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THE REACTION OF DICHLOROCARBENE WITH TERTIARY CARBOXAMIDES. PREPARATION OF α-CHLOROMETHYLENELACTAMS AND (E)-CHLOROACRYLAMIDES

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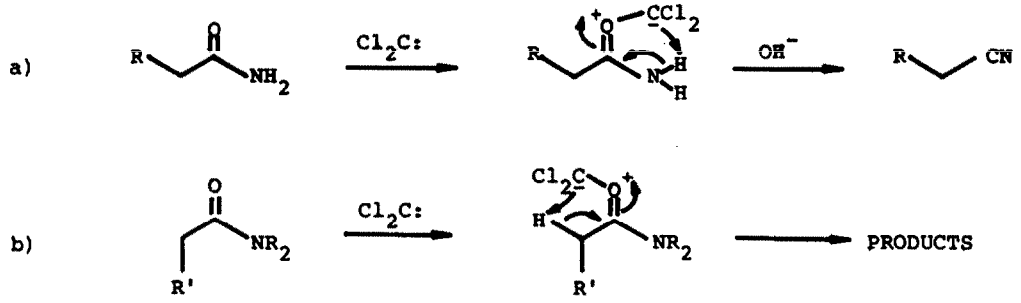
Abstract.- An easy method is described for the preparation of (E)-3-chloroacrylamides and α-chloromethylenelactams which is based on the simple treatment of tertiary carboxamides and lactams with dichlorocarbene.

Further to our work on the reaction of dichlorocarbene with nitrogen compounds[1] we wish now to report an unexpected conversion of tertiary carboxamides and lactams into the corresponding α-chloromethylene derivatives by reaction with Cl_2C: generated by the phase transfer method[2].

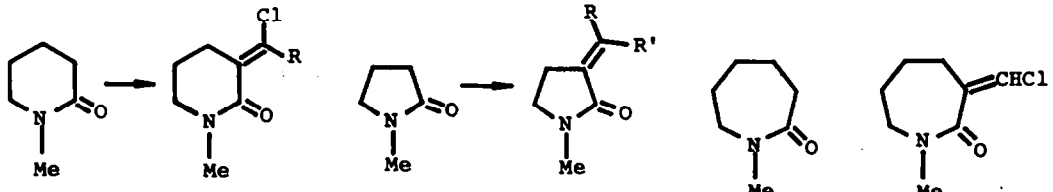
While the reaction of dichlorocarbene with primary carboxamides is known to give nitriles[3] by a mechanism involving a beta-elimination from the carbonyl ylide (Scheme Ia), tertiary carboxamides have been considered to be inert towards Cl_2C:, and have in fact been proposed as protecting groups for secondary amines[4]. This attribution of "inertness" is based on the lack of N-H protons, but we reasoned that an intramolecular beta-elimination could take place by abstraction of a proton alpha to the carbonyl group (Scheme Ib).



Scheme I

When N-methyl-γ-valerolactam 1 was treated with chloroform and aq. NaOH in the presence of tetrabutylammonium chloride (TBAC) as catalyst (24 h, room temperature) the (E)-α-chloromethylenelactam 2a was obtained in 40% isolated yield (74% conversion). Similarly, N-methyl-2-pyrrolidone 3 gave a 6:1 mixture of E and Z α-chloromethylenelactams 4a and 4b respectively (30% isolated yield, 80% conversion). However, N-methyl-caprolactam 5 produced a complex mixture of

compounds from which the α-chloromethylenelactam 6 could not be isolated. The stereochemistry of the exo double bond of 2a, 4a and 4b was established by measurement of nuclear Overhauser effects (nOe). Thus, while in the case of the E-isomers 2a and 4a no nOe was observed between the vinylic proton and the $-CH_2-$ group alpha to the double bond, the Z-isomer 4b showed a positive nOe effect.



