Nonaqueous Diazotization of 5-Amino-1-aryl-1*H*-pyrazole-4-carboxylate Esters

James R. Beck*, Robert P. Gajewski, Michael P. Lynch and Fred L. Wright

Lilly Research Laboratories, Division of Eli Lilly and Company,
Greenfield, Indiana 46140

Received September 8, 1986

5-Amino-1-aryl-1*H*-pyrazole-4-carboxylate esters are converted to the corresponding desamino, chloro, bromo, iodo, and methylthio esters by processes involving nonaqueous diazotization. Diazotizing agents are alkyl nitrites except in the case of chlorine where nitrosyl chloride is used. Evidence is presented that the latter reagent leads to the formation of cationic rather than radical intermediates.

J. Heterocyclic Chem., **24**, 267 (1987).

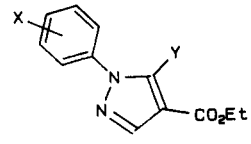
Nonaqueous diazotizations have been reported for the replacement of the amino function in anilines by hydrogen [1a-b], chlorine and bromine [2a-e], iodine [2b,3], and methylthio [2b,4]. Alkyl nitrites [1a-b,2a,2d,3,4], *t*-butyl thionitrite and thionitrate [2b-c] or nitric oxide [2e] were used as diazotizing agents in these aniline studies. Chlorine sources were carbon tetrachloride [2a-b], chloroform [2a], or copper chloride [2c-e]. The first two reagents were used as solvent. Chloroform was not a particularly good chlorine source because competitive hydrogen abstraction predominated [2a]. Brominating agents were bromoform [2a-b] (solvent) or copper (II) bromide [2c-d]. Iodine was the iodinating agent [2b,3], and origin of methylthio was dimethyldisulfide [2b,4]. In related arylation reactions, the process was shown to involve radical intermediates [5a-b].

The reaction has found little application in heterocyclic chemistry. Giam and Kikukawa [4] reported the synthesis of 2-, 3-, and 4-methylthiopyridines from the corresponding amines. Nair and Richardson [6a-b] described the replacement of amino functions by hydrogen, chlorine, bromine, and iodine in purine nucleosides.

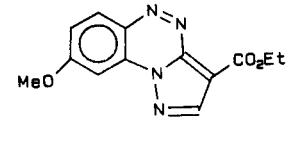
Our interest in this reaction has involved its utility in the conversion of readily available heterocyclic *ortho*-amino esters and nitriles to related desamino, halo, and methylthio esters and nitriles, which are often difficult to synthesize by alternate routes. We have recently reported its utility with respect to 4-amino-3-arylisothiazole-5-carboxylate esters [7] and 5-amino-1-aryl-1*H*-pyrazole-4-carbonitriles [8]. We now wish to report its usefulness starting with 5-amino-1-aryl-1*H*-pyrazole-4-carboxylate esters. A portion of this work recently appeared in a British patent application [9]. Amides derived from certain of the modified esters were found to be herbicides.

The required amino esters **1** were readily prepared by procedures described in the literature [10a-c]. Treatment of these amino esters with isopentyl nitrite in refluxing tetrahydrofuran gave the corresponding desamino esters **2a-f** in 70-90% yield (Table I). Ethyl 1-phenyl-1*H*-pyrazole-4-carboxylate **2a** was originally synthesized by Wislicenus and Bindemann [11] by vacuum distillation of ethyl formylacetate, phenyl hydrazone. No yield was reported. More recently, Takamizawa and Hayashi [12] prepared the phenyl **2a** and 4-nitrophenyl pyrazole esters **2f** by the reaction of ethyl α-diethoxymethyl-ß-ethoxypropionate with the appropriate phenylhydrazine. Their reported yields were 17% for **2a** and 38% for **2f**.

