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AN EFFICIENT SYNTHESIS OF ISOXAZOLES AND ISOXAZOLINES

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Abstract - Isoxazoles and isoxazolines can be efficiently prepared by refluxing a toluene solution of hydroximic acid chloride and dipolarophile.

Among the several methods developed for the "in situ" generation of a nitrile oxide, two have been extensively used: [1] a) the dehydration of primary nitro derivatives (Mukaiyama procedure)[2] and b) the base-induced dehydrohalogenation of hydroxamoyl halides (Huisgen's methodology)[3].

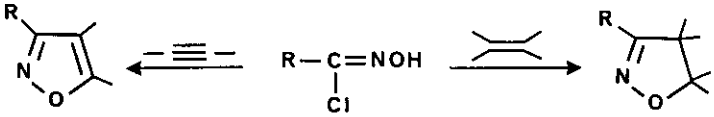
A serious side-reaction associated with these protocols is the competing dimerization to furoxan which prevents their application to sluggish dipolarophiles. This communication deals with a procedure which overcomes this obstacle and renders poor dipolarophiles capable of producing cycloadducts in reasonable yield. This methodology, firstly used by Grünanger et al.[4], has already found some interesting applications in the past[1,5,6], but, up to now, its usefulness in organic synthesis has not fully recognized.

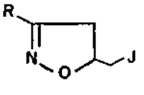
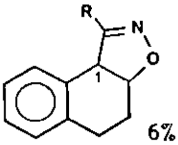
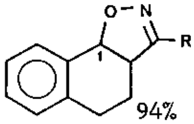
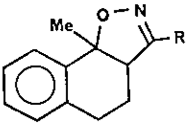
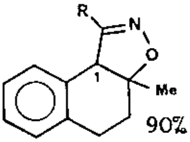
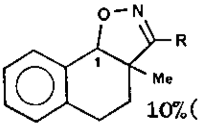
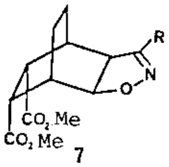
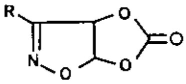
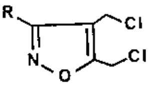
Results gathered in the Table were obtained by heating under reflux a toluene solution of hydroximic acid chloride and dipolarophile and are compared (in parentheses) with those produced by the Huisgen's procedure[7].

Since the two sets of data were obtained with the same ratio between 1,3-dipole and dipolarophile (1:1 or 1:5), it is worth pointing out that the two methods are equivalent with efficient dipolarophiles i.e. allyl iodide and 1,2-dihydronaphthalene, but differ sharply with sluggish dipolarophiles such as trisubstituted olefins and vinylene carbonate.

In particular, vinylene carbonate has been reported to be totally unreactive with some nitrile oxides[8] and to produce low yields of cycloadducts with two aromatic nitrile oxides[9] even if it was used as a solvent.

The present results confirm the low reactivity of vinylene carbonate but put in evidence the usefulness of the thermal generation of the 1,3-dipole in the reaction with poor dipolarophiles.



R	Dipolarophile	Total Yield(%)$^+$	Adducts^7
1) EtO_2C	Allyl iodide	90 (92)	 1
2) EtO_2C	1,2-Dihydronaphthalene	91 (72)	 6% 2 +  94% 3
3) EtO_2C	1-Methyl-3,4-dihydronaphthalene	63 (37)	 4
4) EtO_2C	2-Methyl-3,4-dihydronaphthalene	57 (5)	 90%(92) 5 +  10%(8) 6
5) PhCO	"	54 (12)	93%(95) 7%(5)
6) EtO_2C	Dimethyl bicyclo-[2.2.2]-octen-2,3-dicarboxylate	91 (55)	 7
7) MeCO		98 (50)	
8) PhCO	Vinylene carbonate	55 (<5)	 8
9) EtO_2C	" "	33 (<5)	
10) MeCO	" "	17 (<5)	
11) PhCO	1,4-Dichlorobutyne	65 (<5)	 9
12) EtO_2C	" "	75 (<5)	
13) MeCO	" "	49 (<5)	

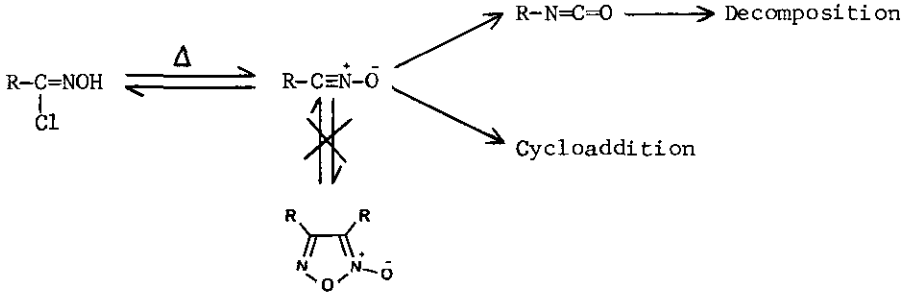
$^+$In parentheses are reported the results obtained with the Huisgen's procedure.