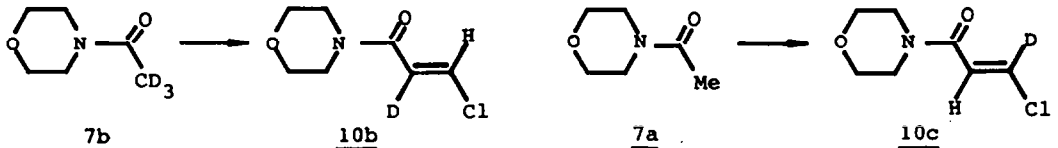
1 2a: R= H 2b: R= D 3 4a: R= Cl, R'= H 4b: R= H, R'= Cl 5 6

The reaction of dichlorocarbene with morpholine, N-methyl-benzylamine and N-methyl-aniline acetamides (7a, 8 and 9 respectively) gave the corresponding (E)-3-chloroacrylamides 10a, 11 and 12 (30-50% isolated yield, 100% conversion). However, the methanesulfonamide of morpholine and the propionamides, phenylacetamides, α-chloroacetamides and α-methoxyacetamides of morpholine and N-methylbenzylamine were recovered unchanged. The inertness of these alpha-substituted amides is probably due to a steric hindrance around the carbon alpha to the carbonyl group.

7a: R^1,R^2= morpholine
8: R^1= Me, R^2= $PhCH_2$-
9: R^1= Me, R^2= Ph

10a: R^1,R^2= morpholine
11: R^1= Me, R^2= $PhCH_2$-
12: R^1= Me, R^2= Ph

Further experiments showed that the trideuteroacetamide 7b gave the acrylamide 10b, monodeuterated at C-2, while the acetamide 7a reacted with Cl_2C: generated from $CDCl_3/D_2O/NaOH$(solid) giving 10c, monodeuterated at C-3 (about 90% deuteration according to HNMR and MS spectra). Similarly, the lactam 1 was converted into the α-chloromethylenelactam 2b, deuterated at the exo-methylene carbon.

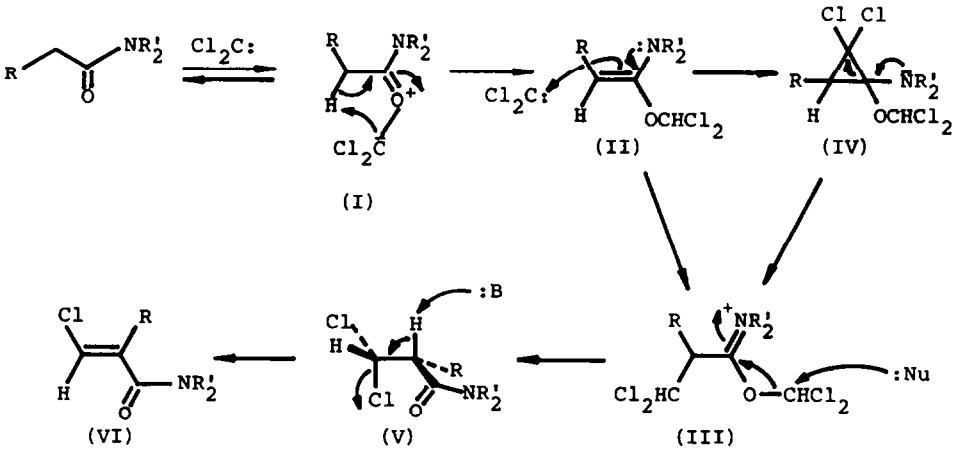


7b 10b 7a 10c

The above results might be explained by assuming simply the insertion of Cl_2C: on the C_α-H bond followed by elimination of HCl. Nevertheless, this mechanism seems improbable because such reactions go well only when the C-H bond is alpha to an activating group. Moreover, the lack of reactivity of substituted acetamides such as α-methoxy and phenylacetamides would not be explained.

