Unusual behaviour of 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt) with 5-aminopyrazoles: a synthetic method of 1*H*-pyrazolo[3,4-*d*]thiazoles

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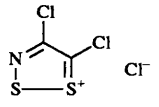
1*H*-Pyrazolo[3,4-*d*]thiazole-5-carbonitriles **9** are obtained by treating 4-unsubstituted 5-aminopyrazoles with Appel's salt at room temperature in the presence of 2,6-dimethylpyridine.

In 1985 Appel *et al.*[1] reported the reaction of chloroacetonitrile with disulfur dichloride to give the title heterocycle **1** as a green crystalline substance. This salt possesses a high reactivity at the 5-position where the chlorine atom is readily displaced by water, hydrogen sulfide, arylamines and active methylene compounds to yield derivatives **2–5**.[1,2] Appel's salt has also found an interesting application in converting carboxylic acids and alcohols into esters under mild conditions.[3]



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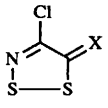
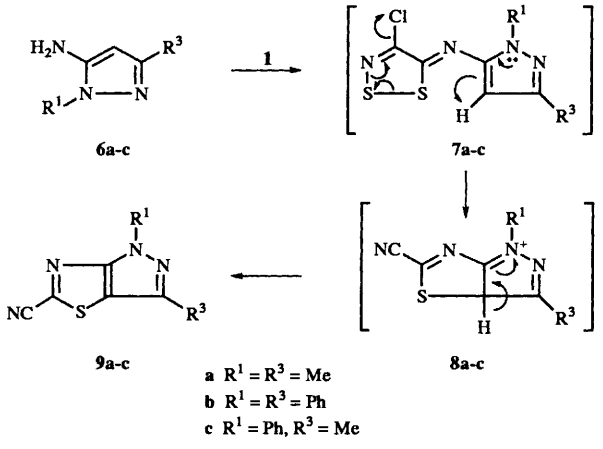


2 X = O
3 X = S
4 X = NR
5 X = CR^1R^2

Very recently, Cuadro and Alvarez-Builla[4] published the reactions of salt **1** with aminoheterocycles to give the corresponding 5-imino-1,2,3-dithiazoles **4** (R = heterocycle). We have obtained similar results with 2-amino-4,5-dihydrothiazole (17%), 2-aminothiazole (25%), 3-amino-5-methylisoxazole (49%), 3-amino-1-methylpyrazole (94%), 3-amino-1-methyl-5-methylsulfanyl-1,2,4-triazole (41%), 2-aminopyridine (69%) and 2-amino-4,6-dimethylpyrimidine (68%). In contrast, the 5-aminopyrazoles **6a–c** reacted with the salt **1** at room temperature to give the 1*H*-pyrazolo[3,4-*d*]thiazoles **9a–c**. We assume that the imines **7a–c** are formed first and then undergo a spontaneous intramolecular cyclization with extrusion of sulfur and hydrogen chloride as shown in Scheme 1. Rees[2] reported similar reactions for the phenyl derivatives **10a,b** but noticed that compound **10b** undergoes this cyclization–elimination only at 250 °C. Evidently, the enamine moiety in pyrazoles **7a–c** is a much better electron-donating group than phenyl in compound **10b**. In fact, this facile pathway seems to be restricted to 4-unsubstituted 5-aminopyrazoles since product **12** derived from 3-amino-1-methylpyrazole was unable to give the 2*H*-pyrazolo-[3,4-*d*]thiazole **13** by a similar mechanism. This compound was unchanged in refluxing toluene overnight, and decomposed to intractable tars when heated at 200 °C. The thermal stability of **12** is attributed to the lower nucleophilicity of the C-4 position compared with **7**, and also to the attractive S · · · N interaction[5] which holds the molecule in a restricted conformation, unfavourable for cyclization.

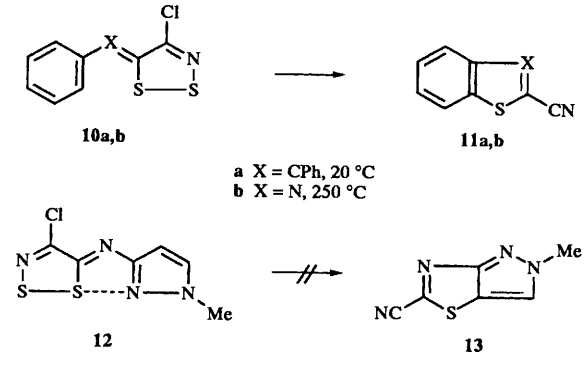
Previous methods for the synthesis of 1*H*-pyrazolo[3,4-*d*]-thiazoles also used 5-aminopyrazoles as starting materials but required multi-step reactions.[6] The present method has the advantage of introducing the S–C–CN unit directly onto the aminopyrazole under mild conditions and in one step from Appel's salt.