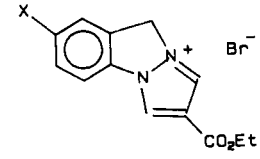
Treatment of the amino esters **1** with excess nitrosyl chloride in chloroform under mild conditions gave the corresponding chloro esters **3a-f** in 60-95% yield (Table I). When ethyl 5-amino-1-(3-methoxyphenyl)-1*H*-pyrazole-4-carboxylate (**1**, X = 3-OMe) was utilized as the starting material, the pyrazolo[5,1-*c*]-1,2,4-triazine derivative **7**, resulting from diazo coupling, was the sole product isolated in 66% yield. Reaction of the same amino ester with *t*-butyl nitrite in bromoform gave the expected bromo ester (**4**, X = 3-OMe) in 80% yield. The latter reaction, of course, involved the intermediacy of a radical [5a-b]. It



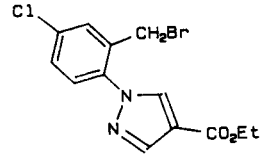
1 Y = NH_2
2 Y = H
3 Y = Cl
4 Y = Br
5 Y = I
6 Y = SMe



7



8a X = H
8b X = Cl



9

Table I

Ethyl 1-Aryl-(1*H*)-pyrazole-4-carboxylates

Compound	X	Y	Yield, %	Mp °C	Calcd. % (Found) C	H	N
2a	H	H	87	99-100 [a]	66.65	5.59	12.96
					(66.37	5.78	12.84)
2b	3-CF_3	H	79	101-102	54.93	3.90	9.86
					(55.04	3.94	9.99)
2c	3-Cl	H	73	95-96	57.50	4.42	11.17
					(57.24	4.16	11.30)
2d	4-Cl	H	78	127-129	57.50	4.42	11.17
					(57.49	4.33	11.46)
2e	4-OMe	H	85	77-79	63.40	5.73	11.38
					(63.14	5.45	11.43)
2f	4-NO_2	H	88	189-191 [b]	55.17	4.24	16.08
					(55.38	4.45	16.04)
3a	H	Cl	67	59-60	57.50	4.42	11.17
					(57.35	4.26	11.36)
3b	3-CF_3	Cl	61	34-35	49.00	3.16	8.79
					(49.18	3.26	8.75)
3c	3-Cl	Cl	77	55-57	50.55	3.54	9.82
					(50.52	3.47	10.03)
3d	4-Cl	Cl	85	81-83	50.55	3.54	9.82
					(50.60	3.31	9.97)
3e	4-OMe	Cl	65	84-85	55.62	4.67	9.98
					(55.67	4.41	10.18)
3f	4-NO_2	Cl	95	131-132	48.75	3.41	14.21
					(48.99	3.33	14.22)
4a	H	Br	61	87-88	48.84	3.76	9.48
					(48.79	3.92	9.43)
4b	3-CF_3	Br	59	45-47	43.00	2.78	7.71
					(43.25	2.76	7.55)
4c	3-Cl	Br	56	73-74	43.73	3.06	8.50
					(43.70	2.87	8.37)
4d	4-Cl	Br	76	100-102	43.73	3.06	8.50
					(43.61	2.89	8.70)
5a	H	I	56	96-97	42.13	3.24	8.19
					(42.39	3.25	8.03)
5b	3-Cl	I	44	89-91	38.27	2.68	7.44
					(38.49	2.63	7.54)
5c	4-Cl	I	55	90-92	38.27	2.68	7.44
					(38.55	2.65	7.63)
6	H	SMe	57	58-59	59.52	5.38	10.68
					(59.74	5.25	10.40)

[a] Lit [12] mp 100°. [b] Lit [12] mp 183-184°.

would thus appear that the nitrosyl chloride process either does not involve radicals or that the rate of diazo coupling is substantially faster than radical formation.

