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CONTRA-THERMODYNAMIC TRANS-ESTERIFICATION OF CARBAMATES BY COUNTER-ATTACK STRATEGY: A VIABLE NON-PHOSGENE, NON-MIC ROUTE TO CARBAMATE PESTICIDES#

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Abstract: Treatment of methyl N-methylcarbamate (1, R= Me) with phosphorus oxychloride and 1-naphthol results in the formation of the trans-esterified product, 1-naphthyl N-methylcarbamate (2, Ar=1-naphthyl) in good yield. Similarly, ethyl N-methylthiocarbamate (5) is converted to 1-naphthyl N-methylcarbamate (2, Ar= 1-naphthyl) on treatment with phosphorus oxychloride and 1-naphthol. The mechanism of these interesting and industrially important transformations is discussed.

The Bhopal tragedy of December 1984 in which more than 3000 people died, was the result of the escape of large volumes of stored methyl isocyanate (MIC) into the atmosphere. Since then, the production of aryl N-methylcarbamate pesticides by the reaction of phenols with MIC has been prohibited. The alternative process involving the initial formation of aryl chloroformates by phosgenation of phenols and subsequent conversion into carbamates by methyl amine is no less hazardous in the view of environmentalists and government agencies. However, from the point of view of agriculturists, there is a definite need for such carbamate pesticides. It was therefore imperative that a new and environmentally acceptable synthetic route be devised for this group of compounds. We now report such a method.

The crux of the problem is the conversion of alkyl carbamates (1) into aryl carbamates (2), since several methods are already known for the synthesis of the former class - inter alia, oxycarbonylation of amines,[1,2] synthesis of alkyl thiocarbamates[3] and their conversion to alkyl carbamates[4], etc. It is well known that acid or base-catalysed trans-esterifi-

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cations in simple esters are reversible reactions, and that the equilibrium lies far to the left when it is sought to convert an alkyl ester into an aryl ester (as in eqn.1). In fact, some recent articles have reported complete failure in such reactions.[5] A successful solution to the problem would therefore hinge crucially on the discovery of a totally new transesterification method for carbamates.

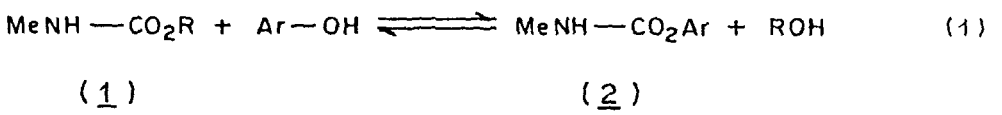
We felt that the best approach would be to generate an intermediate such as (3), in which, it may be expected that the nucleophile (Y) would attack the alkyl group (R) resulting in the cleavage of the O-C bond. The resultant species (4) would be more amenable to attack by phenol. This has recently been termed the " Counter-attack " strategy.[6]

The strategy indeed proved successful. Reaction of methyl N-methyl carbamate (1, R= Me) with 1-naphthol in presence of phosphorus oxychloride (60°, 8h) gave 1-naphthyl N-methylcarbamate (2, Ar= 1-naphthyl) in 88% yield (based on 1-naphthol; a two- fold excess of methyl N-methylcarbamate and $POCl_3$ was used). That the reaction did proceed through an intermediate such as 3 (X= $POCl_2$; Y=Cl) was proved as follows:

In the reaction of ethyl N-methylcarbamate (1, R= Et) under the same conditions, the effluent gas was collected in $CDCl_3$. The ^1H and ^{13}C NMR spectra proved that this was pure ethyl chloride. Similarly, treatment of benzyl N-methylcarbamate (1 R = CH_2Ph) with $POCl_3$ gave benzyl chloride which was identified by both GC and ^1H NMR. No trace of MIC could be detected in either of these samples.

