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Base Mediated Reactions in Solid-Liquid Media. A 1,3-Dipolar Cycloaddition Route to Pyrrolines and Pyrroles from Imino Chlorosulfides.

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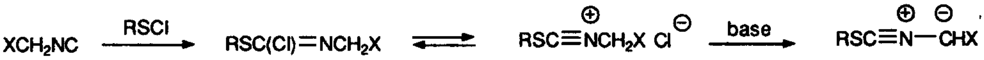
Key words :
Imino chlorosulfides ; alumina-dispersed potassium fluoride and potassium hydroxide ; 1,3-dipolar cycloaddition ; pyrroles.

Summary - Nitrile ylides, generated in basic conditions (HCl abstraction) from N-[tosylmethyl] and N-[diethoxyphosphorylmethyl] imino chlorosulfides, undergo 1,3-dipolar cycloadditions with electron-deficient dipolarophiles to produce pyrroles and pyrrolines. Heterogeneous media are found to furnish the best conditions for these reactions. One pyrrole can also be prepared from methyl N-[ethoxycarbonylmethyl] chlorothioimidate and dimethyl acetylenedicarboxylate on alumina-potassium fluoride mixture as solid support, under microwave irradiation.

Imino chlorosulfides are easily accessible via the insertion reaction of isocyanides into the S-Cl bond of sulfenylchlorides. We [1] and others [2] have shown that they can be effectively used as starting materials in the field of heterocyclic chemistry and we have postulated that their substitution reactions involve the nitrilium chlorides as transient intermediates. The imino chlorosulfides **1** that comprise a methylene activated by an electron-withdrawing group X can also be considered as potential precursors of nitrile ylides **2**, by a 1,3-dehydrohalogenation process in basic media.



$$\mathrm{XCH_2NC} \xrightarrow{\mathrm{RSCl}} \underset{\mathbf{1}}{\mathrm{RSC(Cl){=}NCH_2X}} \rightleftarrows \mathrm{RSC{\equiv}\overset{\oplus}{N}CH_2X\ Cl^{\ominus}} \xrightarrow{\text{base}} \underset{\mathbf{2}}{\mathrm{RSC{\equiv}\overset{\oplus}{N}{-}\overset{\ominus}{C}HX}}$$

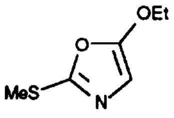
a : R = Me, X = Tos
b : R = Ph, X = Tos
c : R = 2-$NO_2C_6H_4$, X = Tos
d : R = Me, X = $PO(OEt)_2$
e : R = Ph, X = $PO(OEt)_2$
f : R = Me, X = CO_2Et

The use of nitrile ylides as 1,3-dipoles in cycloaddition reactions has received a lot of attention as a route to a variety of five-membered nitrogen-containing rings [3,4]. To date, however, there have been only limited reports about the use of imino chlorosulfides as a source of "thiocyanate ylides" [5]. In the presence of

NEt_3, compounds **1** with X an ethoxycarbonyl or an aminocarbonyl group, readily cyclize to give 5-ethoxyoxazoles [6a], 5-aminooxazoles [6b] or mesoionic 1,3-diazolium-4-olates [6c]. These intramolecular reactions can prevent the 1,3-dipolar cycloaddition route [7].

As an extension of our previous studies on the chemistry of imino chlorosulfides, we now report the treatment of **1a-f** with three electron-deficient dipolarophiles in a basic medium to produce pyrroles and pyrrolines [8]. Several bases are comparatively studied, in homogeneous or solid-liquid heterogeneous media. Indeed, it has been shown that some phosphonium and sulfonium salts are easily dehydrohalogenated to ylides, then trapped by an aldehyde, by anionic activation on alumina or on alumina-supported potassium fluoride [9]. Significant improvements in regioselectivity have also been achieved for a variety of organic reactions by adsorption of substrates onto the surface of inorganic solids [10,11]. For instance, the ability of base-impregnated alumina to promote a high proportion of C-substitution instead of O-substitution has been reported for alkylations of ambident acetoacetate and naphthoxide anions [12]. The use of similar conditions could limit the cyclisation of **1f** to oxazole **3**.

After investigating a range of reagents, solvents and conditions, three protocols have evolved for the generation and cycloaddition of ylides **2** from the imino chlorosulfides **1a-f**, in homogeneous (method A) and solid-liquid media (methods B, C)[13]. Thus, using dimethyl fumarate (ECH=CHE, E = CO_2Me) as dipolarophile, compounds **1a-c** lead to the pyrroles **5a-d** after elimination of p-toluenesulfinic acid (TosH)[17] or thiophenols (table, entries 1-7). The N-substituted pyrrole **6** corresponds to the nucleophilic addition of **5a** to the olefin (entries 3 and 4)[18]. The elimination reactions are not possible in the pyrroline **7** which is the primary cycloadduct of **2d** with ECH=CHE (only one isomer isolated, entry 8). Alumina-dispersed KF and KOH (methods B and C) are generally found to be more efficient than DBN (method A). However, no cycloadduct can be isolated from **1f** that gives only the oxazole **3** or the hydrolysis product ($MeSC(O)NHCH_2CO_2Et$, **4**) using respectively protocols A and B.