6a-c **7a-c** **8a-c** **9a-c**

a $R^1 = R^3$ = Me
b $R^1 = R^3$ = Ph
c R^1 = Ph, R^3 = Me

Scheme 1



10a,b **11a,b**

a X = CPh, 20 °C
b X = N, 250 °C

12 **13**

Experimental

1,3-Dimethyl-1*H*-pyrazolo[3,4-*d*]thiazole-5-carbonitrile 9a

To a stirred suspension of the salt **1** (1 g, 4.8 mmol) in dichloromethane (20 cm^3) under nitrogen atmosphere was added an equimolar amount of the aminopyrazole **6a** (0.54 g) and 2,6-dimethylpyridine (1.03 g, 2 equiv.) in dichloromethane (20 cm^3). After being stirred at room temperature for 1 h, the reaction mixture was concentrated and chromatographed on silica gel with dichloromethane as the eluent to give the bicycle **9a** (0.69 g, 81%), mp 107 °C (from dichloromethane–hexane); ν_{max}(KBr)/cm^{-1} 2217s (CN), 1583s and 1515s; δ_H($CDCl_3$, 400 MHz) 2.53 (3 H, s, Me) and 3.91 (3 H, s, NMe); δ_C($CDCl_3$) 13.1 (q, ^1J 129, Me), 34.75 (q, ^1J 141, NMe), 110.3 (s, CN), 120.4 (s, C-5), 130.3 (q, ^3J 3, C-3a), 135.4 (q, ^2J 7, C-3) and 165.7 (q, ^3J 2, C-6a); *m/z* 178 ($M^{\cdot+}$, 100%), 177 ($M^{\cdot+}$ − H,

46), 163 ($M^{\bullet+}$ − Me, 24), 149 ($M^{\bullet+}$ − NMe, 37), 94 ($M^{\bullet+}$ − NC–CNS, 41), 91 (12), 86 (25), 84 (NC–$CNS^{\bullet+}$, 42), 71 (15), 70 (NC–CS^+, 26), 69 (17), 57 (26), 55 (20), 51 (21), 49 (60), 43 (MeN_2^+, 74) and 41 ($MeCN^{\bullet+}$, 26) (Found: $M^{\bullet+}$, 178.0311. $C_7H_6N_4S$ requires *M*, 178.0313).

The following compounds were similarly prepared.

1,3-Diphenyl-1*H*-pyrazolo[3,4-*d*]thiazole-5-carbonitrile **9b** (52%), mp 160 °C (from dichloromethane); ν_{max}(KBr)/cm^{-1} 2217m (CN), 1599s, 1563s, 1514s and 1501s; δ_H($CDCl_3$, 400 MHz) 7.25 (1 H, t), 7.44–7.53 (5 H, m), 8.06 (2 H, d) and 8.17 (2 H, d); δ_C($CDCl_3$) 110.9 (CN), 117.5, 125.7, 129.3 and 138.2 (NPh), 121.8 (C-5), 127.0, 129.0, 129.7 and 130.3 (Ph), 128.98 (C-3a), 139.2 (C-3) and 163.7 (C-6a); *m*/*z* 302 ($M^{\bullet+}$, 31%), 301 (20), 77 (Ph^+, 100), 70 (NC–CS^+, 14) and 51 (73) (Found: $M^{\bullet+}$, 302.0633. $C_{17}H_{10}N_4S$ requires *M*, 302.0626).

3-Methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]thiazole-5-carbonitrile **9c** (40%), mp 144 °C; ν_{max}(KBr)/cm^{-1} 2225m (CN), 1590s and 1518s; δ_H($CDCl_3$, 400 MHz) 2.63 (3 H, s, Me), 7.24 (1 H, t), 7.48 (2 H, t) and 8.10 (2 H, d); δ_C($CDCl_3$) 13.2 (Me), 110.0 (CN), 117.2, 125.3, 129.4 and 138.4 (Ph), 120.8 (C-5), 132.3 (C-3a), 137.4 (C-3) and 163.2 (C-6a); *m*/*z* 240 ($M^{\bullet+}$, 100%), 239 ($M^{\bullet+}$ − H, 53), 199 ($M^{\bullet+}$ − CN − Me, 10), 118 (38), 91 ($PhN^{\bullet+}$, 30), 77 (Ph^+, 75) and 51 (70) (Found: C, 59.8; H, 3.3. $C_{12}H_8N_4S$ requires C, 59.98; H, 3.36%).

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