Regiospecific Synthesis of Pyrazoles From Vinyl Azides

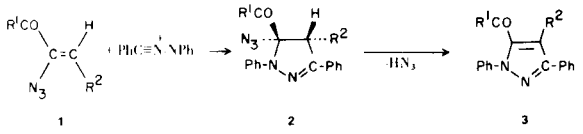
Gerrit L'abbé and Georges Mathys

Department of Chemistry, University of Louvain,
Celestijnenlaan 200F, B-3030 Heverlee, Belgium

Received October 10, 1973

Vinyl azides are versatile reagents in organic syntheses which can react with nucleophiles (1), electrophiles (2), and dipolarophiles (3). No reports are available on the dipolarophilic nature of the C=C bond in vinyl azides. We wondered if the olefinic bond possesses any dipolarophilic character, since self-addition of vinyl azides has never been observed (4). This led us to study the behaviour of diphenylnitrile imine with a variety of vinyl azides. The results are reported in this note.

Three α-azidovinyl ketones (**1a-c**) were treated with equimolar amounts of diphenylnitrile imine at room temperature and furnished pyrazole derivatives (**3a-c**) on the basis of ir, nmr, mass spectra, and microanalyses. The indicated regiochemistry was established beyond doubt by



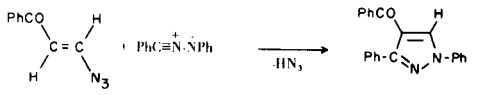
1 2 3

a: R^1 = Me, R^2 = Ph
b: R^1 = R^2 = Ph
c: R^1 = Ph, R^2 = *m*-$NO_2C_6H_4$

comparison of the ir and nmr spectra of **3b** with those of the pertinent 4-acylisomer (see structure **3b**, R^1CO and R^2 interchanged). The latter was prepared by a known procedure from the sodium salt of benzoylacetophenone and *N*-(α-chlorobenzylidene)-*N'*-phenylhydrazine (5).

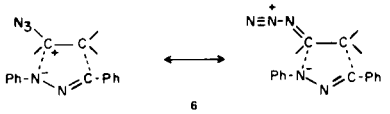
We were able to isolate the precursor of **3** in one case, namely in the reaction of **1b** with the nitrile imine, where **2b** was obtained in 63% yield. Elimination of HN_3 from this compound occurred very slowly at room temperature and rapidly upon warming in toluene. Pyrazoline **2a** was also observed in the nmr spectrum after complete reaction of **1a** with the nitrile imine, but could not be isolated since it decomposed to **3a** during the work-up procedure.

The above reactions are regiospecific with exclusive formation of 5-acylpyrazole derivatives (**3**). Pyrazoles with an acyl function in the 4-position can also be obtained by carrying out the cycloaddition reactions with β-azidovinyl ketones. Thus, when **4** was treated with diphenylnitrile imine at room temperature, 1,3-diphenyl-4-benzoylpyrazole **5** was isolated, although in low yield (10%). In



4 5

this respect, it should be noted that cycloaddition reactions with monosubstituted acetylenes always furnished 5-substituted pyrazoles, irrespective of the nature of the substituent (6). The simple vinyl azide β-azidostyrene reacted with diphenylnitrile imine in a similar manner to give 1,3,5-diphenylpyrazole in moderate yield (31%). In all the examples studied in this work, the regiochemistry of the addition process is controlled by the azide function which can stabilize a partial positive charge in the transition state as shown in **6**.



6

EXPERIMENTAL

Reaction of α-Azidobenzylideneacetone (**1a**) with Diphenylnitrile Imine.

Triethylamine (0.01 mole) in benzene (10 ml.) was added slowly to a stirred solution of **1a** (0.01 mole) and *N*-(α-chlorobenzylidene)-*N'*-phenylhydrazine (7) (0.01 mole) in dry benzene (40 ml.) and the mixture was allowed to react at room temperature for 2 days. The precipitated triethylamine hydrochloride was collected by filtration (97%) and the filtrate was analyzed by nmr (31% of **1a**, τ 8.10, 50% of **2a**, τ 8.04, and 19% of **3a**, τ 8.22). The solvent was then removed under reduced pressure and the residue was crystallized from ether (10 ml.) to give 1,3,4-triphenyl-5-acetylpyrazole (**3a**) in 60% yield, m.p. 160-161.5° (ether); ir (potassium bromide): 1680 cm^{-1} (s, C=O); nmr (deuteriochloroform): τ 7.88 (s, 3 H); mass spectrum: M^{+} at m/e 338 (100%).

Anal. Calcd. for $C_{23}H_{18}N_2O$ (338): C, 81.36; H, 5.32; N, 8.28. Found: C, 81.10; H, 5.25; N, 8.30.

Reaction of α-Azidochalcone (**1b**) with Diphenylnitrile Imine.

Azide **1b** (0.01 mole) was allowed to react with *N*-(α-chlorobenzylidene)-*N'*-phenylhydrazine (0.01 mole) in dry benzene (50 ml.) and in the presence of triethylamine (0.01 mole) at room temperature for 2 days. After removal of the precipitated triethylamine hydrochloride (98%), the solvent was distilled off

under reduced pressure and the residue was analyzed by nmr (deuteriochloroform) (33% of **1b**, τ 3.52, 67% of **2b**, τ 4.6, and no **3b** present). Treatment of the residue with ether (10 ml.) gave 1,3,4-triphenyl-5-azido-5-benzoyl-Δ^2-pyrazoline (**2b**) in 63% yield, m.p. 97° dec. (benzene-pentane); ir (potassium bromide): 2120 (s, N_3), 1682 cm^{-1} (s, C=O); nmr (deuteriochloroform): τ 4.51 (s, 1 H); mass spectrum: no molecular ion, $M^{\cdot+}$ - HN_3 at m/e 400 (100%).

