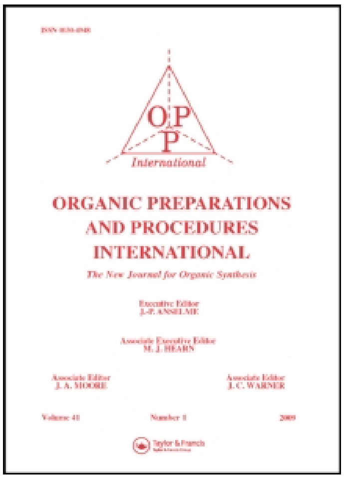

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SYNTHESIS AND THERMOLYSIS OF CYCLOALKENYL AZIDES. A SIMPLE ROUTE TO POLYCYCLIC ISOXAZOLES

Md. Izhar Sami[a]; Gandhi K. Kar[a]; Jayanta K. Ray[a]
[a] Department of Chemistry, Indian Institute of Technology, Kharagpur, India

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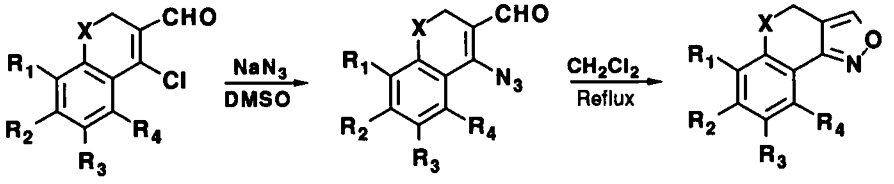
SYNTHESIS AND THERMOLYSIS OF CYCLOALKENYL AZIDES. A SIMPLE ROUTE TO POLYCYCLIC ISOXAZOLES

Submitted by (10/17/89)

Md. Izhar Sami, Gandhi K. Kar and Jayanta K. Ray*

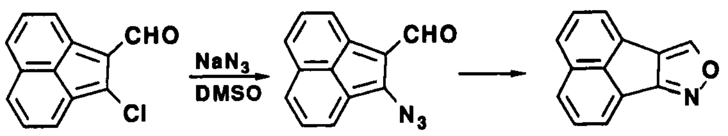
Department of Chemistry
Indian Institute of Technology
Kharagpur 721 302, INDIA

In continuation of our studies directed toward polycyclic heterocycles,[1] we now report a simple synthesis for the preparation of several polycyclic isoxazoles from the chloroaldehydes via the azidoaldehydes. Chloroaldehydes 1 and 4 were obtained in good yields from the corresponding ketones by the Vilsmeier-Haack reaction.[2] Sodium azide in dimethyl sulfoxide (DMSO) converted the chloroaldehydes to azidoaldehydes 2 and 5 in good yields (Table). The azides were cyclized thermally to isoxazoles 3 and 6 in excellent yields by reflux in dichloromethane (Table). The structure of the final products were established by analytical and spectral data (Table) and by analogy with other systems.[3]



1 2 3

a) $R_1 = R_2 = R_3 = R_4 = H, X = CH_2$
b) $R_1,R_2 = -CH{=}CH-CH{=}CH-, R_3 = R_4 = H, X = CH_2$
c) $R_1 = R_2 = H, R_3, R_4 = -CH{=}CH-CH{=}CH-, X = O$



4 5 6

EXPERIMENTAL SECTION

^1H NMR spectra were recorded on a 90 MHz Varian EM 390 spectrometer. IR spectra were determined on a Perkin-Elmer 580B spectrometer; mass spectra were obtained by electron impact on a Finnigan-Mat 3300 mass spectrometer.

General Synthesis of Azides (2a-2c and 5).- To an ice cooled solution of sodium azide (5 mmol) in DMSO (10 ml), a solution of chloroaldehyde in DMSO was added over a period of 15 minutes. The mixture was stirred for 1 hr. at 5-10° and then for 3-5 hrs at 25° (completion of the reaction was monitored by TLC). The reaction mixture was then poured into cold water and extracted with ether or dichloromethane. The organic layer was washed well with water, dried (Na_2SO_4) and evaporated in vacuo to yield the azides. The azides were too unstable to be purified and thus elemental analyses could not be obtained.