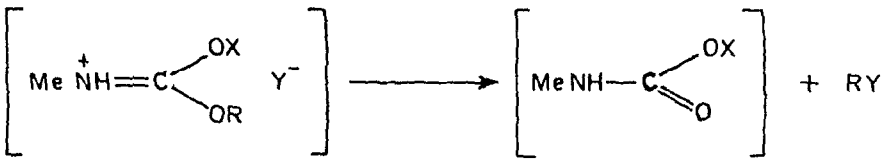
Further proof for the course of the reaction was provided by treatment of ethyl N-methylthiocarbamate (5) with 1-naphthol in presence of phosphorus oxychloride, when 1-naphthyl N-methylcarbamate (2, Ar = 1-naphthyl) was produced, presumably via an intermediate such as (6).

The trans- esterfication route has been successfully extended to a variety of substituted phenolic compounds, including such sterically hindered phenols like 2-chlorophenol, o-cresol, o-sec.butylphenol etc..[7] Resorcinol and 1,5-dihydroxynaphthalene led to the corresponding di-carbamates in good yields. However, when the reaction was carried out with thiophenol the expected phenyl thiocarbamate (7) could be obtained only in 25% yield. Heterocyclic thiols like 2-mercaptopyridine, 4-methyl-3-phenyl-1,2,4-triazole-5-thione failed to give the expected aryl thiocarbamates. However, 2-mercaptobenzothiazole gave the unexpected 2-ethylthio-

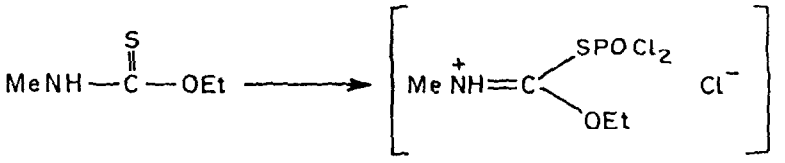


(1) (2)

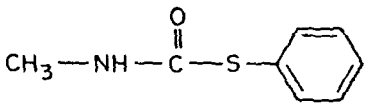
R = alkyl ; Ar = aryl



(3) (4)



(5) (6)



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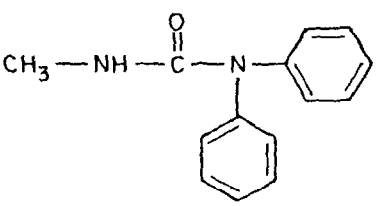

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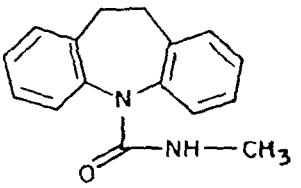

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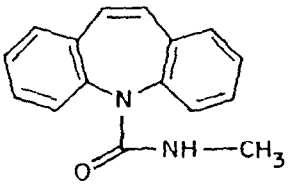

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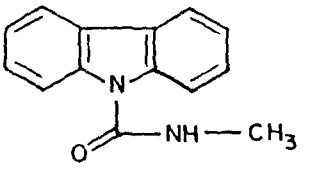

(11)

benzothiazole when reacted with ethyl N-methylcarbamate and $POCl_3$.

Ethyl N,N-dialkyl carbamates also react smoothly with phenol to give the corresponding phenyl carbamates in good yields.

Next,the reaction was carried out on nitrogen nucleophiles. Aniline failed to give the expected product, possibly because of its relatively high basicity (pK_a = 4.63) which might have led to its preferred reaction with $POCl_3$. However, diphenylamine (pK_a = 0.79), and other structurally similar amines like iminodibenzyl (pK_a = -0.78), iminostilbene (pK_a = 0.87) and carbazole (pK_a = -6.0) react readily with methyl N-methylcarbamate to give high yields of the expected substituted ureas (**8**, **9**, **10**, **11**) respectively.[8]

EXPERIMENTAL

General -- Freshly distilled phosphorus oxychloride was used in all experiments. Melting points were determined in capillaries and are uncorrected. ^1H NMR spectra were recorded on WH 90 FT NMR spectrometer (BRUKER) and FT 80A NMR spectrometer (VARIAN) instrument using tetramethylsilane as internal standard. The values of are expressed in ppm downfield from the signal for internal Me_4Si. Elemental analysis were performed at the Organic Chemistry Division, National Chemical Laboratory. IR spectra were recorded with a 599-B double beam IR spectrometer. Mass spectra were run on a Finnigan MAT 1020 automated GC/MS instrument. For t.l.c., plates coated with silica gel were run in benzene, n-hexane, ethyl acetate or their mixtures and spots were developed in an iodine chamber. For column chromatographic purification under gravity, column grade silica gel (60-120 mesh size) activated at 100°C for 1 h. was employed.

