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DIPOLAR ADDITION REACTIONS OF NITRILE OXIDES. VII.*

A NEW GENERAL METHOD OF SYNTHESIS OF 3,5-DISUBSTITUTED 1,2,4-OXADIAZOLES.

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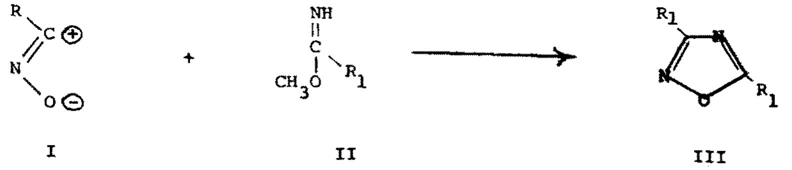
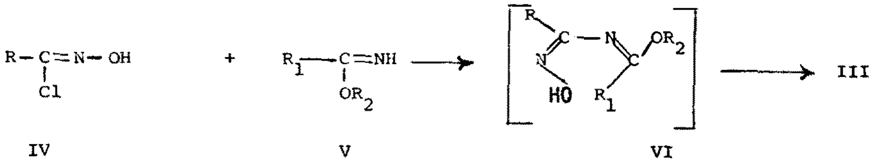
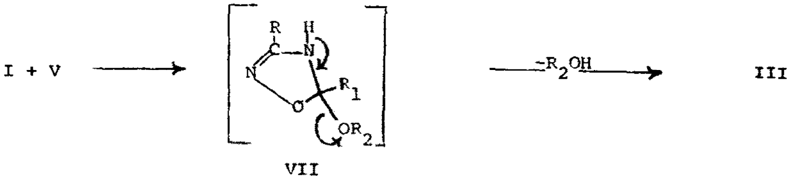
We would like to report that aliphatic and aromatic nitrile oxides (I), as exemplified by pivalonitrile oxide and 4-chlorobenzonitrile oxide respectively, react with methyl imidates (II) at room temperature (in absolute ether) to yield 1,2,4-oxadiazoles of the type III (See Table). Since methyl imidates (II) can easily be prepared from the corresponding nitriles and methanol by the method of Pinner (1), this procedure constitutes another general method of synthesis of the 1,2,4-oxadiazole system.



A few years ago Eloy and Lenaers (2) reported that 1,2,4-oxadiazoles of the type III could be made by the condensation of hydroxamyl chlorides (IV) with two moles of imidic esters (V) and suggested that the reaction might involve the formation of the intermediate VI which would then cyclize to III with the spontaneous elimination of R_2OH.



It is possible that imidic esters (V), being fairly strong bases, might dehydrochlorinate the hydroxamyl chlorides (IV) to the corresponding nitrile oxides (I) which would then react with the excess of the imidic ester present to furnish the oxadiazoles (III) either by the route suggested by Eloy and Lenaers (2) or by the more plausible mechanism outlined below.



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*For Part VI of this series cf. Tetrahedron Letters, 5525 (1966).

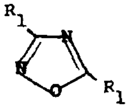
It is well known that nitrile oxides undergo facile cycloaddition to the C,N double bond of azomethines (3). It is possible, then, that the nitrile oxide (I) attacks the imidic ester (V) to form the oxadiazoline intermediate (VII) which is nicely disposed to extrude the elements of R_2OH to furnish the oxadiazole (III).

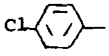
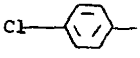
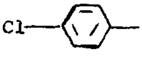
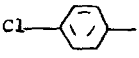
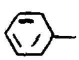
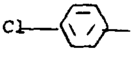
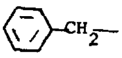
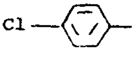
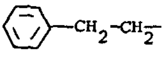
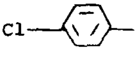
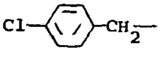
Leandri and Pallotti (4) and Huisgen and his coworkers (5) have prepared 1,2,4-oxadiazoles of the type III by the cycloaddition of nitrile oxides to aromatic and other activated nitriles. It was established (5) that an aliphatic nitrile not bearing an electron withdrawing group failed to react with nitrile oxides. We find that if the unreactive nitrile is first converted into the corresponding imidic ester the reaction proceeds readily. The possibility that the imidic ester (II) might first dissociate into the parent nitrile and methanol followed by the addition of the nitrile oxide to the nitrile thus generated is, therefore, precluded.

Acknowledgement: Thanks are due to Dr. I. J. Pachter for his interest in this work.

REFERENCES

1. R. Roger and D. G. Neilson, Chem. Rev., 61, 179 (1961).
2. F. Eloy and R. Lenaers, Bull. Soc. Chim. Belg., 72, 719 (1963).
3. R. Huisgen, Angew. Chem. Internat. Ed. Engl., 2, 565 (1963).
4. G. Leandri and M. Pallotti, Ann. Chim. (Rome), 47, 376 (1957).
5. R. Huisgen, W. Mack and E. Anneser, Tetrahedron Letters, 587 (1961).



R	R_1	Molecular Formula	M.P.	Yield[a]	Analysis[c]			
						C	H	N
$(CH_3)_3C-$		$C_{13}H_{15}ClN_2O$	75-77°	46%	Calc.	62.30	6.03	11.18
					Found	62.76	6.18	10.77
	CH_3-	$C_9H_7ClN_2O$	89-90°	35%	Calc.	55.55	3.63	14.40
					Found	55.38	3.33	14.12
	$C_2H_5O-CH_2-CH_2-$	$C_{12}H_{13}ClN_2O_2$	38-40°	56%	Calc.	57.03	5.18	11.09
					Found	57.55	4.96	10.91
		$C_{14}H_9ClN_2O$	107-109°[b]	38%	Calc.	65.48	3.53	10.91
					Found	65.29	3.25	10.73
		$C_{15}H_{11}ClN_2O$	92-94°	42%	Calc.	66.55	4.09	10.35
					Found	66.38	4.16	10.19
		$C_{16}H_{13}ClN_2O$	51-53°	32%	Calc.	67.47	4.60	9.84
					Found	67.19	4.83	10.13
		$C_{15}H_{10}Cl_2N_2O$	88-90°	45%	Calc.	59.00	3.30	9.18
					Found	58.81	3.18	9.01

a. Yield of the recrystallized product. The low yields are due to loss of sizeable quantity of the product during recrystallization.

b. M. P. reported (5) for this compound is 111-112°

c. Analyses are by Schwarzkopf Microanalytical Lab., Woodside, New York.