Pergamon

Tetrahedron Letters 39 (1998) 9259–9262

TETRAHEDRON LETTERS

PREPARATION OF TRICHLOROTHIOACETAMIDES AND THEIR UNEXPECTED REARRANGEMENT TO THIOOXAMIDES

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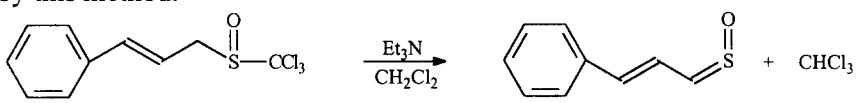
Received 3 July 1998; accepted 1 October 1998

Abstract : The preparation of several N-monosubstituted trichlorothioacetamides by thionation of the corresponding acetamides, with the use of Heimgartner's reagent is described. In contrast to the corresponding amides which undergo base-induced β-elimination of chloroform, the title compounds undergo an unexpected rearrangement to thiooxamides. The reaction mechanism is discussed.

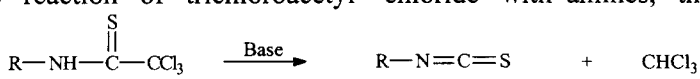
Keywords : Amides, thioamides, Favorskii rearrangement

We have recently reported that allylic and benzylic trichloromethyl sulfoxides undergo an apparently unprecedented base-induced β-elimination of chloroform and afford mono [1] and disubstituted [2] sulfines. The reaction proceeds smoothly under mild conditions (eq.1). As a natural extension of this reaction, we decided to apply our new sulfine synthesis to the predictable and analogous synthesis of heterocumulenes in general. We have thus found that various other heterocumulenes such as sulfinilamines [3] and isocyanates [4] are readily accessible by this method.



(1)

In continuation, we have explored the application of chloroform elimination to the synthesis of isothiocyanates (eq.2). Isothiocyanates, as well as their oxygen analogs, are useful intermediates in organic synthesis. Synthetic interest in these compounds arises from their utility in the synthesis of heterocyclic compounds [5] as well as from application to the synthesis of substituted ureas and thioureas [6]. In order to investigate the preparation of isothiocyanates by the new method, we had to prepare some N-substituted trichlorothioacetamides. However, in contrast to trichloroacetamides, which are readily available by the reaction of trichloroacetyl chloride with amines, the preparation of



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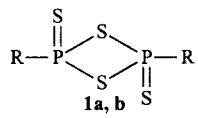
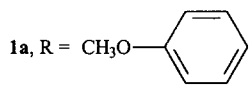
PII: S0040-4039(98)02080-2

trichlorothioacetamides presents some difficulties since trichlorothioacetyl chloride is not commercially available, nor is it easily accessible. Consequently, we attempted to prepare the required compounds by thionation of the corresponding trichloroacetamides.

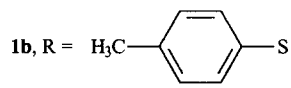
In recent years, Lawesson's reagent (LR) **1a** has become the most favored reagent for the smooth transformation of amides to their thioanalogues [7-11]. LR is easily prepared, reacts in nearly equimolar proportions and usually affords thiocarbonyl compounds in good yields [12,13]. Variously substituted thioamides have been prepared with **1a** [7-11]. However, 2-propenamide and several 2-butenamides react with LR in the presence of HMPA to give phosphorus heterocycles instead of the expected products [14]. Similarly, our efforts to achieve thionation of trichloroacetamides by **1a** under a variety of conditions failed to provide the desired products.



1a, b

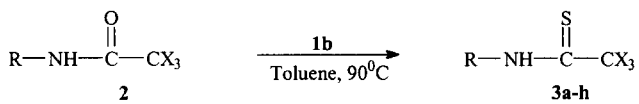


1a, R = CH_3O



1b, R = H_3C

In view of the above results, we decided to examine the use of the novel thionation reagent, Heimgartner's reagent (HR) **1b** [15]. To our delight, we have found that this reagent is quite useful for the preparation of trichlorothioacetamides in reasonable yields (eq.3). The reaction proceeds well also for trifluoroacetamides, as well as for N,N-disubstituted trichlorothioacetamides. For example, *N*-4-chlorophenyltrifluorothioacetamide and *N*- methyl-*N*-phenyltrichlorothioacetamide were obtained in 88% and 78% yield, respectively. It is interesting to note, that thionation of cyclic peptides by the Lawesson reagent **1a** has failed, while the use of Heimgartner's reagent **1b** was successful [16]. While we cannot provide a convincing explanation for the greater reactivity of the latter reagent at present, we wish to note the enhanced solubility of **1b** and its reduced steric congestion due to the longer P-S bonds.