We propose that the nitrosyl chloride reactions, in general, involve cationic, rather than radical, intermediates. We also propose that the chlorine source in the chloro ester is nitrosyl chloride and not chloroform. Cadogan's results [2a] with alkyl nitrite diazotization of anilines (radical intermediates) showed that chloroform was a poor chlorinating agent, and that hydrogen abstraction predominated. In our case, radical intermediacy would have predicted substantial desamino ester formation, and this is in contrast with the high yields of chloro ester obtained (Table I). Small quantities of desamino esters were identified in several crude reaction mixtures, but these could have resulted from the molar equivalent of water formed in the diazotization reaction itself. In addition, the yields were not affected significantly when the reaction was car-

ried out in carbon tetrachloride, in contrast with Cadogan's findings.

Treatment of the amino esters **1** with isopentyl nitrite and bromine in chloroform gave the corresponding bromo esters **4a-d** in 55-75% yield (Table I). When ethyl 5-amino-1-(2-methylphenyl)-1*H*-pyrazole-4-carboxylate (**1**, X = 2Me) was utilized as the starting material, the product obtained after a three hour reflux was the pyrazolo[1,2-*a*]indazolium bromide **8a** in 65% yield. Similar treatment of ethyl 5-amino-1-(4-chloro-2-methylphenyl)-1*H*-pyrazole-4-carboxylate (**1**, **X** = 2-Me, 4-Cl) at room temperature gave the desamino ester **9**, in 64% yield. When **9** was heated in toluene, the product obtained was the quaternary bromide **8b** (60%) formed by intramolecular alkylation [13]. A plausible explanation of these results is that diazotization produced a radical at the 5-position with loss of nitrogen. This radical then abstracted hydrogen from the *ortho*-methyl function, *via* a six-membered ring transition state, yielding a more stable benzyl radical, which reacted with bromine. In the formation of **8a**, intramolecular alkylation occurred under the reaction conditions. In the case of **9**, alkylation did not occur under the milder reaction conditions.

Treatment of the amino esters **1** with isopropyl nitrite and iodine in chloroform gave the corresponding iodo esters **5a-c** in 45-55% yield (Table I). Reaction of **1** (X = H) with *t*-butyl nitrite and dimethyldisulfide in chloroform resulted in the formation of the methylthio ester **6** in 57% yield (Table I).

In conclusion, nonaqueous diazotization of ethyl 5-amino-1-aryl-1*H*-pyrazole-4-carboxylates with alkyl nitrites in the presence of tetrahydrofuran (solvent), bromine, iodine, or dimethyldisulfide yielded the corresponding desamino, bromo, iodo, and methylthio esters, respectively, by processes involving radical intermediates. Similar diazotizations with nitrosyl chloride yielded chloro esters, most likely by a process involving cationic intermediates.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. The following pyrazole amino esters **1** were prepared by literature procedures: X = H [10a], X = 4-NO_2 [10b], X = 3-Cl, 4-Cl, 3-OMe, 4-OMe, and 2-Me [10c]. Ethyl (ethoxymethylene)cyanoacetate was commercially available (Aldrich Chemical Co. or Lancaster Synthesis, Ltd.).

5-Amino-1-(3-trifluoromethyl)phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**1**, X = 3-CF_3).

A solution containing 21.3 g (0.1 mole) of 3-(trifluoromethyl)phenylhydrazine, hydrochloride salt, 18.6 g (0.105 mole) of ethyl (ethoxymethylene)cyanoacetate, and 18.0 g (0.22 mole) of anhydrous sodium acetate in 150 ml of acetic acid and 50 ml of water was heated on the steam bath for 16 hours. The mixture was poured into ice-water. The solid was collected and crystallized from alcohol-water to yield 23.0 g of product, mp 112-113°. The material was recrystallized from toluene to yield 19.0 g (64%) of product, mp 115-117°.

Anal. Calcd. for $C_{13}H_{12}F_3N_3O_2$: C, 52.18; H, 4.04; N, 14.04. Found: C, 52.18; H, 3.99; N, 14.01.

