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Three-Component Cyclocondensations. A Convenient Access to Fused Imidazolium and Dihydropyrimidinium Salts via the Reaction of Methyl Chlorothioimidates with Azines and Isocyanides.

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Abstrnct . A mixture of methyl cklorothioiraidale, isocyanide and pyridine react in a sequence of N-imidoylpyridialwlnformation then cycloe__~_':ion step, to give Iqunino~:_dn_.~[l.5-a] pyr/d/n/amand eventually pyr/d/no[I~2-c] dihydropyrimieh~isunsalts. Similarly, the use of pyri,~, i~e, pyrin6dine and pyrazine allows the preparmion of corresponding fused I-amino-J-(methylthio) i~:_,l,,yol~'nchlorides.

Into chlorosulfi~s are readily obtained from isocyanides and aryl or alkylsulfenyl chlorides and these attractive products have recently been used in various ways in the field of heterocycfic chcn~ 15. In pa~ti'¢ular, we have reported that action of methyl chlorothioimidates 1, on benzaldimdnes affords N-imidoylbenzylideniminhnn species as unstable intenmdiates which are trapped by ~ocyanides to give 4-Rmino-2"-tne~l~'h~j"~ d h m sm~~/~ u~esame way, me~yi"a~ I~Y," ~hbr~'h~ ~ amerCe- with thio-DMF to furnish transient N.(thiocarbonyl) forwamidinium chlorides. [1 + 4] cycloaddition to isocyanides in sire yields a large number of useful 4,5-diaminothiazolium salts 4. The efficiency of these three-¢on!vonem.vr~e~es prompts ~s W exam~e ~e ~>e~a~om" o~ o~er ac~ve com~enbs nnb~ ~m~ar

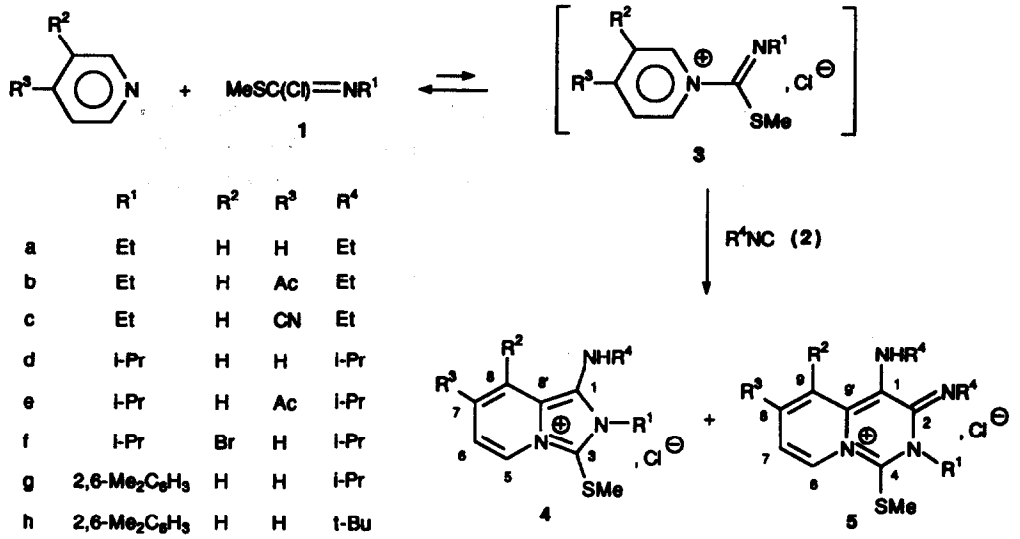
C'-7~k.~ '~~'~ymfi~k~ ~.~~y"~'~_~f~,~ -wt~/~i~ ~,~i~,.my'rl)yr~iinm~ £~r~-h~a.~ -~ is expected (scheme I).

We have found that representative imidoyl chlorides 1 and pyridines undergo slow

at 2~ |r~) for several ~lays. Thus, wc~navcob~nc~ a mixture ot cyc~oe~ta~s • an&$ or 6~h~erv~)cof ~hese *sa~s s~Tng)y pr~po~m'am, ~¢p~n~ng upon ~e na~,v oF~¢ va~ous e~c~s, as hea~beh)n ~w ~ab)¢. The* ra~o ol~.~ sharg"t,v"tacreascs w'aen ster~mg compounds 1 and 2 are N-substimtcdt by ~¢ *"tsopmpylgroup* {~or

The first step of the reaction proceeds most probably as a quaternization at the nitrogen ring. The resulting cationic species 3, in small equilibrium concenlradon 6, are trapped by nucleophilic isocyanides via two competitive process. One way is the [1 + 4] cycl~_d_d_itionmute and subsequent tautomerism to produce 1-amino-3-(methylthio) imidazo [1,5-a] pyridinium chlorides 4. Another way leads to 1-amino-2-imlno~-(methylthio) pyridino [1,2-c] dihydropyrimidinium chlorides 5, according to a [1 + 1 + 4] mechanism 7.