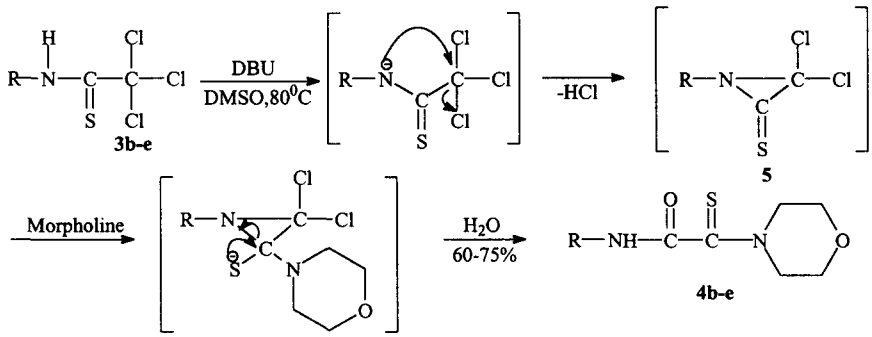


2 → (**1b**, Toluene, 90°C) → **3a-h** (3)

a, R = 4-$CH_3C_6H_4$, X = Cl
b, R = $C_6H_5CH_2$, X = Cl
c, R = 2,6-$(CH_3)_2C_6H_3$, X = Cl
d, R = 2,4,6-$(CH_3)_3C_6H_2$, X = Cl
e, R = $C_6H_5CH_2CH_2$, X = Cl
f, R = 4-$CH_3OC_6H_4$, X = Cl
g, R = 4-ClC_6H_4, X = Cl
h, R = 4-ClC_6H_4, X = F

Having prepared the required starting materials **3**, we proceeded to examine their reactivity under basic conditions. Surprisingly, we have found that contrary to the corresponding trichloroacetamides **2**, the reaction of thioamides **3** under the same conditions affords thiooxamides **4** (eq. 4). This unexpected result may be tentatively explained by the occurrence of a competing reaction similar to the Favorskii rearrangement (eq.4). A possible mechanism involves formation of three-membered cyclic intermediate **5** (α-thiolactam) *via* HCl elimination, with subsequent nucleophilic attack of morpholine on the thiocarbonyl carbon, followed by ring opening, hydrolysis of the CCl_2 group and formation of the observed product **4**. While the intermediacy of α-lactams in the base-induced reactions of 2-haloamides

is well known [17], we are not aware of any reports on the analogous reaction of halothioamides. The difference in reactivity of trichloroacetamides and their thio analogues is of considerable mechanistic interest. We are therefore investigating the source of this contrasting reactivity.



General procedure for the preparation of trichlorothioacetamides 3a-h. To a solution of 1 mmol of trichloroacetamide **2** dissolved in 5 mL of dry toluene under a nitrogen atmosphere, 0.5 mmol of **1b** [15] was added in one portion. The light yellow solution was heated with stirring at 90 °C for 2-4 h until appearance of a light brown color. After cooling to room temperature, the reaction mixture was flash chromatographed under nitrogen using a silica gel column. Hexane was used initially as the eluent, and then was replaced by a mixture of CH_2Cl_2-hexane in the ratio 1:2 (v/v). The thioamides were thus obtained as nice bright yellow crystalline compounds, only stable in the refrigerator. All new compounds prepared gave satisfactory analytical and spectral data, in accord with their structure. Selected data are as follows: **3c**: mp 95-96 °C (yield 62%), ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.26 (6H, s), 7.24 (3H, m), 9.4 (1H, br); ^{13}C NMR ($CDCl_3$): δ 17.59 (**C**H_3), 97.65 (**C**Cl_3), 128.66 (**C**-3), 128.99 (**C**-4), 135.43 (**C**-2), 136.45 (**C**-1), 190.89 (**C**=S); FT-IR (KBr): 3315, 3290. 1492, 1383, 776, 764 cm^{-1}; MS-CI: *m/z* 281.97 (MH^+, 48%); HRMS : calcd. for $C_{10}H_{11}NSCl_3$ 281.9677; found 281.9670; **3d**: mp 103-104 °C (yield 62%), ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.20 (6H, s), 2.31 (3H, s), 6.96 (2H, s), 9.37 (1H, br); ^{13}C NMR ($CDCl_3$): δ 17.55 (**C**H_3), 21.14 (**C**H_3), 96.0 (**C**Cl_3), 129.43 (**C**-3), 130.25 (**C**-4), 134.99 (**C**-2), 138.91 (**C**-1), 191.09 (**C**=S); FT-IR (KBr): 3304, 2931, 1488, 1369, 777 cm^{-1}; MS-CI: *m/z* 295.98 (MH^+, 100%); HRMS: calcd. for $C_{11}H_{13}NSCl_3$ 295.9834; found 295.9840; **3e**; mp 65-66°C (yield 74%); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.03 (2H, t, J = 7.0 Hz), 3.95 (2H, td, J = 5.0, 7.0 Hz), 7.29 (5H, m), 8.4 (1H, br); ^{13}C NMR ($CDCl_3$): δ 33.16 (**C**H_2-α), 48.81 (**C**H_2-β), 97.50 (**C**Cl_3), 127.16 (**C**-4), 128.76 (**C**-3), 129.02 (**C**-2), 137.46 (**C**-1), 191.48 (**C**=S); FT-IR (neat): 3313, 1520, 1383, 1103, 772 cm^{-1}; MS-CI: *m/z* 281.98 (MH^+, 99.78%); HRMS: calcd. for $C_{10}H_{11}NSCl_3$ 281.9677, found 281.9770.