5-Amino-1-(4-chloro-2-methyl)phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**1**, X = 2-Me, 4-Cl).

A solution containing 25.0 g (0.13 mole) of 4-chloro-2-tolylhydrazine, hydrochloride salt, 22.0 g (0.13 mole) of ethyl (ethoxymethylene)cyanoacetate, and 18.0 g (0.13 mole) of anhydrous potassium carbonate in 200 ml of ethanol was stirred and refluxed for 24 hours. The mixture was poured into ice-water. The solid was collected and crystallized from ethanol to yield 26.5 g (73%) of product, mp 89-91°.

Anal. Calcd. for $C_{13}H_{14}ClN_3O_2$: C, 55.82; H, 5.04; N, 15.02. Found: C, 55.61; H, 4.87; N, 14.89.

General Synthesis of Ethyl 1-Aryl-1*H*-pyrazole-4-carboxylates **2a-f**.

A solution containing 0.03 mole of the appropriate **1** and 7.0 g (0.06 mole) of isopentyl nitrite in 80 ml of tetrahydrofuran was stirred and refluxed for 16 hours. The solvent was removed *in vacuo*, and the crude material was crystallized from ethanol to yield the desired product (Table I).

General Synthesis of Ethyl 1-Aryl-5-chloro-1*H*-pyrazole-4-carboxylates **3a-f**.

Into a cold solution containing 0.02 mole of the appropriate **1** in 60 ml of chloroform was bubbled excess nitrosyl chloride [14] for several minutes. The solution was then refluxed in an open flask for 5 minutes. The solvent was removed *in vacuo*, and the crude material was crystallized from ethanol-water to yield the desired product (Table I).

General Synthesis of Ethyl 1-Aryl-5-bromo-1*H*-pyrazole-4-carboxylates **4a-d**.

To a solution containing 0.02 mole of the appropriate **1** and 2.5 ml (0.046 mole) of bromine in 60 ml of chloroform was added dropwise 3.5 g (0.03 mole) of isopentyl nitrite. The solution was stirred at ambient temperature for 4 hours. Removal of the solvent and excess bromine *in vacuo* and crystallization of the crude material from ethanol or ethanol-water yielded the desired product (Table I).

General Synthesis of Ethyl 1-Aryl-5-iodo-1*H*-pyrazole-4-carboxylates **5a-c**.

To a solution containing 0.03 mole of the appropriate **1** and 17.8 g (0.07 mole) of iodine in 150 ml of chloroform was added dropwise 4.7 g (0.04 mole) of isopentyl nitrite. The mixture was stirred and refluxed for 2 hours. The cooled mixture was washed with aqueous sodium thiosulfate solution and then water. The organic layer was dried with magnesium sulfate. Removal of the solvent *in vacuo* and crystallization from ethanol yielded the desired product (Table I).

5-(Methylthio)-1-phenyl-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**6**).

To a cold solution containing 13.9 g (0.06 mole) of **1** (X = H) and 11.4 g (0.12 mole) of dimethyldisulfide in 100 ml of chloroform was added dropwise 8.1 g (0.079 mole) of *t*-butyl nitrite. A vigorous reaction ensued with evolution of nitrogen. The mixture was stirred in the cold for 1 hour. An additional 2.7 g of *t*-butyl nitrite was added, and the mixture was stirred in the cold for 1 more hour. The solution was washed with saturated brine solution. Removal of the solvent *in vacuo* and crystallization from ethanol-water yielded 11.2 g of product, mp 54-57°. Recrystallization yielded 9.0 g (57%) of product, mp 58-59° (Table I).

8-Methoxypyrazolo[5,1-*c*]-1,2,4-benzotriazine-3-carboxylic Acid, Ethyl Ester (**7**).