1-Naphthyl N-methylcarbamate (Carbaryl): Phosphorus oxychloride (30.8g, 0.2 mole) was added dropwise under stirring to a mixture of methyl N-methylcarbamate (17.89 g, 0.2 mole) and 1-naphthol (14.4 g, 0.1 mole). The reaction mixture was stirred for 7 h. at 60°C. The effluent gas was collected in $CDCl_3$. The ^1H and ^{13}C NMR spectra proved that this was pure ethyl chloride. The reaction contents were then cooled to room temperature. The reaction was quenched by slow and careful addition of ice-cold water, neutralised with aqueous $NaHCO_3$ solution and extracted thrice with dichloromethane. The combined extract was washed with cold 5% NaOH (to remove unreacted naphthol), water and brine and dried over anhydrous

Na_2SO_4. Evaporation of solvent afforded a solid which was purified by recrystallisation (n-Hexane:Benzene). (17.6g, 88% yield). m.p. 141°C. IR : 3305 (N-H), 1715 (-C=O), 1600, 1540, 770 (aromatic). ^1H NMR ($CDCl_3$) : 2.86 (d,3H, J=7Hz, NH-CH_3); 5.14 (b,1H NH); 7.17-8.00 (m, 7H, aromatic). Analysis calculated for $C_{12}H_{11}NO_2$: C, 71.64 ; H, 5.47. Found: C, 71.42 ; H, 5.41. Effluent gas ^1H NMR ($CDCl_3$) : 1.46 (t, 3H, -CH_3); 3.53 (q, 2H, CH_2-Cl). ^{13}C NMR ($CDCl_3$) : 39.92 (-CH_2Cl) ; 19.69 (-CH_3).

Reaction of benzyl N-methylcarbamate with $POCl_3$: Phosphorus oxychloride (1.5g, 0.01 mole) was added to benzyl N-methylcarbamate (1.65g, 0.01 mole) and stirred for 7 h. at 60°C. The reaction was quenched by addition of ice cold water and extracted thrice with dichloromethane. The combined extract was washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of solvent in vacuo afforded benzyl chloride (1.0g) which was identified both by GC and ^1H NMR.
^1H NMR ($CDCl_3$): 4.43 (s, 2H,CH_2Cl); 7.2 (s, 5H, aromatic).

Reaction of 1-naphthol with ethyl N-methylthiocarbamate (5) : To a stirred mixture of ethyl N-methylthiocarbamate (5) (1.19g, 0.01 mole) and 1-naphthol (1.44g, 0.01 mole), phosphorus oxychloride (1.54 g, 0.01 mole) was added and stirred for 8 h. at 60°C. After work up followed by chromatography carbaryl (0.66g; 33% yield) was obtained.

General procedure for reaction of methyl N-methylcarbamate with phenols : Phosphorus oxychloride (3.08g, 0.02 mole) was added to a stirred mixture of methyl N-methylcarbamate (1.78g, 0.02 mole) and the phenol (0.01 mole). The reaction mixture was stirred for 7-8 h. at 60°C. It was worked up as described earlier and purified by chromatography (eluent ; pet.ether : ethyl acetate 70:30) to give the corresponding carbamates.

a. **Phenyl N-methylcarbamate.** : Yield 55% ; m.p. 111-112°C.
^1H NMR ($CDCl_3$) : 3.10 (d, 3H, N-CH_3); 5.20 (b, 1H, N-H); 7.2 (m, 5H, aromatic). Analysis calculated for $C_8H_9NO_2$: C, 63.56; H, 6.00. Found: C, 63.21; H,5.70.

b. **4-Methylphenyl N-methylcarbamate.** : Yield 50% ; m.p. 93°C.
^1H NMR ($CDCl_3$) : 2.33 (s, 3H, Ar-CH_3) ; 2.88 (d, 3H, N-CH_3); 5.11 (b, 1H, N-H); 7.06 (m, 4H, aromatic). Analysis calculated for $C_9H_{11}NO_2$: C, 65.45 ; H, 6.71. Found : C, 65.38; H, 6.31.

c. **2-Methylphenyl N-methylcarbamate.** : Yield 25% ; m.p. 100°C.

