Direct conversion of *N*-ethylamines into functionalised amides by S_2Cl_2

Lidia S. Konstantinova,[a] Oleg A. Rakitin*[a] and Charles W. Rees*[b]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 095 135 5328; e-mail: orakitin@ioc.ac.ru*

[b] *Department of Chemistry, Imperial College of Science, Technology and Medicine, London SW7 2AY, UK. E-mail: c.rees@ic.ac.uk*

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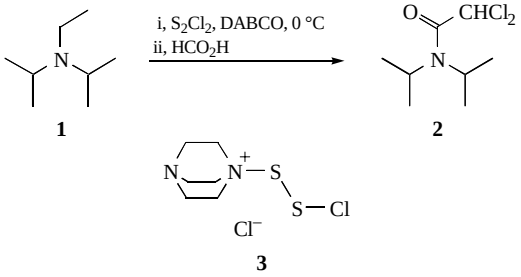
Hünig's base 1 is known to react extensively with S_2Cl_2 to give monocyclic, bicyclic and fused tricyclic 1,2-dithioles with the *N*-ethyl group intact, but with S_2Cl_2 and DABCO in chloroform at 0 °C 1 is converted into dichloroacetamide 2 by selective reaction of the *N*-ethyl group in a new one-pot transformation; ethyl-substituted derivatives of 1, diethylisopropylamine 17 and triethylamine react similarly though the last, less bulky, amine also gives trichloroacetamide 20.

We have recently shown that the complex reaction between Hünig's base **1** and disulfur dichloride, S_2Cl_2, which gives bicyclic bis(1,2-dithiol-4-yl)amines[1] and tricyclic bis[1,2]dithiolo[1,4]thiazines[2] can, with a deficiency of S_2Cl_2, also give intermediate monocyclic 1,2-dithioles in low to moderate yield.[3] Since this reaction is an unusually mild route to 1,2-dithioles,[4] we attempted to increase its synthetic utility by replacing that part of the Hünig's base which neutralises the hydrogen chloride liberated, by another amine DABCO; also the reaction temperature was lowered to 0 °C to minimise conversion of the second isopropyl group.

Unexpectedly, these conditions led to an entirely different reaction in which the isopropyl groups are unchanged and the ethyl group is transformed into a dichloroacetyl group, which, as far as we are aware, is a new transformation. Thus, Hünig's base with S_2Cl_2 (7 equiv.) and DABCO (7 equiv.) in chloroform at 0 °C for 3 days followed by addition of formic acid[1–3] and heating for 1.5 h gave (*N*-dichloroacetyl)diisopropylamine **2**† (41%) (Scheme 1).

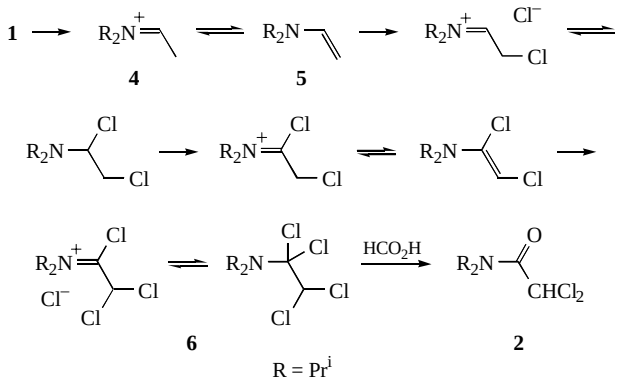
This conversion of Hünig's base into amide **2** is the first example that we have encountered, in many such S_2Cl_2 reactions, of attack at its ethyl rather than isopropyl group, in the presence or absence of other bases.[1,2] The key reaction is presumably oxidation of the tertiary amine to an iminium ion by S_2Cl_2–DABCO complex **3**,[3] which is a potential source of Cl^+ and Cl^-, and the outcome depends upon which iminium ion is formed. We assume that the present mild (0 °C) conditions result in oxidative removal of the less hindered α-hydrogen, *i.e.*, from



1 **2** **3**

Scheme 1

ethyl rather than isopropyl, to give kinetically controlled iminium ion **4** (Scheme 2) rather than the, presumably more stable, alternative. Ion **4** can isomerise to enamine **5**, which can be oxidised further, as shown in Scheme 2, to give ultimately tetrachloro species **6**, which is converted into product **2** by formic acid. Once the ethyl group has been oxidised (Scheme 2), the *N*-isopropyl groups will be deactivated to electrophilic attack. *N*-Dichloroacetyl diisopropylamine **2** is inert to the reaction mixture even at room temperature, and we have previously shown that *N*-acetyl- and *N*-cyanodiisopropylamine are inert to S_2Cl_2 under similar conditions.[2]



Scheme 2

The formation of iminium ion **4** to the exclusion of its isomer has previously been demonstrated by Schreiber[10] in the oxidation of Hünig's base with trifluoroacetic anhydride in dichloromethane at 0 °C; no attack at isopropyl was detected.