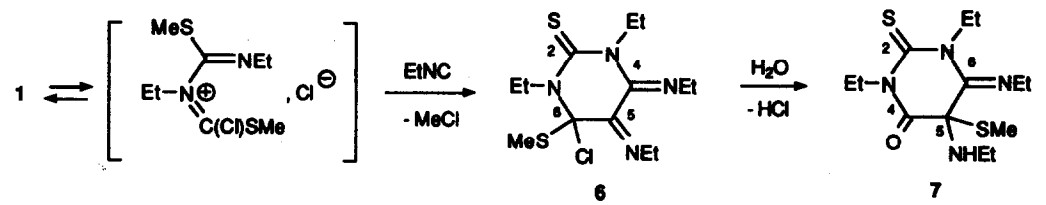
A third product can also be obtained in noticeable quantities, especially with the ethyl group as RI and R4 substituents (entries 1-4), and identified as the 6-chloro-4,5-diimino-6-(methylthio)-l,6-dihydro-2-pyrimidinethione 6.



	R^1	R^2	R^3	R^4
a	Et	H	H	Et
b	Et	H	Ac	Et
c	Et	H	CN	Et
d	i-Pr	H	H	i-Pr
e	i-Pr	H	Ac	i-Pr
f	i-Pr	Br	H	i-Pr
g	2,6-$Me_2C_6H_3$	H	H	i-Pr
h	2,6-$Me_2C_6H_3$	H	H	t-Bu

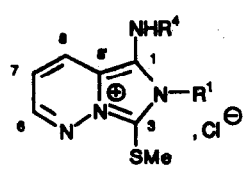
Scheme 1

The undesirable formation of **6** is rationalized assuming the self-addition of **1**, the irreversible [1 + 1 + 4] cyclization of the in situ generated iminium salt and the fast demethylation of the resulting tetrahydropyrimidinium chloride (scheme 2). This reaction is competitive to the usual route giving pyridinium salts **3**, then **4** and **5** and strongly dominates with some substituted pyridines (entries 3, 4) [7]. We have verified that the N-ethyl compounds **1** and **2** produce **6** and MeCl in a quasi-quantitative yield by using similar conditions without pyridine (rt, 4 days, isolated 70 %). **6** is sluggishly transformed into the 5-amino-5-(methylthio)-4-pyrimidone **7** on standing at rt under atmospheric moisture. This hydrolysis presumably takes place via chlorine substitution, cyclic elimination then 1,2 migration of thiolate ion (scheme 2).



Scheme 2

The mildness of the methodology allows also the preparation of 1-amino-3-(methylthio) imidazo [1,5-x] diazinium chlorides **8**, **9**, **10** in the presence of nucleophilic diazines such as pyridazine, pyrimidine and pyrazine. On the contrary, the addition of triazine do not promote any reaction (entry 13). An interesting feature is the regioselectivity of the cyclization step when 3-bromopyridine and pyrimidine are used as starting products (entries 7, 11, 15).



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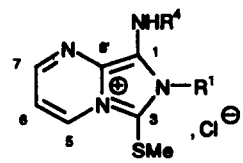

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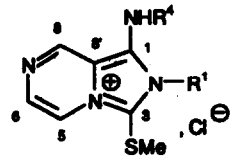

10

a) $R^1 = R^4 = Et$
b) $R^1 = R^4 = i\text{-}Pr$

Table - Reactions of methyl chlorothioimidates **1** with isocyanides **2** and pyridines or diazines [a].