Compound **2b** (0.5 g.) was treated with triethylamine (0.3 ml.) in chloroform (5 ml.) at 50° for 20 hours (monitored by nmr). The solvent was then removed and the residue was treated with methanol (5 ml.) to give **3b** in 80%, m.p. 168-169° (chloroform-pentane). Similarly, when **2b** (1 g.) was heated in dry toluene (10 ml.) at 98-100° for 4 days (monitored by nmr) and then worked up in the same manner, compound **3b** was obtained in quantitative yield; ir (potassium bromide): 1655 cm^{-1} (s, C=O); mass spectrum: $M^{\cdot+}$ at m/e 400 (100%).

Anal. Calcd. for $C_{28}H_{20}N_2O$ (400): C, 84.00; H, 5.00; N, 7.00. Found: C, 84.05; H, 5.00; N, 7.05.

For comparison, the regioisomer of **3b** was prepared by the method of Fusco (5) and showed a different ir and nmr absorption pattern.

Reaction of α-Azido-*m*-nitrobenzylideneacetophenone (**1c**) with Diphenylnitrile Imine.

Azide **1c** (0.01 mole), *N*-(α-chlorobenzylidene)-*N'*-phenylhydrazine (0.01 mole) and triethylamine (0.01 mole) were allowed to react in dry benzene (50 ml.) for 2 days. After filtration of triethylamine hydrochloride (96%), the solvent was removed and the residue was dissolved in ether (15 ml.) and cooled at -25° to give 1,3-diphenyl-4-(*m*-nitrophenyl)-5-benzoylpyrazole (**3c**) in 19%, m.p. 134.5-135° (ether); ir (potassium bromide): 1660 cm^{-1} (s, C=O); mass spectrum, $M^{\cdot+}$ at m/e 445 (100%).

Reaction of α-Azidovinyl Phenyl Ketone (**4**) with Diphenylnitrile Imine.

Equimolar amounts (0.01 mole) of **4**, the dipole precursor and triethylamine were allowed to react in dry benzene (50 ml.) for 2 days. After filtration of the precipitate, the solvent was distilled off and the residue was treated with pentane (50 ml.) to remove the unreacted azide. The residue was then crystallized from acetone-pentane (10 ml.) and gave 1,3-diphenyl-4-benzoylpyrazole (**5**) in 10%, m.p. 114-115° (methanol); ir (potassium bromide): 3130 (w, =CH), 1640 cm^{-1} (s, C=O); nmr (deuteriochloroform): τ 1.76 (s, 1 H); mass spectrum: $M^{\cdot+}$ at m/e 324 (100%).

Anal. Calcd. for $C_{22}H_{16}N_2O$ (324): C, 81.48; H, 4.94; N, 8.64. Found: C, 81.30; H, 4.95; N, 8.60.

Reaction of α-Azidostyrene with Diphenylnitrile Imine.

Equimolar amounts (0.01 mole) of α-azidostyrene, the dipole precursor and triethylamine were allowed to react in benzene (40 ml.) for 2 days. The precipitate was collected and the residue, after removal of the solvent, was crystallized from methanol (10 ml.) to give 1,3,5-triphenylpyrazole in 31%, m.p. 135-136.5° (methanol) (lit. (7) 138-139°).

Acknowledgement.

The authors are indebted to the IWONL (Belgium) for a fellowship to one of them (G. M.).

REFERENCES

(1) S. Maiorana, *Ann. Chim. (Rome)*, **56**, 1531 (1966); G. R. Harvey and K. W. Ratts, *J. Org. Chem.*, **31**, 3907 (1966); G. L'abbé and A. Hassner, *ibid.*, **36**, 258 (1971), *J. Heterocyclic Chem.*, 7, 361 (1970).

(2) A. Hassner, E. S. Ferdinandi, and R. J. Isbister, *J. Am. Chem. Soc.*, **92**, 1672 (1970); A. Hassner and A. B. Levy, *ibid.*, **93**, 2051 and 5469 (1971).

(3) G. L'abbé, J. E. Galle, and A. Hassner, *Tetrahedron Letters*, 303 (1970); G. L'abbé and A. Hassner, *Bull. Soc. Chim. Belges*, **80**, 209 (1971); P. Ykman, G. Mathys, G. L'abbé, and G. Smets, *J. Org. Chem.*, **37**, 3213 (1972).

(4) For reviews on vinyl azides, see G. L'abbé and A. Hassner, *Angew. Chem.*, **83**, 103 (1971); *Angew. Chem. Intern. Ed. Engl.*, **10**, 98 (1971); G. Smolinsky and C. A. Pryde in, "The Chemistry of the Azido Group", Ed., S. Patai, Wiley-Interscience, London, 1971, p. 555.

(5) R. Fusco, *Gazz. Chim. Ital.*, **69**, 364 (1939).

(6) For a review, see R. A. Firestone, *J. Org. Chem.*, **37**, 2181 (1972).

(7) R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, **17**, 3 (1962).