^{1}H NMR ($CDCl_3$) : 2.24 (s, 3H, Ph-CH_3); 2.88 (d, 3H, N-CH_3) ; 5.04 (b, 1H, N-H); 7.2 (m, 4H, aromatic). Analysis calculated for $C_9H_{11}NO_2$: C, 65.45 ; H, 6.71. Found : C, 65.35; H, 6.41.

d. 2-Chlorophenyl N-methylcarbamate. : Yield 33% ; m.p. 82-84°C.
^{1}H NMR ($CDCl_3$) : 2.92 (d, 3H, N-CH_3); 5.12 (b, 1H, N-H); 7.36 (m, 4H, aromatic). Analysis calculated for $C_8H_8ClNO_2$: C, 51.89 ; H, 4.32. Found : C, 51.72 ; H, 4.29.

e. 2-sec Butylphenyl N-methylcarbamate : Yield 60%; b.p. 60-65°C at 1mm. ^{1}H NMR ($CDCl_3$) : 0.81 (t, 3H, primary methyl of side chain); 1.18 (d, 3H, J=7Hz,secondary methyl of side chain); 1.58 (m, 2H, methylene protons of side chain); 2.88 (doublet overlapping a multiplet, 4H, NH-CH_3 and benzylic proton); 4.97 (b, 1H, N-H); 6.95-7.25 (m, 4H, aromatic). Analysis calculated for $C_{12}H_{17}NO_2$: C, 69.56; H, 8.21 ; Found : C, 68.95; H, 7.93.

f. Phenyl 1,3-bis N-methylcarbamate. : Yield 28% ; m.p. 160-162°C.
^{1}H NMR ($CDCl_3$) : 2.88 (d, 6H, N-CH_3), 5.00 (b, 2H, N-H), 7.00-7.32 (m, 4H, aromatic). Mass spectrum : (m/z) 224 (10), 167 (100).Analysis calculated for $C_{10}H_{12}N_2O_4$: C, 53.57 ; H, 5.37. Found : C, 53.48 ; H, 5.21.

g. Naphthyl 1,5-bis N-methylcarbamate. : Yield 58% ; m.p. > 240°C
^{1}H NMR ($CDCl_3$ + TFA): 3.02 (s, 6H, N-CH_3), 7.44 (m, 6H, aromatic).
Mass spectrum :(m/z) 274 (2),160(100).Analysis calculated for $C_{14}H_{14}N_2O_4$: C, 61.31 ; H, 5.10. Found : C, 61.23 ; H, 4.97.

Methyl carbamothioic acid S-phenyl ester : Phosphorus oxychloride (2.31 g, 0.015 mole) was added to a mixture of methyl N-methylcarbamate (1.33g, 0.015 mole) and thiophenol (3.3g, 0.03 mole) and stirred for 10 h. at 70°C. Work-up as described earlier yielded a yellowish residue (4g). Chromatographic separation furnished diphenyldisulfide (first fraction, eluent; petroleum ether. m.p. 60°C) and methyl carbamothioic acid S-phenyl ester. (720 mg, yield 25% ; m.p. 104-105°C).^{1}H NMR ($CDCl_3$) : 2.84 (d, 3H, N-CH_3); 5.4 (b, 1H, N-H); 7.52 (m, 5H, aromatic). Analysis calculated for C_8H_9NOS : C, 57.48; H, 5 39. Found : C, 57.36; H, 5.32.