		Educts		reaction	Products distribution[c]			
Entry	1 (R^1)	azine	2 (R^4)	time[b] (days)	4	5	6	Yields[d],%
1	Et	pyridine	Et	3	15	55	30	51 (4a+5a)[e]
2	Et	4-acetylpyridine	Et	2.5	60	-	40	36(4b);25(6)
3	Et	4-cyanopyridine	Et	4	25	-	75	19(4c);46(6)
4	Et	3-bromopyridine	Et	3	-	-	100	60(6)
5	i-Pr	pyridine	i-Pr	3	15	85	f	63(5d)
6	i-Pr	4-acetylpyridine	i-Pr	3.5	20	80	f	12(4e) ; 55(5e).
7	i-Pr	3-bromopyridine	i-Pr	9	10	90	f	55 (5f)
8	2,6-$Me_2C_6H_3$	pyridine	i-Pr	7	100	-	-	45(4g)
9	2,6-$Me_2C_6H_3$	pyridine	t-Bu	8	100	-	-	50(4h)
10	Et	pyridazine	Et	1	only 8a			69
11	Et	pyrimidine	Et	4	75:25 (9a/6)			35(9a)
12	Et	pyrazine	Et	3	50:50 (10a/6)			26(10a); 36(6)
13	Et	s-triazine	Et	3	only 6			61
14	i-Pr	pyridazine	i-Pr	2	only 8b			66
15	i-Pr	pyrimidine	i-Pr	5	9b [f]			35
16	i-Pr	pyrazine	i-Pr	4	10b [f]			35

[a] All reactions are conducted in $CHCl_3$ at rt with equimolar quantities of 1 and azines (2,5 M) and a 3-fold excess of 2. [b] Time required for the complete transformation of 1. [c] The distributions between 4, 5, 6 or 8-10, 6 are estimated on the basis on the ^1H NMR spectra of the crude mixtures. [d] Isolated products yields based on starting 1. [e] These salts have not been separated (4a/5a = 25 : 75). [f] Another product, presumably diimino dihydropyrimidinethione similar to 6, is also formed in smaller quantities but it cannot be purified and identified.

When $R^1 = R^4$, the experimental procedure is a simple addition first of MeSCl (10 mmol) then of azine (10 mmol) to a 4-fold amount of isocyanide 2, in anhydrous $CHCl_3$ (4 mL). These mixtures are maintained at rt for the times indicated in the Table. Crude salts are purified with some difficulty by aqueous dissolution, etheral washing and CH_2Cl_2 extraction as precedently described in related cases [3]. Most salts are isolated as brownish solids and recrystallized from CH_2Cl_2/Et_2O to give satisfactory elemental analysis. All compounds 4-10 are identified by their ^1H and ^{13}C NMR spectroscopic data and mass spectra [8].

In the literature, there are only limited reports on similar fused 1-aminoimidazolium species [9]. Condensed heterocycles 4, 8-10 can be described as Reissert-like salts [10] and compared to the related salt that derived from the reaction of N-phenylbenzimidoyl chloride with pyridine and anhydrous HCN [11].

In conclusion, methyl chlorothioimidates **1** easily react with pyridines or diazines in the presence of isocyanides. This three-component method is a simple and useful route to a variety of fused imidazolium and dihydropyrimidinium salts which are thus prepared for the first time. Extension of the scope of such approach to the one-pot synthesis of other heterocycles is under investigation.

References and notes :

1 Berrée, F. ; Marchand, E. ; Morel, G. Tetrahedron Lett. **1992**, *33*, 6155-6158 and references therein.

2 Bossio, R. ; Marcaccini, S. ; Pepino, R. ; Polo, C. ; Torroba, T. Heterocycles **1990**, *31*, 1287-1290. Bossio, R. ; Marcaccini, S. ; Paoli, P. ; Pepino, R. ; Polo, C. *Ibid* **1990**, *31*, 1855 - 1860 and earlier reports.

3 Malvaut, Y. ; Marchand, E. ; Morel, G. J. Org. Chem., **1992**, *57*, 2121-2127.

4 Berrée, F. ; Malvaut, Y. ; Marchand, E. ; Morel, G., submitted.

5 Pyridine and its homologues have been shown to react with a few imidoyl chlorides to produce stable pyridinium salts : Kost, A.N. ; Suminov, S.I. ; Sheinkman, A.K. in "Iminium Salts in Organic Chemistry" ; Böhme, H. ; Viehe, H.G. Eds ; Wiley, J. : N.Y. **1979**, part 2, p. 579.

6 In absence of isocyanide, a mixture of N-isopropyl imidoyl chloride **1** and pyridine in $CDCl_3$ was analyzed by ^1H NMR, but no reaction was detected after 4 days at rt (compare with entry *5*, table).

7 This reaction was not previously observed [3] in the presence of acyclic aldimines and ketimines which reacted more rapidly with **1** + **2** than pyridines.

8 Physical and characteristic ^{13}C NMR data (δ ppm, J Hz ; $CDCl_3$, 75.469 MHz), MS parent radical ion or (and) elemental analysis are given below for selected examples of compounds **4-10**.

