

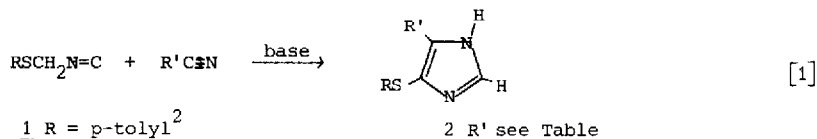
REACTION OF THIOMETHYL ISOCYANIDES WITH NITRILES,  
SYNTHESIS OF 4(5)-THIOIMIDAZOLES

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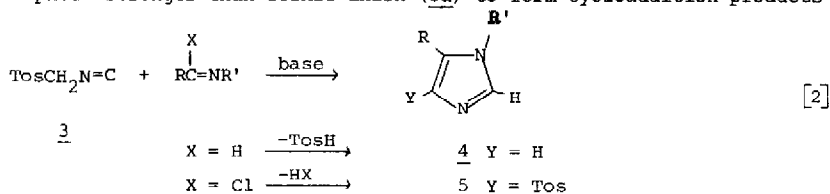
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Herein we describe a simple and high yield conversion of nitriles to imidazoles. This method involves a [3+2] anionic cycloaddition of p-tolylthiomethyl isocyanide<sup>1</sup> (1) to a series of alkyl and aryl cyanides to give the 4(5)-thioimidazoles 2.

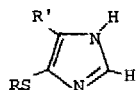


In a related investigation, the sulfone corresponding to 1, 1 e tosylmethyl isocyanide (TosMIC, 3), has also been used in imidazole synthesis. Reaction with aldimines and imidoyl chlorides yields 1,5-disubstituted imidazoles<sup>3</sup> 4 and 1,4,5-trisubstituted imidazoles<sup>4</sup> 5, respectively. However, a reaction of TosMIC with acetonitrile or benzonitrile has not been realized so far.<sup>5</sup> Apparently, nitriles require a nucleophile stronger than TosMIC-anion (3a) to form cycloaddition products.<sup>6</sup>



It now appears that the anion derived from isocyanide 1 (1 e  $\text{RSCH}^-\text{N}=\text{C}$ , 1a) fulfils this requirement.<sup>7</sup> According to eq [1], 4,5-disubstituted imidazoles (2) are synthesized readily from abundantly available nitriles. Also, desulfurization of 2 will lead to 4(5)-monosubstituted imidazoles (see below). Thus, reaction [1] provides an imidazole synthesis supplementary to eq [2], both in the type of substrate as well as the substitution pattern obtainable in the products.

TABLE

R = p-tolyl<sup>2</sup>

Compd <sup>a</sup>	R'	% yield, method		mp (°C)	
		A	B		
<u>2a</u>	C <sub>6</sub> H <sub>5</sub>	90	97	200	-201.5
b	p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	94	94	178	-179
c	p-CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	86	93	233	-234
d	p-ClC <sub>6</sub> H <sub>4</sub>	87	93	236	-237
e	p-N≡CC <sub>6</sub> H <sub>4</sub>		98 <sup>b</sup>	162	-163
f	p-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>		0	—	—
g	2-pyridyl	73	93	223	-223.5
h	Me	86	85	152	-153
i	Et	64	84	151	-152
j	n-Pr		88	112	-113
k	c-Pr		85	183	-183.5
l	t-Bu	82	49	222.5	-223.5
m	1-Ad	91		293	-296
n	2-Ad	85	60	244	-245
o	CH <sub>3</sub> OCH <sub>2</sub>		91	105.5	-106.5
p	CH <sub>3</sub> SCH <sub>2</sub>	68	75	116	-117
q	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	0		—	—

a All imidazoles listed here are new compounds, which gave correct elemental analysis

b. This mono-adduct is obtained when 1 eq of 1 is used, with 2 eq of 1 (Method B) the di-adduct is formed in 76% yield, mp > 345°C 1,4-di[4(5)-p-tolylthio-5(4)-imidazolyl]benzene

The anion 1a is formed from 1 with n-BuLi at  $-75^{\circ}$  (in THF-hexane) Addition of a nitrile at the same temperature, followed by warming up to  $0^{\circ}$  and treatment with water provides the imidazoles 2 collected in the Table (Method A) <sup>8</sup>

Although the results with Method A are quite satisfactory, the activating influence of RS in 1 allows for an even more convenient procedure a THF solution of equimolar quantities of 1 and R'C≡N is simply added at room temperature (in 10-15 min) to a stirred suspension of t-BuOK in THF Addition of water (after 15 min) gives high yields of pure imidazoles 2 (Method B).

Method A is of advantage only with sterically hindered nitriles, e.g. R' = t-Bu, Ad (compounds 2l-n). Proton exchange between 1a and benzyl cyanide presumably prevents the formation of imidazole 2g

Treatment of 4(5)-phenyl-5(4)-p-tolythioimidazole (2a) with Raney nickel gave the well-known 4(5)-phenylimidazole (58% yield) This together with IR, PMR and CMR spectral evidence gives the structures of the new compounds 2 a firm basis.

Further applications of 1 in heterocyclic synthesis are currently under investigation For example, reaction of 1 with carbodiimides gives 5-amino-4-p-tolythioimidazoles

Acknowledgement These investigations were supported by the Netherlands Foundation for Chemical Research (SON)

#### References and Notes

- 1 For the synthesis of thiomethyl isocyanides and some reactions, see a) A M van Leusen and H E van Gennep, Tetrahedron Lett , 1973, 627, b) U Schöllkopf and E Blume, *ibid*, 1973, 629.
- 2 Reactions of this type are not restricted to p-tolythiomethyl isocyanide (1), similar reactions with R = p-chlorophenyl, p-methoxyphenyl and tert-butyl have also been studied and will be reported in a full paper
- 3 A M. van Leusen, J Wildeman and O H Oldenziel, in preparation.
- 4 A M van Leusen and O H Oldenziel, Tetrahedron Lett , 1972, 2373
- 5 B E Hoogenboom, O Possel and D van Leusen, unpublished results
- 6 A I Meyers and J C Sircar in "The Chemistry of the Cyano Group" (Patai, ed), Interscience 1970, p 341, T Kauffmann, A Busch, K Habersaat and E Köppelmann, Angew Chem Int Ed 12, 569 (1973).

- 7 The difference in reactivity between the anions 1a and 3a is also reflected in their reaction with esters; 3a gives no reaction, whereas 1a forms oxazoles, A M van Leusen and H E van Gennep, unpublished results, cf ref 1b also
- 8 The only previous example known to us is the reaction of  $\alpha$ -lithiomethyl isocyanide with benzonitrile to give 4(5)-phenylimidazole (40% yield), cited in U. Schöllkopf, Houben-Weyl, Methoden der Org Chemie, 4<sup>e</sup> Aufl Bd. 13/1, p 246 (1970)
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