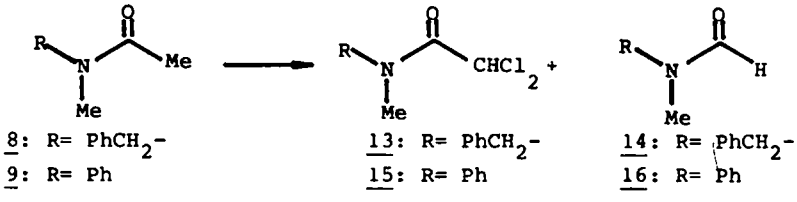
A more satisfactory mechanism is shown in Scheme II, where the reversible

formation of a carbonyl ylide followed by an intramolecular beta-elimination gives an enamine (II). Subsequent reaction of (II) with dichlorocarbene gives (III), either by a cyclopropanation or due to the well known C-β reactivity of enamines. The latter appears to be the most probable path, because the opening of adduct (IV) required by the former has never been reported as far as we know. Finally, the recovery of the carbonyl group and beta-elimination of HCl gives the most stable (E)-3-chloroacrylamide (VI).



Scheme II

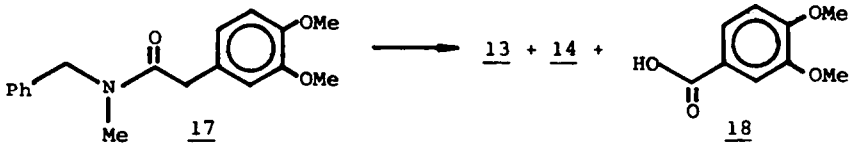
The reactivity of tertiary carboxamides when Cl_2C: was generated by other methods was found to be quite different. Thus the amides 7a, 8 and 9 were recovered unchanged when $PhHgCCl_3$, $PhHgCCl_2Br$ and $PhHgCBr_3$ were subjected to thermal decomposition in their presence (Benzene, 80º, 24-48 h). The acetamide 8 surprisingly gave a mixture of α,α-dichloroacetamide 13 (40% yield) and the formamide 14 (15% yield) when treated with $K^tBuO/HCCl_3$/benzene. The same result was obtained when the tertiary carboxamide 9 was reacted with CCl_4/nBuLi/THF, giving the α,α-dichloroacetamide 15 and the formamide 16 (55% and 8% yield respectively). The formation of 13, 14, 15 and 16 points to the radical nature of these reactions, which must involve homolytic cleavage of the C_1-C_2 bond. Further support is obtained from the reaction of arylacetamide 17 with $K^tBuO/HCCl_3$, which gives the benzoic acid 18 (50% yield) in addition to the amides 13 and 14 (40% and 15% yield).



8: R= $PhCH_2$-
9: R= Ph

13: R= $PhCH_2$-
15: R= Ph

14: R= $PhCH_2$-
16: R= Ph



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The above results clearly show that tertiary carboxamides are only inert towards Cl_2C: generated from phenyl(trihalometyl)mercury compounds. Under phase transfer conditions, the reaction constitues a very simple method for preparing (E)-3-chloroacrylamides without having to resort to the expensive (E)-3-chloroacrylic acid, and allows direct preparation of α-chloromethylenelactams. Further experiments on the synthetic use of these compounds are in progress.

Finally, it is worth noting that for the protection of secondary amines we have recently found that the trifluoracetyl group is very convenient as it resists dichlorocarbene (PTC conditions) and is easily removable[5].

EXPERIMENTAL

IR spectra were obtained with a PYE-UNICAM 1100 spectrometer and NMR spectra using a BRUKER WM 250 spectrometer. All signals are expresed as δ values ppm downfield from TMS. MS measurements were taken on a KRATOS MS-25 mass spectrometer. The silica gel and aluminium oxide for chromatography were obtained from MERCK.

Reaction of tertiary carboxamides and lactams with dichlorocarbene. General procedure.

A solution of 1-4 mmol of the amide in 50 ml of $CHCl_3$ was magnetically stirred with 10 ml 50% aqueous NaOH and TBAC (10 mg). After 24-48 h the mixture was poured into water (40 ml) and decanted. The organic layer was washed with water (2x15 ml), dried (Na_2SO_4) and concentrated. The residue was purified by preparative TLC on silica gel, and/or by distillation.

