride was heated with phosphorus pentachloride yielding 1,1-dichloro- 2,2,2-trifluoroethyl isocyanate [166].

(11.3) The reaction of aliphatic N-arylcarbamates with dichlorocarbene generated from chloroform and sodium hydroxide leads to dichloromethylation at nitrogen. Subsequent hydrolysis produces alkyl N-formyl-N-arylcarbamates [171].

(11.4) Aliphatic or aromatic aldehydes or their hydrates react with alkyl carbamates in acid media giving dialkyl alkylidendicarbamates [172]. Condensation of polyfluoroaldehydes with alkyl carbamates afforded α-hydroxypolyfluoroalkyl carbamates (in 78 – 83% yield), which upon subsequent treatment with posphorus pentachloride gave 1-chloropolyfluoroisocyanates (76 – 86%). Condensing ethyl N-phenylcarbamate with 37% formalin in toluene in the presence of an ion-exchange agent or aqueous acid as the catalyst at 90 °C gave a 55% yield of diethyl 4,4′-methylene-bis(alkyl N-phenylcarbamate) along with its 2,4′-isomer and poly-

methylene polyphenylcarbamate [173].

$$2\ PhNHCO_2Me \xrightarrow{CH_2O/H^+} MeO_2CNHC_6H_4CH_2C_6H_4NHCO_2Me$$

(11.5) Nitrosation of alkyl or aryl N-arylcarbamate proceeds by treatment with nitrosyl chloride in pyridine even at -20 °C with high yields [174].

(11.6) Alkyl N-nitrocarbamates are produced by a reaction of nitration mixture with alkyl carbamates at -45 to -35 °C in acetonitrile or ethyl acetate. Alkyl N-nitrocarbamates undergo a subsequent nitration with nitronium tetrafluoroborate to N,N-dinitrocarbamates [175].

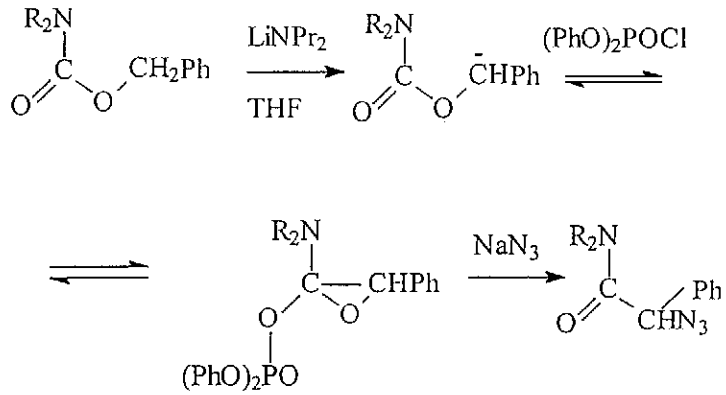
(11.7) The electrophilic anion in cesium fluoroxysulphate ($Cs^{+-}OSO_2OF$) reacts with prim. carbamates to give N-fluorocarbamates. The reaction proceeds in polar aprotic solvents at the temperature of 0 °C, but the reaction yields are low (9%) [176].

(11.8) N-Chlorocarbamates are readily produced when the carbamate, disolved in methanol, is reacted with an equivalent of tert-butyl hypochlorite. Addition of alcoholic sodium hydroxide generates the salt N-chloro-N-sodiocarbamate. It can react in THF at 60 – 70 °C with trialkylborane to give N-dialkylborano-N-alkylcarbamate which is split to N-alkylcarbamate in alkali metal hydroxide medium [177].

(11.9) Methyl N-phenylcarbamate reacts with chlorosulfonic acid in the presence of thionyl chloride in DMF to give N-methoxycarbonylsulphanilic acid chloride [178].

(11.10)Esters of 4-arylsulphonylallophanic acid are products of reaction of prim. carbamates with arylsulphonylisocyanates [179].