Into a solution containing 13.33 g (0.051 mole) of **1** (X = 3-OMe) in 100 ml of chloroform was bubbled hydrogen chloride gas for 1 minute. Excess nitrosyl chloride was then bubbled in for 5 minutes. A precipitate rapidly formed. Sodium acetate was added to dissolve the precipitate, and the mixture was retreated with nitrosyl chloride. More sodium ace-

tate was added, and the mixture was washed twice with water. The organic layer was dried with sodium sulfate. Removal of the solvent *in vacuo* yielded 12.9 g of product, mp 159-164°. Crystallization from ethanol yielded 9.1 g (66%) of **7**, mp 166-168°; nmr (DMSO-d_6): δ 8.77 (s, 1H), 8.58 (d, 1H), 7.70 (s, 1H), 7.45 (d, 1H), 4.42 (q, 2H), 4.08 (s, 3H), 1.40 (t, 3H); ms: m/e 272 (M^+).

Anal. Calcd. for $C_{13}H_{12}N_4O_3$: C, 57.40; H, 4.45; N, 20.60. Found: C, 57.60; H, 4.46; N, 20.37.

5-Bromo-1-(3-methoxyphenyl)-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**4**) (X = 3-OMe).

To a cold solution containing 6.6 g (0.025 mole) of **1** (X = 3-OMe) in 40 ml of bromoform was added dropwise 5.2 g (0.05 mole) of *t*-butyl nitrite. The mixture was stirred and heated on the steam bath for 15 minutes. The solvent was removed *in vacuo*. The residue was chromatographed on silica gel (hplc) using hexane/ethyl acetate 4:1 as the eluent. The product obtained (6.5 g, 80%) was an oil, which slowly solidified, mp 77-79°.

Anal. Calcd. for $C_{13}H_{13}BrN_2O_3$: C, 46.03; H, 4.18; N, 8.95. Found: C, 46.27; H, 3.94; N, 8.68.

2-(Ethoxycarbonyl)-9*H*-pyrazolo[1,2-*a*]indazol-10-ium Bromide (**8a**).

To a solution containing 5.0 g (0.02 mole) of **1** (X = 2-Me) and 2.4 g (0.031 mole) of bromine in 200 ml of chloroform was added dropwise 4.7 g (0.04 mole) of isopentyl nitrite. The mixture was stirred and refluxed for 3 hours. The solvent and excess bromine was removed *in vacuo*. The crude product was crystallized from ethanol to yield 4.1 g (65%) of product, mp 194-197°; nmr (DMSO-d_6): δ 9.95 (s, 1H), 9.55 (s, 1H), 7.5-8.3 (m, 4H), 5.85 (s, 2H), 4.35 (q, 2H), 1.35 (t, 3H).

Anal. Calcd. for $C_{13}H_{13}BrN_2O_2$: C, 50.51; H, 4.24; N, 9.06. Found: C, 50.32; H, 4.22; N, 8.86.

1-[2-(Bromomethyl)-4-chlorophenyl]-1*H*-pyrazole-4-carboxylic Acid, Ethyl Ester (**9**).

To a solution containing 10.0 g (0.035 mole) of **1** (X = 2-Me, 4-Cl) and 3.2 g (0.04 mole) of bromine in 100 ml of chloroform was added dropwise 6.2 g (0.053 mole) of isopentyl nitrite. The mixture was stirred at ambient temperature for 3 hours. Removal of the solvent and excess bromine *in vacuo* and crystallization from ethanol yielded 7.7 g (64%) of **9**, mp 71-73°; nmr (DMSO-d_6): δ 8.25 (s, 1H), 8.08 (s, 1H), 7.15-7.60 (m, 3H), 4.56 (s, 2H), 4.30 (q, 2H), 1.36 (t, 3H).

Anal. Calcd. for $C_{13}H_{12}BrClN_2O_2$: C, 45.44: H, 3.52; N, 8.15. Found: C, 45.63; H, 3.26; N, 8.33.

7-Chloro-2-(ethoxycarbonyl)-9*H*-pyrazolo[1,2-*a*]indazol-10-ium Bromide (**8b**).