N,N',N' Trisubstituted ureas : To a mixture of ethyl N-methylcarbamate (2.06 g, 0.02 mole) and amine (0.01 mole), phosphorus oxychloride (3.08g, 0.02 mole) was added dropwise and stirred for 10-12 h. at 80-90°C (Benzene (2ml) was added in case of iminostilbene to prevent polymerisation). The mixture was cooled to room temperature and quenched by careful

addition of ice cold water, neutralised with aqueous $NaHCO_3$ solution and extracted thrice with dichloromethane. The combined organic extract was washed with water and brine , dried over anhydrous Na_2SO_4. Solvent evaporation in vacuo afforded a crude solid which was chromatographed. The fractions eluted with pet.ether-ethyl acetate (80:20) gave t.l.c pure solid (Benzene, R_f 0.7) which was further purified by crystallisation.

a N-Methyl N,'N'- diphenyl urea (8) : Yield 83% ; m.p. 190°C. ^1H NMR ($CDCl_3$) : 2.8 (d, 3H, N-CH_3), 7.3 (m, 10H, aromatic), 5.4 (b, 1H, N-H). Mass spectrum : (m/z) 226 (25), 169 (100). Analysis calculated for $C_{14}H_{14}N_2O$: C, 74.33 ; H, 6.19. Found : C, 74.18 ; H, 6.12.

b. 5H-Dibenz [b,f] 10,11, dihydro azepine-5-N-methyl carboxamide (9) : Yield 37% ; m.p. 174°C.^1H NMR ($CDCl_3$) : 2.75 (d, 3H, N-CH_3), 3.04 (s, 4H, -CH_2-CH_2-), 4.4 (b, 1H, N-H), 7.1 (m, 8H, aromatic). Mass spectrum : (m/z) 252 (25), 195 (100). Analysis calculated for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.35. Found : C, 75.97 ; H, 6.48.

c. 5H-Dibenz [b,f] azepine-5N-methyl carboxamide (10) : Yield 80% ; m.p.> 240°C.^1H NMR ($CDCl_3$) : 2.66 (d, 3H, N-CH_3), 4.17 (b, 1H, N-H), 6.82 (s, 2H, -CH=CH-), 7.37 (m, 8H, aromatic). Mass spectrum : (m/z) 250 (25), 193 (100). Analysis calculated for $C_{16}H_{14}N_2O$: C, 76.80 ; H, 5.60. Found : C, 76.85; H, 5.51.

d. 9H-Carbazole-N-methyl carboxamide(11).:Yield 63%; m.p.164-166°C. ^1H (NMR $CDCl_3$) : 3.06 (d, 3H, NH-CH_3), 5.66 (b, 1H, NH), 7.28 and 7.88 (m, 8H, aromatic). Mass spectrum : (m/z) 224 (25), 167 (100). Analysis calculated for $C_{14}H_{12}N_2O$: C, 75.00; H, 5.35. Found: C,74.29; H, 4.92.

Phenyl N,N-dimethylcarbamate : To a mixture of ethyl N,N-dimethylcarbamate (1.17 g, 0.01 mole) and phenol (470 mg. 0.005 mole), phosphorus oxychloride (1.5g, 0.01 mole) was added and stirred for 22 h. at 100°C. The usual work up afforded a yellowish oil which was distilled (90-100°C, 8mm) to give phenyl N,N-dimethylcarbamate (587 mg; 35%). ^1H NMR ($CDCl_3$) : 3.2 (s, 6H, N-Me_2), 7.28 (m, 5H, aromatic). Analysis calculated for $C_9H_{11}NO_2$: C, 65.45; H, 6.66. Found : C, 65.57; H, 6.59.

Phenyl N,N-diethylcarbamate : Procedure same as above. Yield 30% ; b.p. 90-100°C at 2 mm. ^1H NMR ($CDCl_3$) : 1.15 (t, 6H, -CH_2), 3.3 (q, 4H, -CH_2), 7.1 (m,5H,aromatic). Analysis calculated for

$C_{11}H_{15}NO_2$: C, 68.39, H, 7.77. Found : C, 68.22; H, 7.85.

Acknowledgement

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8. The reaction, of course, is a hitherto unknown variant of the classical Vilsmeier-Haack reaction.