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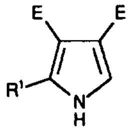
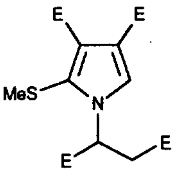


5a, R^1 = MeS **5c**, R^1 = 2-$NO_2C_6H_4S$
5b, R^1 = PhS **5d**, R^1 = Tos



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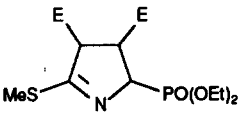

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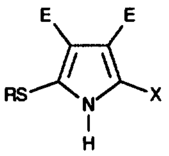
In a heterogeneous medium, dimethyl acetylenedicarboxylate (E-C≡C-E) produces pyrroles **8** in good to moderate yields. We have noted that method C is the most efficient. Starting from **1a**, a long reaction time leads to the formation of the N-vinyl pyrrole **9** (entry 11, two isomers) [18,19]. Starting from **1f**, use of method B restricts the formation of the methyl thioimidate **4** and also gives the cycloadduct **8f** (entry 15).

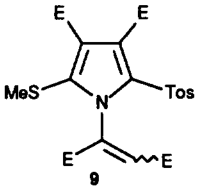
The cycloaddition of **2a** with methyl acrylate is not regioselective (entry 16) [20] and produces pyrroline **10** (one isomer) and two pyrroles **11a**, **b**. We have verified that a mixture of **10** and DBN, in refluxing THF for 1 h, gives **11b** quantitatively.

Entry	Educts	Method	Time(h)[a]	Temp. or MW power	Products (yields, % [b])
1	**1a**, ECH=CHE	A	10	reflux	**5a** (45) [c]
2	**1a**, ECH=CHE	B	24	reflux	**5a** (68) [d]
3	**1a**, ECH=CHE	C	2	rt	**5a** (68) ; **6** (16)
4	**1a**, ECH=CHE	C	4	rt	**5a** (49) ; **6** (39)
5	**1b**, ECH=CHE	A	10	reflux	**5b** (25) ; **5d** (12)[d]
6	**1b**, ECH=CHE	B	6	reflux	**5b** (34) ; **5d** (26)[d]
7	**1c**, ECH=CHE	C	1	rt	**5c** (15) ; **5d** (20)[e]
8	**1d**, ECH=CHE	C	1	rt	**7** (61)
9	**1f**, ECH=CHE	A	17	rt	**3** (86)
10	**1f**, ECH=CHE	B	1	125 W	**4** (92)
11	**1a**, E-C≡C-E	B	40	reflux	**9** (39)
12	**1a**, E-C≡C-E	C	1	rt	**8a** (76)
13	**1d**, E-C≡C-E	C	1	rt	**8d** (39)
14	**1e**, E-C≡C-E	C	1	rt	**8e** (68)
15	**1f**, E-C≡C-E	B[f]	1	125 W	**4** (43) ; **8f** (48)
16	**1a**, CH_2=CHE	B	30	reflux	**10** (27) ; **11a** (21) ; **11b** (7)[g]

[a] Time required for the entire conversion of starting compound **1**. [b] Yields of isolated products. [c,d] Accompanied by 44 %[c] or small quantities [d] of TosC(H)ECH$_2$E which results from the addition of the tosyl anion to ECH=CHE. [e] Nineteen per cent of the substitution product (2-NO$_2$C$_6$H$_4$S)$_2$C=NCH$_2$Tos was also isolated. [f] The mixture KF/Al$_2$O$_3$ is dehydrated in the MW oven just before use (45 mn, 440 W). [g] Accompanied by 50 % of the addition product TosCH$_2$CH$_2$E.



8a, d-f



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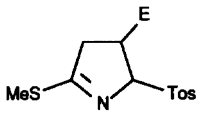

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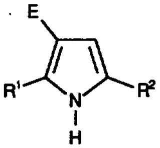

11a, R¹ = MeS, R² = H
11b, R¹ = H, R² = MeS

We have thus defined conditions for the generation of new nitrile ylides **2** from the imino chlorosulfides **1** and for their conversions in situ to pyrrolines and pyrroles. Alumina-dispersed KF and KOH are effective reagents and the cyclization of **1f** to oxazole **3** is entirely avoided on KF/Al$_2$O$_3$. To date, 1,3-dipolar cycloaddition reactions have rarely been performed on solid supports [22,23].

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13. All reactions are performed from a solution of **1** (5 mmol) and dipolarophile (10 mmol) in dry THF (10 ml). (A) : 1,5-diazabicyclo [4.3.0] non-5-ene (DBN, 1.25 g) is added dropwise to this solution which is either refluxed or allowed to stand at room temperature (rt). (B) : commercial KF (0.65 g) is simply mixed with alumina 90 (Merck n° 1076, 1.15 g) without impregnation [14]. The suspension obtained by pouring the above-mentioned solution is either refluxed or irradiated in a domestic microwave oven (MW) [15]. (C) : the solution is added to a mixture of Al_2O_3 90 (1.15 g) and freshly powdered KOH [16] (1.25 g) then stirred at rt.

   After an appropriate time of treatment (table), the inorganic part is filtered and washed with THF. Filtrates are concentrated and the products are isolated by crystallization, silica gel column chromatography or bulb-to-bulb distillation. Pyrroles **8** are extracted from the KOH/Al_2O_3 support, after aqueous dilution. All isolated compounds give spectral data (^1H and ^{13}C NMR, Mass) in accord with the assigned structure, and satisfactory elemental analyses.
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