4c : yellow crystals, mp 250°C (decomp). ^{13}C NMR δ 109.9 (m, C-3), 115.5 (ddd, ^1J = 176, ^2J and ^3J = 3.2 and 6.6, C-6), 115.8 (d.d, ^2J and ^3J = 5.8 and 8.4, C-8'), 117.2 (dd, ^1J = 179, ^3J = 5.2, C-8), 128.0 (dd, ^1J = 197, ^2J = 4.7, C-5), 132.6 (m, C-7), 138.1 (d, ^2J = 1.4, C-1). MS calcd for $C_{13}H_{16}N_4S$, m/z 260.1096 (HCl elim), found 260.1088. Anal. calcd for $C_{13}H_{17}ClN_4S$: C, 52.61 ; H, 5.73 ; Cl, 11.97 ; N, 18.88 ; S, 10.79. Found : C, 52.71 ; H, 5.80 ; Cl, 12.25 ; N, 18.60 ; S, 10.70.

5d : Yellowish powder, mp 150°C (decomp). ^{13}C NMR δ 118.5 (m, C-9'), 119.0 (dt, ^1J = 190, ^2J = ^3J = 6, C-6), 120.6 (ddd, ^1J = 169, ^2J and ^3J = 1.8 and 9, C-7), 120.9 (dd, ^1J = 171, ^3J = 7, C-8), 121.4 (dd, ^1J = 172, ^3J = 7, C-9), 121.9 (d, ^3J = 9, C-1), 132.6 (s, C-2), 148.9 (m, C-4). MS calcd for $C_{18}H_{28}N_4S$, m/z 332.2035 (HCl elim.), found 332.204.

6 : crude oil. ^{13}C NMR δ 80.0 (m, C-6), 138.0 (t, ^3J = 10.5, C-5), 148.6 (m, C-4), 181.0 (m, C-2). MS calcd for $C_{13}H_{23}{}^{35}ClN_4S_2$, m/z 334.1053, found 334.105.

7 : mp 86°C (Et_2O/petroleum ether). ^{13}C NMR δ 77.6 (q, ^3J = 4.1, C-5), 149.6 (m, C-6), 163.7 (td, ^3J = 3.6, C-4), 180.6 (m, C-2). MS calcd for $C_{13}H_{24}N_4OS_2$, m/z 316.1391, found 316.1383.

8a : orange crystals, mp 150°C (decomp). ^{13}C NMR δ 109.8 (m, C-3), 110.6 (ddd, ^1J = 177.3, ^2J and ^3J = 1 and 6.2, C-7), 122.8 (m, C-8'), 130.6 (dd, ^1J = 172, ^3J = 5.7, C-8), 135.5 (t, ^3J = 3.5, C-1), 151.3 (ddd, ^1J = 184.9, ^2J and ^3J = 4.1 and 7.6, C-6). Anal. calcd for $C_{11}H_{17}ClN_4S$: C, 48.44 ; Cl, 13.02 ; N, 20.55 ; S, 11.74. Found : C, 48.87 ; Cl, 12.95 ; N, 20.28 ; S, 11.70.

9b : darkish crude oil. ^{13}C NMR δ 109.6 (m, C-3), 112.5 (dd, ^1J = 176, ^2J = 8.7, C-6), 134.3 (s, C-1), 136.0 (dt, ^1J = 197, ^2J = ^3J = 5, C-5), 137.5 (m, C-8'), 155.4 (ddd, ^1J = 190, ^2J and ^3J = 2.5 and 6, C-7). MS calcd for $C_{12}H_{18}N_4S$, m/z 250.1252 (MeCl elim), found 250.124.

10a : yellow crystals, mp 210°C (decomp). ^{13}C NMR δ 109.0 (m, C-3), 118.4 (dd, ^1J = 196.5, ^3J = 14.2, C-8), 128.3 (m, C-8'), 132.6 (ddd, ^1J = 191.6, ^2J and ^3J = 4.7 and 12.1, C-6), 136.8 (dd, ^1J = 196.7, ^2J = 11.1, C-5), 137.3 (s, C-1). MS calcd for $C_{11}H_{16}N_4S$, m/z 236.1096 (HCl elim), found 236.1100.

9 A few 1-aminoimidazo [1,5-a] pyrazinium derivatives have been synthesized via the cyclization of 4-amino-3-aryl-5-carboxamido-1-ethoxycarbonylmethylimidazolium bromides : El-Bayouki, Kairy A.M. ; Hammad, M. ; Osman, S.A. ; Basyouni, W.M. Orient. J. Chem. **1986**, 2, 45-50 (CA *106*, 196367z). See also the preparation of cationic azo dyes based on preformed 3-substituted imidazo [1,5-a] pyridines : Parton, B. ; Rose, F.L. GB 1531752, **1978** (CA *90*, 205761d).

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