(E)-α-Chloromethylenelactam 2a

N-methyl-γ-valerolactam 1 was converted into 2a following the general procedure (36 h of stirring). The crude of the reaction was purified by preparative TLC on silica gel (CH_2Cl_2-3% EtOH) followed by distillation to give an oil ($b.p._{0.1}$=129-132º) wich solidified on standing.
HNMR: δ 7.33 (t,J=2.2 Hz,1H,-CHCl), 3.37 (t,J=5.0 Hz,2H,-CH_2N), 3.03 (s,3H,N-Me), 2.62 (dt,J=2.2 and 6.3 Hz,2H,-CH_2-C=C),1.90 (m,2H,-CH_2-); CMR: δ 162.63 (s), 131.69 (s), 128.08 (d), 49.51 (t), 35.02 (q), 24.87 (t) and 21.65 (t); IR (film): 1650, 720 cm^{-1}; MS: m/e 162 (10), 161 (21), 160 (36), 159 ($M^{+\cdot}$,53), 158 (16), 124 (16), 96 (26), 81 (16), 67 (11), 53 (58) and 43 (100).
Found: C 52.71, H 6.50, N 8.65. $C_7H_{10}ClNO$ requires: C 52,67, H 6.32, N 8.78 %.

(E) and (Z) α-chloromethylenelactams 4a and 4b

The reaction of Cl_2C: with N-methyl-pyrrolidone 3 (48 h) gave, after preparative TLC (aluminium oxide, benzene) and distillation, a 6:1 mixture of E and Z α-chloromethylenelactams 4a and 4b respectively ($b.p._{0.1}$=75-77º) as an oil which solidified on standing.
IR (film): 1650, 720 cm^{-1}; MS:m/e 148 (2), 147 (4), 146 (5), 145($M^{+\cdot}$,9), 144 (3).
Found: C 49.43, H 5.66, N 9.41. C_6H_8ClNO requires: C 49.50, H 5.54, N 9.62 %.

Both isomers could be separated by preparative TLC (aluminium oxide, hexane-8% isopropanol; 4a, rf=0.40; 4b, rf=0.35).

4a.- HNMR: δ 6.79 (t,J=3.0 Hz,1H,CHCl), 3.46 (dd,J=6.30 and 6.90 Hz,2H,-CH_2-N), 2,94 (s,2H,N-Me), 2.79 (m,2H,-CH_2-); CMR: δ 165.15 (s), 134.74 (s), 121.69 (d), 45.56 (t), 29.39 (q) and 22.21 (t); UV (EtOH): λ_{max} 245 nm (ε 4200).

4b.- HNMR: δ 6.68 (t,J=4.6 Hz,1H,CHCl), 3.47 (t,J=7.2 Hz,2H,-CH_2-N), 3.03 (s,3H, N-Me), 2.48 (dt,J=4.6 and 7.2 Hz,-CH_2-); CMR: δ 160.59 (s), 134.83 (d), 127.93 (s), 47.38 (t), 35.25 (q) and 24.33 (t); UV (EtOH): λ_{max} 233 nm (ε 1700).

(E)-3-Chloroacrylamides 10a,11 and 12

After stirring the tertiary carboxamides 7a,8 and 9 for 12-24 h, the corresponding (E)-3-chloroacrylamides 10a,11 and 12 were obtained in 50,30 and 40% isolated yield respectively (silica gel, CH_2Cl_2-3% EtOH). Authentic samples of 10a,11 and 12 were synthesized from the corresponding secondary amines and (E)-3-chloroacrylic acid chloride[6].

10a.- HNMR: δ 7.31 (d,J=12.9Hz,1H,H-3), 6.65 (d,J=12.9 Hz,1H,H-2), 3.66 (broad s,8H, morpholine).

11.- HNMR: δ 7.40-7.15 (m,6H,Ar and H-3), 6.74 and 6.68 (two d,J=12.8 Hz,1H,H-2), 4.64 and 4.67 (two s,2H,Ar-CH_2-), 3.12 and 3.00 (two s,3H,NMe), The complex HNMR data of 11 correspond to a mixture of rotamers and upon warming to 56º colapsed to the following: δ 7.34 (m,6H), 6.70 (d,J=12.7 Hz,1H), 4.61 (broad s,2H) and 3.05 (s,3H).