A suspension of 3.0 g (0.0087 mole) of **9** in 100 ml of toluene was stirred and refluxed for 72 hours. The mixture was cooled and the product was collected to yield 1.8 g (60%) of **8b**, mp 200-202°; nmr (DMSO-d_6): δ 9.88 (s, 1H), 9.48 (s, 1H), 7.75-8.25 (m, 3H), 5.85 (s, 2H), 4.37 (q, 2H), 1.30 (t, 3H); ms: m/e 342 (M^+).

Anal. Calcd. for $C_{13}H_{12}BrClN_2O_2$: C, 45.44; H, 3.52; N, 8.15; Br, 23.25; Cl, 10.32. Found: C, 45.42; H, 3.78; N, 8.23; Br, 23.05; Cl, 10.25.

REFERENCES AND NOTES

[1a] J. I. G. Cadogan and G. A. Molina, *J. Chem. Soc., Perkin Trans. I*, 541 (1973); [b] W. Zerweck, M. Schubert and R. Fleischauer, German Offen., 905,014 (1954); *Chem. Abstr.*, **50**, 12111 (1956).

[2a] J. I. G. Cadogan, D. A. Roy and D. M. Smith, *J. Chem. Soc. (C)*, 1249 (1966); [b] S. Oae, K. Shinhama and Y. H. Kim, *Bull. Chem. Soc. Japan*, **53**, 2023 (1980); [c] Y. H. Kim, K. Shinhama and S. Oae, *Tetrahedron Letters*, 4519 (1978); [d] M. P. Doyle, B. Siegfried and J. F. Dellaria, Jr., *J. Org. Chem.*, **42**, 2426 (1977); [e] W. Brackman and P. J. Smit, *Rec. Trav. Chim.*, **85**, 857 (1966).

[3] L. Friedman and J. F. Chlebowski, *J. Org. Chem.*, **33**, 1636 (1968).

[4] C. S. Gaim and K. Kikukawa, *J. Chem. Soc., Chem. Commun.*, 756 (1980).

[5a] J. I. G. Cadogan, *J. Chem. Soc.*, 4257 (1962); [b] L. Friedman and J. F. Chlebowski, *J. Org. Chem.*, **33**, 1633 (1968).

[6a] V. Nair and S. G. Richardson, *Tetrahedron Letters*, 1181 (1979); [b] V. Nair and S. G. Richardson, *J. Org. Chem.*, **45**, 3969 (1980).

[7] J. R. Beck and R. P. Gajewski, *J. Heterocyclic Chem.*, submitted for publication.

[8] J. R. Beck and M. P. Lynch, U.S. Patent 4,563,210 (1986).

[9] J. R. Beck and M. P. Lynch, British Patent Application 2,149,402A (1985).

[10a] P. Schmidt and J. Druey, *Helv. Chim. Acta*, **39**, 986 (1956); [b] C. Alberti and C. Tironi, *Farmaco, Ed. Sci.*, **22**, 418 (1967); *Chem. Abstr.*, **68**, 12896 (1968); [c] *ibid.*, **22**, 58 (1967); *Chem. Abstr.*, **67**, 32640 (1967).

[11] W. Wislicenus and W. Bindemann, *Ann. Chem.*, **316**, 18 (1901).

[12] A. Takamizawa and S. Hayashi, *Yakugaku Zasshi*, **83**, 318 (1963); *Chem. Abstr.*, **59**, 5147 (1963).

[13] In the nmr spectrum of **9**, the benzyl protons appeared as a singlet at 4.56 ppm. With both **8a** and **8b** this singlet was shifted downfield to 5.85 ppm. Similar downfield shifts were noted for both pyrazole protons, thus confirming the quaternary nature of both compounds.

[14] J. R. Morton and H. W. Wilcox, *Inorg. Synth.*, **4**, 48 (1953).