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A Novel Synthesis of Isocyanates and Ureas *via* β-Elimination of Haloform

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Abstract: A novel synthesis of isocyanates *via* base-induced β-elimination of haloform from N-monosubstituted trihaloacetamides is described. The rate of reaction exhibits a strong dependence on the nature of the trihalomethyl group. Thus, while the reaction of tribromoacetamides proceeds at room temperature and the reaction of trichloroacetamides requires heating in polar solvents, no reaction could be observed for any of the corresponding trifluoro derivatives. This novel β-elimination of haloform from stable and readily available trihaloacetamides was applied to a "one-pot" synthesis of ureas which avoids the use of phosgene and isolation of isocyanates.
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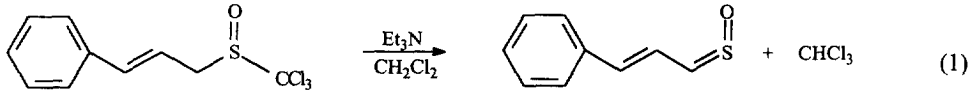
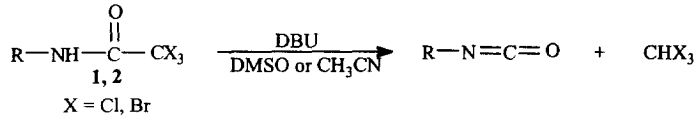
Key words: Isocyanates, ureas, N-monosubstituted trihaloacetamides, β-elimination of haloform.

The apparent lack of earlier documented examples of β-elimination of haloform is rather surprising not only because of the leaving group ability of the trihalomethyl anion, which is well demonstrated by the old haloform reaction [1], but also because of the α-elimination of haloform which has been thoroughly studied and extensively used for the preparation of dichlorocarbene in the past [2]. We have recently reported that allylic and benzylic trichloromethyl sulfoxides undergo a facile and unprecedented base-induced β-elimination of chloroform, and afford the corresponding sulfines in good yields [3-5] (eq. 1).



(1)

As a natural extension of this reaction, we decided to apply our new sulfine synthesis to the predictable and analogous synthesis of various other heterocumulenes such as N-sulfinylamines and isocyanates. We have thus found that treatment of N-monosubstituted trichloromethanesulfinamides with DBU in dichloromethane at room temperature results in a practically spontaneous elimination of chloroform and formation of the corresponding N-sulfinylamines [6]. We now wish to report our results on the synthesis of isocyanates by the use of the same approach (eq. 2).



(2)

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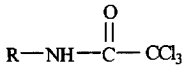
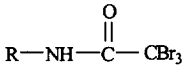
Isocyanates are useful intermediates in organic synthesis [7], especially in the construction of heterocycles [8] and substituted ureas [9]. These compounds can be prepared by various procedures, the choice of which depends on the target molecule. The most common method comprises the reaction of phosgene with aliphatic and aromatic amines [7,10]. This method was modified over the years using various substitutes for the highly toxic phosgene [11]. However, no final satisfactory and economical solution has yet been discovered. Following our approach of preparing heterocumulenes by β-elimination of haloform, we decided to examine the preparation of isocyanates from readily available and substantially less toxic starting materials.

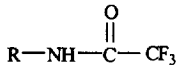
The required trichloro- and tribromoacetamides (**1a-j, 2a-e**) were easily prepared by reaction of the appropriate amines with commercial trichloro- and tribromoacetyl chloride, respectively. Similarly, trifluoroacetamides **3a-d** were prepared by reaction of the appropriate aniline with trifluoroacetic anhydride. It is obviously an advantage to have these acetylating agents commercially available at reasonable prices. All trihaloacetamides were prepared in good yield (80-90%) as nice crystalline solids with long shelf life, a further obvious advantage.



1a, R = Ph
b, R = *p*-Tol
c, R = 2,6-$(CH_3)_2C_6H_3$
d, R = 2,4,6-$(CH_3)_3C_6H_2$
e, R = 4-$CH_3OC_6H_4$
f, R = 4-ClC_6H_4
1g, R = 2-ClC_6H_4
h, R = 3,4-$Cl_2C_6H_3$
i, R = $C_6H_5CH_2$
j, R = $C_6H_5CH(CH_3)$
k, R = $C_6H_5CH_2CH_2$
l, R = $(CH_3)_3C$



2a, R = *p*-Tol
b, R = 2,6-$(CH_3)_2C_6H_3$
c, R =2,4,6-$(CH_3)_3C_6H_2$
d, R = 4- ClC_6H_4
e, R = $C_6H_5CH_2$