(11.11)Treatment of benzyl carbamates with lithium diisopropylamide, diphenylphosphorochloridate and sodium azide yields the corresponding α-azidobenzeneacetamides. The product of rearrangement of benzyl group is formed (45 – 50%) according to the reaction scheme [180]

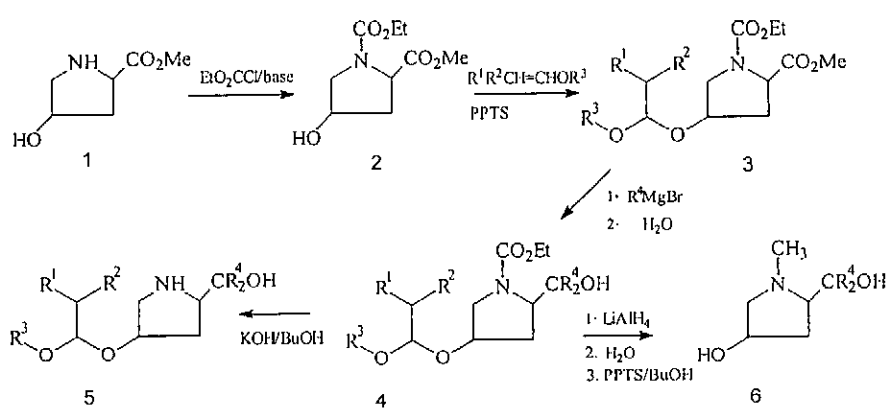


12 Application of Carbamates to Sytheses

Synthetic applications of carbamates are extensive. In this part of our work we give those published during the last ten years.

12.1 Carbamates as Protective Tool of Amino Group

Chemical stability of carbamates to many chemical reagents is higher than the stability of amines. Since carbamates can easily be prepared from amines and vice versa, they are utilised as amine protective groups. Protecting of amino groups is used mainly in syntheses of peptides and proteins [181]. The synthesis of 2-pyrrolidinemethanol ligands [182] is given as an example of protective use of carbamates.

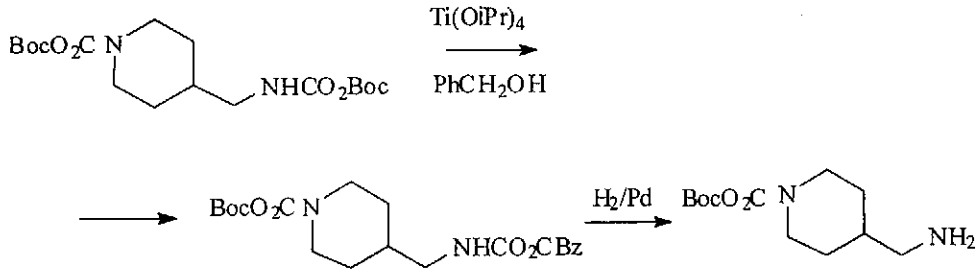


4-Hydroxyproline methyl ester (1) reacts with ethyl chloroformate in the presence of sodium carbonate to give carbamate (2). Its coupling to an enolether (under acid catalysis of *p*-toluenesulfonic acid pyridium salt (PPTS)) leads to acetal (3). Addition of excess Grignard reagent to (2) and subsequent neutral hydrolysis provides alcohol (4). Deprotection of (4) by refluxing with KOH in butanol provides free amine (5). 4-Hydroxy-1-methyl-2-pyrrolidine methanol (6) is obtained by reduction of acetal (4) with hydride and subsequent cleavage of hydroxy protected group with PPTS/BuOH.