One more advantage of the present method is the lack of furoxan which, in many instances, hinders the purification of the adducts; as a consequence the reactions can also be carried out with a slight excess of hydroxamoyl chloride and the dipolarophile as the limiting reagent.

Consequently the present protocol can be successfully applied to precious dipolarophiles; its application to the synthesis of natural products is under active investigation in these laboratories.

If we consider the formation of furoxan as the sole evidence for the intermediacy of a nitrile oxide, we should exclude its intervention in reactions (1-13). On the other hand, a cycloreversion of the furoxan (Scheme 1) seems not conceivable since previous data[10] show that such a reaction requires higher temperatures and yields complex mixtures. In addition, by refluxing a toluene solution of furoxan ($R=CO_2Et$) and 1-methyl-3,4-dihydronaphthalene no adduct <u>4</u> was obtained.

Scheme 1



We believe that in refluxing toluene the hydroxamoyl chloride is in equilibrium with a low concentration of nitrile oxide which prefers to react with the dipolarophile or decompose to tarry material[11].

In summary, the success of the present methodology in the cases where other procedures fail can be ascribed to the concurrence of two positive factors: a) the slow release of hydrochloric acid which limits the "in situ" concentration of the nitrile oxide and b) the high temperature which enhances the rate of the cycloaddition process.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1) G.Bianchi, R.Gandolfi and P.Grünanger, "The Chemistry of the Cyano Group" Suppl.C (Ed. S.Patai and Z.Rappoport), John Wiley and Sons, London-New York,

1983, pp.737-804 and references cited therein.
C.Grundmann and P.Grünanger, "The Nitrile Oxide", Springer Verlag, Berlin Heidelberg-New York, 1971.

2) T.Mukaiyama and T.Hoshino, *J.Am.Chem.Soc.*, **82**, 5339 (1960).

3) M.Christl and R.Huisgen, *Chem.Ber.*, **106**, 3345 (1973).

4) M.Arbasino and P.Grünanger, *Ric.Sci.*, **34**, 561 (1964).
P.Vita Finzi and M.Arbasino, *Ric.Sci.*, **35**, 1484 (1965).

5) T.Sasaki and T.Yoshioka, *Bull.Chem.Soc.Jpn.*, **40**, 2604 (1967).

6) L.Gajsler and R.M.Paton, *J.Polym.Sci.: Polym.Lett.Ed.*, **18**, 635 (1980).
R.M.Paton and D.G.Hamilton, *Tetrahedron Letters*, **24**, 5141 (1983).

7) Typical procedure: A toluene solution (5ml) of hydroximic acid chloride (5mmol) is added dropwise to a solution of the dipolarophile (5mmol) in toluene (10ml) under reflux and stirring. The reaction is kept under reflux for 18 h, then chromatographed on a silica gel column.
Reactions (1-3) and (11-13) have been carried out with a five fold excess of dipolarophile; reactions (6-7) have been carried out with 20% excess of hydroximic acid chloride.
Structural assignments are based on ^{1}H-NMR spectra. In particular, regioisomers **2** and **3**, **5** and **6** have been differentiated by taking into account the chemical shift of H-1; the deshielding effect of the oxygen on H-1 is particularly evident in **3** and **6** (**2**: H-1= 4.7 δ; **3**: H-1= 5.5 δ; **5**: H-1= 4.4 δ; **6**: H-1= 5.3 δ).

8) K.E.Larsen and K.B.G.Torsell, *Tetrahedron*, **40**, 2985 (1984).

9) G.Desimoni, P.Grünanger and S.Servi, *Annali di Chimica*, **58**, 1363 (1968).

10) G.Bianchi and R.Gandolfi in "1,3-Dipolar Cycloaddition Chemistry" (Ed. A. Padwa), John Wiley and Sons, London-New York, 1984, pp.477-482.
T.Shimizu, Y.Hayashi and K.Teramura, *J.Org.Chem.*, **48**, 3053 (1983).
T.Shimizu, Y.Hayashi, T.Taniguchi and K.Teramura, *Tetrahedron*, **41**,727(1985).

11) For an alternative view about the mechanism which excludes the transient formation of the nitrile oxide as intermediate see reference 5).

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