Effective Methods for the Syntheses of 2-Pyrazolines and Pyrazoles from Diazocarbonyl Compounds

Michael P. Doyle*, Mark R. Colsman, and Roberta L. Dorow

Department of Chemistry, Hope College, Holland, Michigan 49423

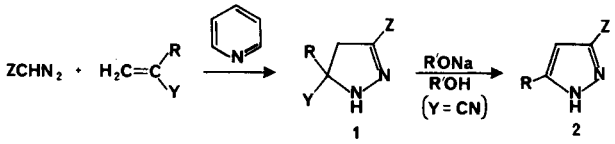
Received November 15, 1982

Dipolar addition of diazocarbonyl compounds to α,β-unsaturated esters and nitriles in the presence of pyridine results in the production of 2-pyrazolines in nearly quantitative yields. In one case, reaction of α-diazoacetophenone with acrylonitrile, Michael addition of the 2-pyrazoline to the conjugated olefin is observed, but this process is minimized by limiting the amount of pyridine employed. 5-Cyano-2-pyrazolines are converted to derivative pyrazoles through alkoxide promoted hydrogen cyanide elimination. With vinyl sulfone, α-diazoacetophenone undergoes sequential dipolar addition, Michael addition, and vinyl sulfite elimination under exceptionally mild conditions to form the derivative β-(1-pyrazolyl)ethyl vinyl sulfone in good yield.

J. Heterocyclic Chem., **20**, 943 (1983).

Diazo compounds readily undergo 1,3-dipolar addition to α,β-unsaturated carbonyl compounds and nitriles [1-3]. The resulting 1-pyrazoline, if formed from an activated olefin or a diazocarbonyl compound that possesses an α-hydrogen, is subject to rapid tautomerization that produces normally isolable 2-pyrazoline products [4,5]. If the reactants possess α-substituents, cyclopropane and vinyl C-H insertion products are formed by dinitrogen extrusion from the initially formed 1-pyrazoline [6]. Competition between tautomerism and dinitrogen extrusion of 1-pyrazolines with a single unsaturated polar substituent at the 3-position usually affords product mixtures that are unsuitable for further synthetic utilization [7,8].

We have recently reported methodology for the synthesis of cyclopropane compounds by dipolar addition of diazocarbonyl compounds to α,β-unsaturated carbonyl compounds and nitriles followed by dinitrogen extrusion [9]. Transition metal promoters, particularly $Mo(CO)_6$ and $Mo_2(OAc)_4$, were found to be effective in inhibiting competitive tautomerization to 2-pyrazolines. In the absence of these or related promoters, a combination of 2-pyrazoline, cyclopropane, and vinyl C−H insertion products were obtained, product yields were markedly dependent on the olefin employed and on the reaction conditions, and even more complex reaction mixtures were obtained in several cases. In the course of these investigations we observed that relatively weak bases catalyzed tautomerization of those 1-pyrazolines that were particularly sensitive to dinitrogen extrusion. We now report the utilization of this base catalyzed methodology in the synthesis of 2-pyrazolines **1** from reactions of ethyl diazoacetate (Z = COOEt) or α diazoacetophenone (Z = PhCO) with activated alkenes (Y = COOR', CN) and describe the synthesis of pyrazoles **2** from 2-pyrazolines derived from α,β-unsaturated nitriles and sulfones.



1 2

Treatment of ethyl diazoacetate or α-diazoacetophenone at 60° with representative α,β-unsaturated esters and nitriles in the presence of anhydrous pyridine resulted in the exclusive formation of 2-pyrazolines (Table I). Although the olefinic substrate was ordinarily employed in 10-fold molar excess relative to the diazo compound, satisfactory yields of 2-pyrazoline products (60-90%) could be obtained when the molar ratio of olefinic substrate to diazo compound was 3.0, particularly when ethyl diazoacetate was employed. The choice of the weak base pyridine to catalyze tautomerization of the initially formed 1-pyrazoline avoided competitive self-condensation reactions of these α-diazocarbonyl compounds [10,11] or of the olefinic substrates. The identity of the 2-pyrazolines obtained in this investigation was established by proton nmr analyses. In all reactions of ethyl diazoacetate and α-diazoacetophenone only one tautomeric 2-pyrazoline product was obtained. Chemical shift and coupling constant analyses are described in Table II.