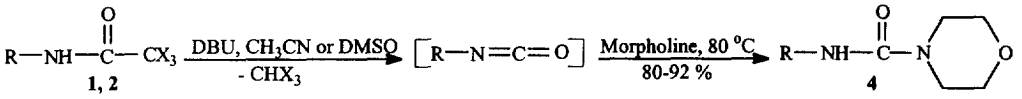
3a, R = *p*-Tol
b, R = 4-ClC_6H_4
c, R = 4-$CH_3OC_6H_4$
d, R = 2,6- $(CH_3)_2C_6H_3$

As expected from the reaction mechanism, we have found that the rates of reaction of these compounds with base exhibit a strong dependence on the nature of the trihalomethyl group. Thus, while tribromoacetanilides **2a-e** undergo β-elimination of bromoform in DMSO in the presence of DBU at room temperature (eq. 2), and elimination of chloroform from trichloroacetamides **1a-j** requires heating at 80° in a polar solvent for several hours, no reaction is observed for any of the trifluoroacetanilides **3a-d** even on heating at 120° for 2 days. These results are in full agreement with data for alkaline cleavage of trihalomethyl ketones in aqueous solution [12]. The relative rates were found to be in the ratio $PhCOCF_3$: $PhCOCCl_3$: $PhCOCBr_3$ - 1: $5.3x10^{10}$: $2.2x.10^{13}$. These results demonstrate the extremely low stability of the CF_3^- anion and are in agreement with results of studies of base-catalyzed hydrogen-deuterium exchange rates [13] which follow the order $HCBr_3$ >$HCCl_3$ >>HCF_3.

The formation of bromoform or chloroform and the corresponding isocyanates is readily detected by carrying out the reaction in DMSO-d_6 in the NMR tube. It should be emphasized that due to the excessive sensitivity of isocyanates to moisture and their base catalyzed hydrolysis [7b], as well as their facile di- and trimerization [8] isolation was rather difficult. However, by working with sterically hindered trihaloacetanilides **1c,d** and **2b,c**, possessing the 2,6-dimethyl- and 2,4,6-trimethylphenyl substituents, this problem was solved. For example, mesityl isocyanate could be isolated in 75% yield from the reaction of **2c**, extracting the product with hexane and addition of 40% H_2SO_4 in acetonitrile to enable separation of the product from DBU.

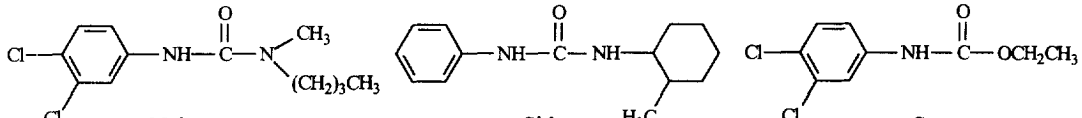
All N-monosubstituted trichloroacetamides examined react with DBU in refluxing acetonitrile affording the corresponding isocyanates, as evidenced by isolation of the unsymmetrical ureas **4** from trapping by morpholine (eq. 3). Although elimination of $CHBr_3$ occurs at r.t., conversion of **2a-e** to ureas was enhanced by brief heating. Similar yields were obtained with both systems **1** and **2**. To ensure that the ureas indeed arise by elimination of haloform, followed by addition of morpholine and not by an alternative mechanism involving

nucleophilic addition-elimination to the carbonyl group, a control experiment on a N,N-disubstituted substrate was required. We have thus found that N-aryl-N-methyltrichloroacetamides remain unchanged under these conditions.

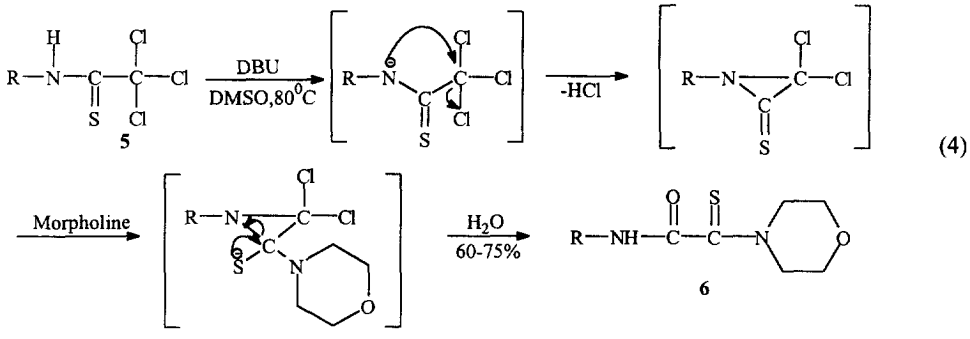


(3)