In the Hünig's base–S_2Cl_2 reactions, there is a relatively fine balance between conversion of the ethyl group into dichloroacetyl (Schemes 1 and 2) and the isopropyl group into dithioles,[3] bisdithioles[1] and bisdithiolothiazines.[2] It could be instructive to see how substituents on the ethyl group influence this balance. We therefore treated *N*-(2-chloroethyl)diisopropylamine **7** with S_2Cl_2, DABCO and formic acid under the same conditions as for **1**. Two products were isolated: the same dichloroacetyl compound **2** (21%) as from **1** and 1,2-dithiole-3-one **8**[3] (34%) (Scheme 3). The chloroethyl group has been oxidised like the ethyl group but presumably more slowly, thus allowing competing oxidation of isopropyl to give dithiolone **8**. On the above

† *General procedure for the reaction of tertiary amines with S_2Cl_2.* Disulfur dichloride (0.8 ml, 10 mmol) was added dropwise at –15–20 °C to a stirred solution of a corresponding amine (2 mmol) and DABCO (10 mmol) (in the case of *N*-ethyldiisopropylamine without DABCO) in chloroform (25 ml). The mixture was stirred at 0 °C for 72 h. Formic acid (3.75 ml, 100 mmol) was added, the mixture was refluxed for 1.5 h and filtered; and the solvents were evaporated. The residue was separated by column chromatography (Silica gel Merck 60, light petroleum and then light petroleum–CH_2Cl_2 mixtures).

All new compounds were fully characterised by elemental analysis, ^{1}H and ^{13}C NMR, IR and mass spectra, and HMRS.

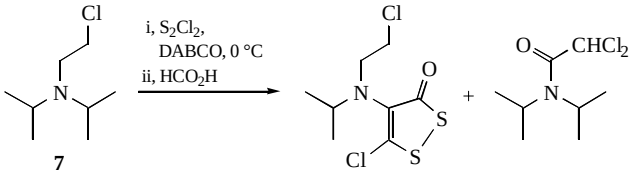
Dichloroacetamides **2**, **18**, **19**, trichloroacetamide **20** and compound **11** are identical with the known compounds.[5–9]

9: an oil prepared from **7** and sodium azide in DMSO at room temperature in 88% yield.

10: yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.10 (d, 6H, 2Me, J 6.5 Hz), 3.10–3.45 (m, 5H, CH, 2CH_2). ^{13}C NMR ($CDCl_3$) δ: 187.42 (C=O), 154.87 and 137.02 (2sp^2 tertiary C), 54.33 and 50.80 (2CH_2), 44.98 (CH), 21.50 (Me). IR, ν/cm^{-1}: 2980 (CH), 2120 (N_3), 1660 (C=O). MS, m/z (%): 278 (M^+, 11%), 222 (69), 180 (100).

13: yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.12 (d, 6H, 2Me, J 6.6 Hz), 3.51 (q, 1H, CH, J 6.5 Hz), 4.01 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 187.17 (C=O), 155.97 and 136.12 (2sp^2 tertiary C), 117.15 (CN), 53.59 (CH), 35.93 (CH_2), 21.17 (Me). IR, ν/cm^{-1}: 2980 (CH), 2140 (CN), 1660 (C=O). MS, m/z (%): 248 (M^+, 74%), 233 (47), 206 (61), 179 (33).

14: yellow crystals, mp 75–78 °C. ^{1}H NMR ($CDCl_3$) δ: 1.35 (d, 6H, 2Me, J 6.2 Hz), 1.57 (d, 6H, 2Me, J 6.2 Hz), 4.26 (br. s, 2H, 2CH). ^{13}C NMR ($CDCl_3$) δ: 163.74 (C=S), 113.02 (CN), 51.86 (CH), 21.42 and 18.53 (2Me). IR, ν/cm^{-1}: 2980 (CH), 2150 (CN). MS, m/z (%): 170 (M^+, 87%), 127 (86), 113 (14), 101 (43).

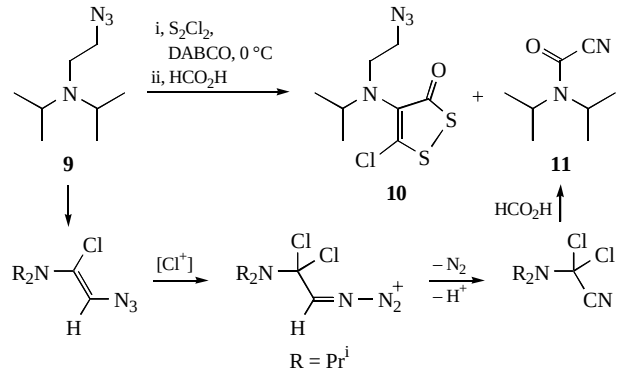


7 **8** **2**

Scheme 3

mechanism (Scheme 2) formation of isopropyl-functionalised product **8** should be favoured by a higher reaction temperature and formation of ethyl-functionalised product **2** by a lower reaction temperature. Some evidence for this was obtained by running the reaction exactly as before but in boiling chloroform (61 °C) when several products, all of which were cyclic 1,2-dithiole derivatives,[1–3] were formed in low yields, and only traces of compound **2** were seen (TLC). When the same reaction was run at –20 °C, all transformations were much slower and only a low yield (12%) of compound **8** could be isolated.