Although pyridine was effective in promoting tautomerism even when employed in catalytic amounts [9], excess pyridine ensured the absence of even trace amounts of cyclopropane and vinyl C−H insertion products from resultant reaction mixtures. In one case, however, the use of excess pyridine and long reaction times led to subsequent Michael addition of the 2-pyrazoline product. Treatment of α-diazoacetophenone with a 10-fold molar excess of acrylonitrile in the presence of 1.0 equivalent of pyridine, based on diazo compound, at 60° for 18 hours resulted in the production of **3**, which was isolated in 50% yield. This same compound was not produced when the same reaction

Table I

Product Yields of 2-Pyrazolines **1** and Derivative Pyrazoles **2**

Olefin	Diazo Compound	Equiv Pyridine	Time, hours	1(a)	R	Y	Z	% Yield	2 (b)	Base	% Yield
$H_2C=CHCOOEt$	$N_2CHCOOEt$	5.0	3	**1a**	H	COOEt	COOEt	99			
	$N_2CHCOPh$	10.0	12	**1b**	H	COOEt	COPh	95			
$H_2C=C(CH_3)COOMe$	$N_2CHCOOEt$	5.0	3	**1c**	CH_3	COOMe	COOEt	99			
	$N_2CHCOPh$	10.0	32	**1d**	CH_3	COOMe	COPh	98			
$H_2C=CHCN$	$N_2CHCOOEt$	5.0	3	**1e**	H	CN	COOEt	100	**2a**	NaOEt	74
	$N_2CHCOPh$	0.20	6	**1f**	H	CN	COPh	94	**2b**	NaOMe	81
$H_2C=C(CH_3)CN$	$N_2CHCOOEt$	5.0	3	**1g**	CH_3	CN	COOEt	90	**2c**	NaOEt	70
	$N_2CHCOPh$	10.0	86	**1h**	CH_3	CN	COPh	95	**2d**	NaOMe	85

(a) Reactions were performed at 60° using a 10-fold molar excess of the olefin. (b) Reactions were performed with **1** at 60° for 3 hours in alcohol solvent.

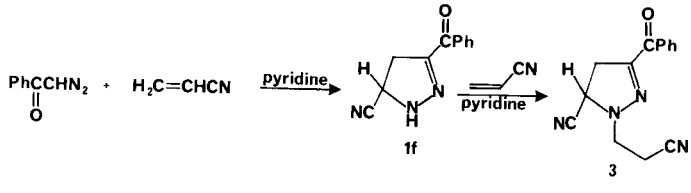
Table II

Nmr Analysis of 2-Pyrazolines **1** (a)

1	NH	H^5	H^{4t}	H^{4c}	$J_{5,4t}$	$J_{5,4c}$	$J_{4c,4t}$	$5-CH_3$	Other: δ
1a	6.68	4.51	3.26	3.23	6.3	11.8	17.2		3-COOEt: 4.30 (q), 1.34 (t) 5-COOEt: 4.22 (q), 1.29 (t)
1b	7.00	4.47	3.42	3.37	6.6	11.3	17.2		3-COPh: 8.3-8.1 (m), 7.7-7.3 (m) 5-COOEt: 4.22 (q), 1.29 (t)
1c	6.85		3.51	2.78			17.6	1.52	3-COOEt: 4.28 (q), 1.32 (t) 5-COOMe: 3.74 (s)
1d	6.94		3.67	2.96			17.6	1.58	3-COPh: 8.2-8.0 (m), 7.6-7.2 (m) 5-COOMe: 3.77 (s)
1e	6.62	4.63	3.31	3.30	8.3	9.8	17.2		3-COOEt: 4.34 (q), 1.36 (t)
1f	6.77	4.47	3.41	3.37	6.8	11.5	17.1		3-COPh: 8.3-8.1 (m), 7.7-7.3 (m)
1g	6.42		3.49	2.98			17.4	1.72	3-COOEt: 4.32 (q), 1.36 (t)
1h	6.72		3.65	3.14			17.3	1.74	3-COPh: 8.2-8.0 (m), 7.6-7.2 (m)

(a) The pyrazoline ring numbering system is used. H^{4t} is the hydrogen *trans* to H^5. H^{4c} is the hydrogen *cis* to H^5.