TABLE. Yields, Spectral and Analytical Data of Compounds 2,3,5,6

Cmpds.	Yield (%)	mp. (°C)	IR (cm^{-1})	NMR (δ) (CDCl$_3$)	MS (M$^+$)	Elemental Analyses Calcd. (Found)		
						C	H	N
2a	87	Oil	2120,1650	9.5(s,1H),7.1-7.9 (m,4H),2.5-3.5 (m,4H).	-	-	-	-
2b	97	101-102	2100,1650	- -	-	-	-	-
2c	68	119-120	2120,1625	- -	-	-	-	-
5	84	106-108	2100,1650	- -	-	-	-	-
3a	72	Oil[a] (neutral Al$_2$O$_3$/ Benzene	3040,2980 1608,1672 1402,1269	8.1(s,1H),7.8-8.1 (m,1H),7.1-7.4 (m,4H),2.6-3.0 (m,4H).	171	77.2 (77.1)	5.3 (5.1)	8.2 (7.9)
3b	98	110-111[b]	3052,2968 1611,1561 1401,1264	7.5-8.2(m,7H),3.4 (t,2H),2.9(t,2H).	221	81.5 (81.3)	4.9 (4.7)	6.3 (6.1)
3c	75	181-182[c]	3077,2940 1606,1571 1379, 1268	9.1(d,1H),7.1-7.8 (m,6H),5.5(s,2H).	223	75.3 (75.1)	4.0 (3.8)	6.3 (6.1)
6	67	98-99[b]	2960,1610 1575,1408 1270	8.5(s,1H),7.5-8.2 (m,6H).	193	80.8 (80.5)	3.6 (3.3)	7.2 (6.9)

a) Purified by column chromatography on neutral alumina and elution with benzene; b) From 60-80° pet-ether; c) From benzene.

General Preparation of Isoxazoles (3a-3c and 6).- A solution of the azide (1 mmol) in dichloromethane (50 ml) was heated at reflux for 24 hrs. Removal of the solvent in vacuo produced the isoxazoles which were purified by column chromatography or by recrystallization (Table).

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AN IMPROVED SYNTHESIS OF 5-METHYLPYRAZINE-2-CARBOXYLIC ACID

Submitted by (06/04/90)
I. Iovel, Yu. Goldberg* and M. Shymanska

Institute of Organic Synthesis
Latvian Academy of Sciences
Riga 226006, USSR

5-Methylpyrazine-2-carboxylic acid (4) is known to be an intermediate[1,2] in the synthesis of Glypizide (Minidiab). This drug is structurally related to the latest generation of sulfonylurea derivatives and is used in the treatment of insulin-independent diabetes.[3] The known route to 4 involves the oxidation of 2,5-dimethylpyrazine (1) with H_2O_2 to mono-N-oxide 5[4] which with Ac_2O, gave 2-acetoxymethyl-5-methylpyrazine (6). Hydrolysis of 6 with aqueous alkali yielded 2-hydroxymethyl-5-methylpyrazine (3).[5] Oxidation [6] of 3 with aqueous $KMnO_4$ afforded acid 4 in 18% yield from 1. Recently, the electrochemical oxidation of 1 was reported[7] to afford 4 in low yield (28%). We now report a modified procedure for the preparation of 4.

Free-radical chlorination of 1 with N-chlorosuccinimide in the presence of benzoyl peroxide as initiator[8,9] afforded 2-chloromethyl-5-methylpyrazine (2) in 80% yield. Refluxing a mixture of 2 and anhydrous NaOAc in absolute EtOH under argon gave acetoxymethyl derivative 6 (GLC yield