General procedure for the preparation of thiooxamides 4b-d. To a solution of 1 mmol of trichlorothioacetamides **3** in 5 mL of dry DMSO, 1 mmol of DBU and 1.2 mmol of morpholine were added simultaneously and in one portion and reaction mixture was heated at 85^{0}C for 3 hrs. After cooling to room temperature, the reaction mixture was diluted with 20 mL of Et_20 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

$CHCl_3$/hexane, mp 161-163^{0}C (dec), yield 65 %. All new compounds prepared gave satisfactory analytical and spectra data, in accord with their structure. Selected data are afollows: **4b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ : 3.69 (2H, t, J=5 Hz), 3.73 (2H, t, J=5 Hz), 3.81 (2H, t, J=5 Hz), 4.13 (2H, t, J=5 Hz), 4.42 (2H, d, J=6 Hz), 6.95 (1H, br), 7.24 (5H, m); ^{13}C NMR δ : 43.77 (CH2), 49.04 (**C**H_2N), 52.55 (**C**H_2N), 66.18 (**C**H_2O), 66.81 (**C**H_2O), 127.56 & 128.81 (**C**-2 & **C**-3), 127.73 (**C**-4), 137.21 (**C**-1), 164.27 (**C**=O), 192.15 (**C**=S); FT-IR (KBr) cm^{-1} : 3293, 2978, 1651, 1504, 1285, 1123, 817; MS-CI(CH_4) m/z : 293 ($MC_2H_5^+$, 17.1%), 265 (MH^+, 100%), 219 (5.5%), 91 (20.7%); HRMS: calcd. for $C_{13}H_{17}N_2O_2S$ 265.1011; found 265.1000. **4c** : mp 181-182^{0}C (dec.), yield 51 %; ^{1}H NMR (300 MHz, $CDCl_3$) δ : 2.25 (6H, s), 3.82 (2H, t, J=5 Hz), 3.88 (2H, t, J=5 Hz), 4.02 (2H, t, J=5 Hz), 4.28 (2H, t, J=5 Hz), 7.12 (3H, m), 8.08 (1H, br); ^{13}C NMR : 18.49 (**C**H_3), 49.49 (**C**H_2N), 52.75(**C**H_2N), 66.31 (**C**H_2O), 66.93 (**C**H_2O), 127.91 (**C**-4), 128.38 (**C**-3), 132.53 (**C**-1), 135.47 (**C**-2), 162.48 (**C**=O), 192.20 (**C**=S); FT-IR (KBr) cm^{-1}: 3242, 1648, 1499, 1274, 1237, 1110; MS-CI(NH_3) m/z: 279 (MH^+, 100%), 263 (9.3%), 245 (19.6%), 122 (5.2%), 88 (8.8%); HRMS: calcd. for $C_{14}H_{19}N_2O_2S$ 279.1167; found 279.1176.

Acknowledgment : The financial support by the ISRAEL SCIENCE FOUNDATION of this work is gratefully acknowledged.

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