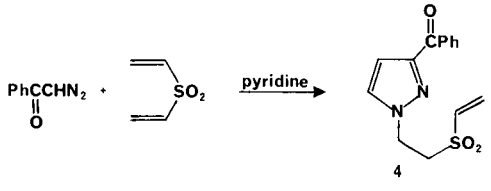
was performed with only 0.20 equivalent of pyridine (Table I), nor were similar products obtained from reactions between either α-diazoacetophenone or ethyl diazoacetate and α,β-unsaturated esters or nitriles other then acrylonitrile. Attempts to optimize this nucleophilic addition process were not undertaken, but Michael addition of pyrazolines appears to be readily attainable under mild conditions.



2-Pyrazolines are useful precursors to pyrazoles, and a variety of procedures are available for this conversion [12]. Elimination reactions have been previously employed, but only in a limited number of cases, ordinarily with chloride as the leaving group [13] or, in acidic media, from nitropyrazolines through elimination of nitrous acid [14,15]. With the 2-pyrazoline derived from cinnamonitrile and diazomethane, von Auwers and Ungemach observed thermal elimination of hydrogen cyanide [16], but a similar approach with methacrylonitrile resulted in products from the loss of dinitrogen [17]. We have found that 2-pyrazolines formed from diazocarbonyl compounds and α,β-unsaturated nitriles are readily converted to the corresponding pyrazoles through hydrogen cyanide elimination by alkoxide bases. These reactions are performed at 25°C

with 2.0 molar equivalents of alkoxide in alcohol solvent and result in 70-85% isolated yields of pyrazole product (Table I). This methodology affords convenient access to pyrazoles from readily available α,β-unsaturated nitriles that is not available from alternative dipolar addition-elimination methods.

The use of vinyl sulfone provides a strikingly unique example of the transformations that we have reported. Treatment of α-diazoacetophenone with a 10-fold molar excess vinyl sulfone in the presence of pyridine resulted in the production of pyrazole **4** as the sole isolable product. Although initial reactions were performed at 60° this product, formed through a combination of dipolar addition, Michael addition, and formal vinyl sulfite elimination, was also obtained at 25° in the presence of excess pyridine without evidence of **1i** (R = H, Y = PhCO, Z = $SO_2CH=CH_2$), the Michael addition product from **1**, or **2b**. Structural assignment of **4** was inferred from spectral analysis based on the formation of a single product, not two isomeric products anticipated from Michael addition of vinyl sulfone to **2b** (18), and the mechanistic interpretation that **4** must have arisen from the Michael adduct of **1i**. Similar treatment of ethyl diazoacetate with vinyl sulfone resulted in a complex reaction mixture from which the carboethoxy analog of **4** could be discerned but was not separately isolated.



4

EXPERIMENTAL

Instrumentation has been previously described (9). Melting points were determined using a Mel-Temp melting point apparatus which was calibrated against known standards. Elemental analyses were performed by Galbraith Laboratories, Inc. of Knoxville, TN. Ethyl diazoacetate was commercially available, and α-diazoacetophenone was prepared from benzoyl chloride and diazomethane [1]. The conjugated olefins employed for this investigation were commercially available and used without further purification. Pyridine was distilled from solid potassium hydroxide.

Physical constants and analytical values for previously unreported 2-pyrazolines and pyrazoles are reported in Table III. Pyrazoline **1a** [19] and pyrazoles **2a-c** [20,21] have been previously reported. Pyrazolines **1b-h,f,h** were liquids that, because of their thermal instability [12], were not further purified. However, spectral analyses [21,22] and their conversion to pyrazoles through elimination of hydrogen cyanide confirmed their indentity.

2-Pyrazolines **1a-h** from Diazocarbonyl Compounds. General Procedure.

The diazocarbonyl compound (20 mmoles for ethyl diazoacetate and 2.0 moles for α-diazoacetophenone) was added to a stirred solution containing 10.0 molar equivalents of the α,β-unsaturated ester or nitrile in excess anhydrous pyridine. The resultant solution was heated at 60° for 3 hours in reactions with ethyl diazoacetate or, in reactions with α-diazoacetophenone, until the diazo compound was no longer present in the reaction mixture. In accord with prior investigations of the reactivities of diazocarbonyl compounds as 1,3-dipoles [22], α-diazoacetophenone was much less reactive than ethyl diazoacetate and, as has been previously determined for ethyl diazoacetate [9], reactivity was dependent on the nature of the olefinic substituents. Following complete reaction, pyridine and excess olefin were evaporated under reduced pressure. The purity of pyrazoline products, as determined by nmr analyses, was greater than 95%. Solid pyrazolines **1a,e,g** formed upon cooling and were recrystallized from ethyl ether. Attempts to further purify liquid pyrazolines by column chromatography on either silica gel or alumina were only moderately successful. Attempted distillation resulted in the production of cyclopropane and formal vinyl C-H insertion products from dinitrogen extrusion [9] in low yield.