12.- HNMR: δ 7.44-7.16 (m,6H,Ar and H-3), 6.15 (d,J=12.9 Hz,H-2), 3.33 (s,3H,NMe).

(E)-3-Chloro-2-deuteroacrylamide 10b

The reaction of trideutero acetamide 7b gave a 48% isolated yield of an 88:12 mixture of deuterated 10b and the undeuterated compound 10a (HNMR and MS spectra).

10b.- HNMR: δ 7.31 (t,1H,H-3), 3.61 (broad s,8H,morpholine); CMR: δ 162.88 (C=O), 135.66 (C-3), 122.45 (as triplet,C-2), 66.60 (morpholine); MS: m/e 178 (5), 176 ($M^{+\cdot}$,16), 141 (93), 90 (100), 86 (72).

Reaction of N-acetyl morpholine and N-methyl-γ-valerolactam 1 with $CDCl_3/D_2O/NaOH$ (A).

A solution of 0.7 mmol of 7a in $CDCl_3$ (5 ml) was stirred with 3 ml of D_2O containing 200 mg of solid NaOH and TBAC[3]. After 24 h the usual workup gave 10c in 51% isolated yield.

10c.- HNMR: δ 6.65 (t,J=1.7 Hz,1H,H-2), 3.60 (broad s,8H,mopholine); MS: m/e 178 (10), 176 ($M^{+\cdot}$,29), 141 (90), 90 (100), 86 (70).

The lactam 1 gave the exomethylene deuterated compound 2b in 38% isolated yield.

2b.- HNMR: δ 3.37 (t,J=5.8 Hz,$-CH_2-N$), 3.02 (s,3H,NMe), 2.62 (t,J=6.3 Hz,2H, $-CH_2-C=C$), 1.90 (m,2H,$-CH_2-$).

Reaction of 8 with Cl_2C: generated by the Doering-Hoffmann procedure[7].

To a stirred mixture of 1.2 mmol (200 mg) of the amide 8 and 12 mmol (1.36 g) of K^tBuO in 25 ml of dry benzene, 24 mmol (2.7 g) of $CHCl_3$ in 30 ml of dry benzene were added dropwise under an argon atmosphere, the temperature being kept below 30º. The resulting brown mixture was stirred for an additional period of 12 h, washed with water (5x10 ml) and the organic layer was dried (Na_2SO_4) and evaporated. The remaining oil was filtered through a short column of silica gel with CH_2Cl_2-3%EtOH as eluent, to eliminate the brown polymeric material. The resulting light yellow oil was purified by preparative TLC (silica gel, CH_2Cl_2-3% EtOH) to give 100 mg of the initial compound 8, 14 mg of the formamide 14 and 55 mg of α,α-dichloroacetamide 13 (15 and 40% yield based on recovered 8).

Authentic samples of 13 and 14 were prepared by conventional methods from N-methylbenzylamine.

Reaction of 17 with $K^tBuO/CHCl_3$/benzene

The reaction of 17 with Cl_2C: under the same conditions described for the amide 8 gave, in addition to 13 and 14 (14 and 43% yield, 50% conversion), 65 mg of homoveratic acid 18 (50% yield) isolated from the alkaline layer.

Reaction of 9 with Cl_4C/n-BuLi

To a stirred solution of 9 (50 mg, 0.3 mmol) in dry THF (15 ml) and Cl_4C (0.5 ml, 5 mmol) was added dropwise by syringe, under an argon atmosphere, 0.4 mmol of n-BuLi (0.5 ml of 1.6 M hexane solution), the temperature being kept at -78º. Stirring was continued, and after 1 h the reaction was allowed to continue at room temperature. After 10 h the mixture was poured into ice-water and extracted with methylenechloride, dried (Na_2SO_4) and concentrated. Preparative TLC (silica gel, CH_2Cl_2) gave 25 mg of the initial compound 9 (50% conversion), 5 mg (22% yield) of N-methyl-N-formyl-aniline 16 and 20 mg (55% yield) of N-methyl-α,α-dichloroacetylaniline 15, which were shown by HNMR to be identical with authentic samples.

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