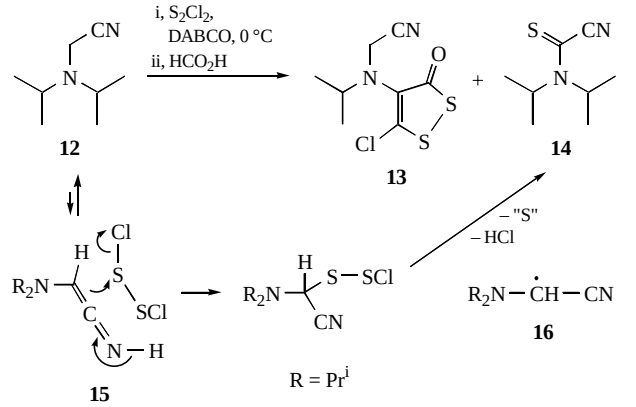
N-(2-Azidoethyl)diisopropylamine **9** treated similarly also reacted by both pathways to give corresponding dithiolone **10**[3] (12%) and an acyldiisopropylamine; the latter was not the analogous 2-azidoacetyl derivative but cyanoformyl derivative **11** (19%) (Scheme 4) obtained as a yellow oil. This product could arise readily by the general mechanism of Scheme 2 with a late diversion, caused by elimination of nitrogen and formation of the cyano group, as shown in Scheme 4.



9 **10** **11**

Scheme 4

Formation of cyanoformamide **11** from azidoethyl compound **9** prompted similar treatment of *N*-(cyanomethyl)diisopropylamine **12**,[11] which was expected to give the same product **11** but possibly in higher yield. However, cyanothioformyl derivative **14** (24%), mp 75–77 °C, was formed instead, together with dithiolone **13**[3] (20%) (Scheme 5). Formation of thioamide **14** instead of carboxamide **11**, after formic acid treatment, suggests that a different mechanism is operating. It seems reasonable that S_2Cl_2 could be reacting, through sulfur, with the activated methylene group of **12**. This could be through its ketenimine tautomer **15** as shown in Scheme 5 or by a radical mechanism induced by the enhanced stabilisation of captodative radical **16**.[12]

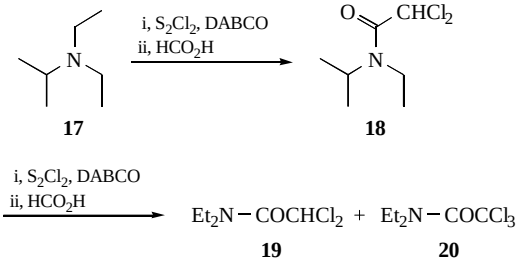


12 **13** **14** **15** **16**

Scheme 5

When one of the isopropyl groups of Hünig's base was replaced by ethyl, the same conversion of ethyl into dichloroacetyl by S_2Cl_2 was observed. Thus, diethylisopropylamine **17** with S_2Cl_2 and DABCO in chloroform at 0 °C for 3 days, followed by the formic acid treatment, gave dichloroacetamide **18** (34%); when run at 20 °C for 3 days, the yield was 54% (Scheme 6). When both isopropyl groups of Hünig's base were replaced by ethyl, the same reaction was observed, to give dichloroacetamide **19** in 51% yield; however, at lower temperatures (0 °C and –20 °C), the yield of **19** is much reduced (to 8% and to traces, respectively) and the major product is now trichloroacetyl derivative **20** (22%). The direct transformation of *N*-Et to *N*-$COCCl_3$ also appears to be new. Formation of **20** in addition to **19** could result from reduced steric hindrance by the ethyl groups in the chlorination sequence of Scheme 2, before the formic acid reaction.

The established formation of monocyclic, bicyclic and fused tricyclic 1,2-dithioles from ethylisopropylamines and S_2Cl_2 requires attack at the isopropyl groups. We have now shown that the presence of DABCO in the cold reaction mixture favours selective attack at the ethyl group to give *N*-dichloroacetyl derivatives such as **2**, **18** and **19**, probably by the mechanism of Scheme 2. Ethyl-substituted diisopropylamines behave similarly, by minor variations of this mechanism, to give **2**, **11** and **14**, and the less bulky triethylamine also gives some of trichloroacetyl derivatives **20**.



17 **18** **19** **20**

Scheme 6

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