Aliphatic and arylaliphatic carbamates are used to a great extent as protective groups. They are introduced into amine molecules by some of the methods mentioned in Section 6. The decomposition of carbamates to amines is specific to the selected structure of alkoxycarbonyl group in carbamate. This group enables the decomposition of carbamate to amine by other agents at milder conditions than are those required for their hydrolysis. These include first of all benzyloxycarboxyl (Cbz) or analogous groups with some ring substituents. For their deprotection, the catalytic reduction or acidolysis by trifluroacetic acid are mainly used. Terc-butoxy-carbonyl group (Boc) is split by the same acid or using $AlCl_3$ with microwawe irradiation [183]. Deprotection of Boc group was carried out by trimethyltin hydroxide [184] or $(NH_4)_2Ce(NO_3)_6$/MeCN (Ref. [185]). Allyloxycarbonyl (Alloc) group was easily split by Pd/Et_2NH (Ref. [186]). 9-Fluorenyl-methyl group (Fmoc) is split by $Pd(PPh_3)_4$/morpholine [187]. Carbamate group facilitates the splitting of sulfoaryl group from nitrogen. Otherwise, such splitting is possible only at drastic conditions. Magnesium in methanol as the cleaving agent with ultrasonic stirring at room temperature easily converts N-sulphonylcarbamates to carbamates almost quantitatively [188]

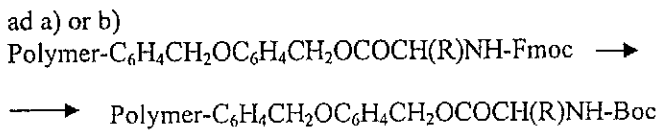
$$RNHSO_2Ar \xrightarrow[\text{DMAP}]{(tBuO)_2CO} RN(SO_2Ar)CO_2tBu \xrightarrow{Mg/MeOH} RNHCO_2tBu \xrightarrow{CF_3CO_2H} RNH_2$$

From among the selective deprotection methods, a general selective removal of primary amine tert-Boc protecting group in the presence the secondary group seems to be especially interesting. For instance, the treatment of tert-butyl [1-(tert-butoxy-carbonyl)piperidin-4-yl(methylcarbamate with 4 equivalents of $Ti(O-iso-Pr)_4$ in benzyl alcohol at 120 °C for 18 h resulted in 85% yield of the primary t-Boc transesterification which can be easily deprotected [189]



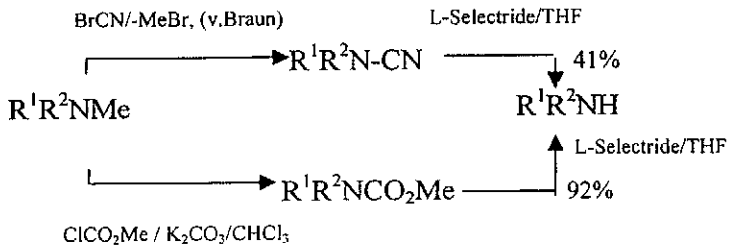
The most commonly used amino protecting groups are Boc and Fmoc. These protecting groups complement each other. Solid-phase conversion of fluorenymethylcarbamate linked to Wang resin can be carried out using two different procedures. (a) Potassium fluoride/Boc-S-2-mercapto-4,6-dimethyl-pyrimidine, or (b) potassium fluoride/di-tert-butyl dicarbonate. Both give the corresponding tert-butylcarbamate in 70 – 100% yields. The resin was separated from peptide with trimethyltin hydroxide [190,191].

ad a) or b)



12.2 N-Demethylation of Methyl Dialkyl Amines *via* Carbamates

Demethylation of tertiary methylamines has been accomplished in several ways. The classic von Braun reaction using cyanogene bromide was improved upon for many amines by use of benzyl or ethyl chloroformate .The intermediate carbamate formed is cleaved in a second step by lithium hydridotrisisopropylborate (L-Selectride) at mild conditions in high yields (82 – 92%) [192–194]. Another efficient reagent for the cleavage of methylcarbamates is methyllithium/lithium bromide (96%) [195] or sodium hydrogen telurite with lower yields (53%) [196]. Phenyl chloroformate with dialkylmethylamines gives phenyl N,N-dialkylcarbamates. Subsequent hydrazine-mediated cleavage gives sec.amines [197]. The method of conversion of N-methyl bond into methyl N,N-dialkylcarbamates and their subsequent splitting with concomitant formation of N–H bond was compared with von Braun's preparative alternative as an example of dihydrocodeinone-6-ethylene ketal preparation [192].



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