One should point out that our "one-pot" synthesis of unsymmetrical ureas from readily available and stable trihaloacetamides has the clear advantage that it avoids the need to isolate the highly toxic isocyanates, illustrated by methyl isocyanate and the Bhopal disaster of recent memory. A number of different unsymmetrical ureas were thus obtained as nice crystalline solids according to the above procedure in good to excellent yields under relatively mild and safe conditions. Since a variety of mixed ureas and urethanes are well known for their biological activity and are widely used as herbicides, pesticides and fungicides [14]; the three herbicides shown below have also been prepared by our method. It thus appears that this method may also be of practical advantage since it avoids the use of both toxic phosgene and isocyanates at a reasonable cost.



It is interesting to note the great difference in reactivity between trichloroacetamides and the analogous trichloromethanesulfinamides with regard to β-elimination of chloroform. Thus, while the latter react almost spontaneously even with weak bases such as Et_3N, the former react only on heating in refluxing acetonitrile in the presence of a strong base such as DBU. Similarly, while we were able to observe even base-induced elimination of fluoroform from monosubstituted trifluoromethansulfinamides [15], no reaction occurred with the corresponding trifluoroacetamides. We believe that this striking difference may be explained in part by the large difference in bond strength of the C-C (*ca.* 83 Kcal/mole) and C-S (*ca.* 62 Kcal/mole) bonds, which must be cleaved in the rate-determining step.



(4)

Finally, an even more striking contrast has been observed between the base induced reactivity of trichloroacetamides and their thio analogues. We have thus found that contrary to the corresponding trichloroacetamides **1**, the reaction of thioamides **5**, under similar conditions affords thiooxamides **6** (eq.4) [16]. This unexpected result may be tentatively explained by the occurrence of a competing reaction similar to the

Favorskii rearrangement as indicated in equation 4. In view of its mechanistic interest we are now investigating the source of this contrasting reactivity.

General procedure for the preparation of ureas. To a solution of 0.5 mmol of trihaloacetamide **1** or **2** and 0.5 mmol of the appropriate amine in 3 mL of dry DMSO, 0.5 mmol of DBU were added and reaction mixture heated at 80 °C for 4 hrs for **1a-l** and 0.5 hr for **2a-e**. After cooling to room temperature, the reaction mixture was diluted with 10 mL of CH_2Cl_2 and washed with solutions of 3% HCl, $NaHCO_3$ and saturated NaCl solution. After drying over $MgSO_4$ and removal of solvent, the product was recrystallized from suitable solvent. All compounds thus prepared gave satisfactory analytical and spectral data, in accord with their structure. The products were obtained with the yields of 80 - 92%. Selected data are as follows: **N-(1-phenylethyl)-4-morpholine-carboxamide**: mp 83-84 °C (from Et_2O/hexane), yield 84 %, ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 2.83 (2H, t, J=7 Hz), 3.27 (4H, t, J=5 Hz), 3.50 (2H, dt, J=5, 7 Hz), 3.67 (4H, t, J=5 Hz), 4.51 (1H, br), 7.25 (5H, m); ^{13}C NMR δ : 36.26 (α-CH_2), 41.99 (β-CH_2), 43.91 (CH_2-N), 66.46 (CH_2-O), 126.44 (C-4), 128.80 & 128.60 (C-2 &C-3), 139.25 (C-1), 157.68 (C=O); IR (KBr): 3317, 2858, 1624, 1544, 1261, 1118, 754, 703 cm^{-1}; Analysis: calcd. for $C_{13}H_{18}N_2O_2$ C 66.64, H 7.74, N 11.96; found C 66.63, H 7.62 N 12.01. **N-(4-chlorophenyl)-N'-*t*-butyl urea** : mp 193-194 °C (from $CHCl_3$), yield 92 %, ^{1}H NMR(300 MHz, DMSO-d_6) δ: 1.28 (9H, s), 6.00 (1H, br), 7.23 (2H, d, J=9 Hz), 7.37 (2H, d, J=9Hz), 8.36 (1H, br); ^{13}C δ : 29.40 (CH_3), 49.90 (C_q), 119.27 (C-2), 124.59 (C-4), 128.87 (C-3), 140.06 (C-1), 154.63 (C=O); MS-CI(CH_4): *m/z* 227.1 (MH^+, 100), 171.0 (70.51), 156.1 (9.49), 127.0 (89.18); HRMS: calcd. for $C_{11}H_{16}N_2OCl$ 227.0951; found 227.0929.

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