Pyrazoles **2a-d** from 5-Cyano-2-pyrazolines.

To 2.0 mmoles of the 5-cyano-2-pyrazoline was added 20 ml of alcohol containing 2.0 molar equivalents of preformed sodium alkoxide. Ethanol was employed for reactions with the carboethoxy derivatives, otherwise methanol was the solvent of choice. The continually stirred solution was heated at 60° for 3 hours, then cooled to room temperature and diluted with 100 ml of ether. The resultant solution was washed twice with 100-ml portions of saturated aqueous ammonium chloride, the aqueous solution was then washed with 50 ml of ether and the combined ether solution was dried over anhydrous magnesium sulfate. Ether was distilled under reduced pressure and the residual solid was recrystallized from ether; nmr (deuteriochloroform): **2d** δ 13.2 (s, NH, 1H), 8.14-8.01 (m, *o*-hydrogens, 2H), 7.63-7.30 (m, *m,p*-hydrogens 3H), 6.66 (d, pyrazole CH, 1H, J = 0.5 Hz), 2.37 (d, CH_3, 3H, J = 0.5 Hz).

1-(β-Cyanoethyl)-3-benzoyl-5-cyano-2-pyrazoline (**3**).

α-Diazoacetophenone (1.46 g, 10.0 mmoles) was added to 6.6 ml of acrylonitrile containing 0.85 g of anhydrous pyridine (10 mmoles) and then heated at 60° for 18 hours. Pyridine and excess acrylonitrile were

Table III

Physical Constants and Elemental Analyses for 2-Pyrazolines and Pyrazoles

	Mp °C	Empirical Formula	Calcd. C	Calcd. H	Calcd. N (S)	Found C	Found H	Found N (S)
1e	97-98	$C_7H_9N_3O_2$	50.28	5.44	25.14	50.30	5.41	25.22
1g	74-75	$C_8H_{11}N_3O_2$	53.02	6.13	23.19	53.17	6.09	23.37
2d	115.5-116.0	$C_{11}H_{10}N_2O$	70.94	5.42	15.05	71.07	5.52	14.98
3	86.5-87.5	$C_{14}H_{12}N_4O$	66.91	4.42	22.30	66.90	4.63	22.12
4	99-100	$C_{11}H_{14}N_2O_3S$	57.91	4.87	(11.04)	57.93	5.06	(10.95)

evaporated under reduced pressure. The resulting brown residue was suction filtered through neutral alumina using ether as the solvent to produce a light yellow solution which, following evaporation of ether, yielded a light yellow oily solid composed of pyrazoline **1f** and **3**. Further purification by column chromatography on neutral alumina with ether solvent followed by recrystallization from ether-pentane yielded 1.02 g (52%) of white solid, mp 86.5-87.5; ir (potassium bromide): 2246 cm^{-1} (C≡N) and 1633 cm^{-1} (C=O); nmr (deuteriochloroform): δ 8.20-8.08 (m, *o*-hydrogens, 2H), 7.70-7.35 (m, *m,p*-hydrogens, 3H), 4.60 (d of d, H^5, 1H, $J_{5,4t}$ = 7.6 Hz, $J_{5,4c}$ = 9.6 Hz), 3.80-3.52 (m, CH_2N, 2H), 3.55 (d, H^{4t}, 1H, $J_{5,4t}$ = 7.6 Hz), 3.52 (d, H^{4c}, 1H, $J_{5,4c}$ = 9.6 Hz), 2.90 (d of t, CH_2CN, 2H, J = 6.6, 1.9 Hz).

β-(3-Benzoyl-1-pyrazolyl)ethyl Vinyl Sulfone (**4**).

The reaction of α-diazoacetophenone (10.0 mmoles) with vinyl sulfone (100 mmoles) was initially performed as previously described for the preparation of **3**. After 5 hours at 60°, 100 ml of ether was added to the cooled reaction mixture which was then filtered to remove the light colored vinyl sulfone polymer that had formed during the reaction. The ether solution was washed four times with 100-ml portions of water, dried over anhydrous magnesium sulfate, and the ether was evaporated under reduced pressure to yield a light yellow solid that, after recrystallization from ether-pentane, was isolated in 44% yield, mp 99-100°; ir (potassium bromide): 1650 cm^{-1} (C=O), 1615 cm^{-1} (C=C), 1260 and 1110 cm^{-1} (SO_2); nmr (deuteriochloroform): δ 8.30-8.10 (m, *o*-hydrogens, 2H), 7.65-7.30 (m, *m,p*-hydrogens, 3H), 7.56 (d, H^5 1H, J_{45} = 2.3 Hz), 6.92 (d, H^4, 1H, J_{45} = 2.3), 6.5-5.9 (m, CH=CH_2, 3H), 4.67 (t, CH_2N, 2H, J = 6.4 Hz), 3.68 (t, CH_2SO_2, 2H, J = 6.4 Hz). When this same reaction was performed at 25° for 3 hours, **4** was isolated in 70% yield.

Acknowledgment.

We are grateful to the National Science Foundation for their generous support of this research. We wish to thank William H. Tamblyn for initial investigations of pyrazoline production.

REFERENCES AND NOTES

[1] B. Eistert, M. Regitz, G. Heck, and H. Schwall, "Methoden der Organischen Chemie" (Houben-Weyl-Müller), 4th Ed, Georg Thieme Verlag, Stuttgart, 1968, Vol IV, p 714.

[2] R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).

[3] R. Huisgen, *J. Org. Chem.*, **41**, 403 (1976).

[4] E. Buchner and A. Papendieck, *Ann. Chem.*, **273**, 232 (1893).

[5] R. H. Wiley and P. Wiley, "The Chemistry of Heterocyclic Compounds", Vol 20, A. Weissberger, ed, Wiley, New York, NY, 1964.

[6] P. S. Engel, *Chem. Rev.*, **80**, 99 (1980).

[7] K. MacKenzie, "The Chemistry of the Hydrazo, Azo, and Azoxy Groups", S. Patai, ed, Wiley, New York, NY, 1975.

[8] A. F. Noels, J. N. Braham, A. J. Hubert, and Ph. Teyssie, *Tetrahedron*, **34**, 3495 (1978).

[9] M. P. Doyle, R. L. Dorow, and W. H. Tamblyn, *J. Org. Chem.*, **47**, 4059 (1982).

[10] P. Yates, R. G. F. Giles and D. G. Farnum, *Can. J. Chem.*, **47**, 3997 (1969).

[11] E. Wenkert and C. A. McPherson, *J. Am. Chem. Soc.*, **94**, 8084 (1972).

[12] A. N. Kost and I. I. Grandberg, "Advances in Heterocyclic Chemistry", Vol 6, A. R. Katritzky and A. J. Boulton, eds, Academic Press, New York, NY, 1966, p 347.

[13] L. N. Owen and H. M. Babatunde Somade, *J. Chem. Soc.*, ¼1030 (1947).

[14] W. E. Parham and W. R. Hasek, *J. Am. Chem. Soc.*, **76**, 799 (1954).

[15] I. L. Finar and B. H. Walter, *J. Chem. Soc.*, 1588 (1960).

[16] K. von Auwers and O. Ungemach, *Chem. Ber.*, **66**, 1690 (1933).

[17] D. Gotkis and J. B. Cloke, *J. Am. Chem. Soc.*, **56**, 2710 (1934).

[18] G. Tarrago, A. Ramdani, J. Elguero, and M. Espada, *J. Heterocyclic Chem.*, **17**, 137 (1980).

[19] E. Buchner, *Chem. Ber.*, **21**, 2637 (1888).

[20] R. Gompper and R. Sobotta, *Synthesis*, 385 (1979).

[21] L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966).

[22] A. Hassner and M. J. Michelson, *J. Org. Chem.*, **27**, 3974 (1962).

[23] E. E. Schweizer and C. S. Labaw, *ibid.*, **38**, 3069 (1973).