Heteroatom Chemistry
Volume 6, Number 6, 1995

Pyrazoline Derivatives: a Convenient Synthetic Route to New Pyrazolo-benzothia-(oxa) or Diazepinone Derivatives

Fawi M. Abd El Latif

Department of Chemistry, Faculty of Science, Aswan, Egypt

Received 1 March 1995; revised 26 April 1995

ABSTRACT

New pyrazolo-[3,4-b]-[1,5]-benzoazepinone derivatives are reported. One pot reactions of 5-chloro-4-carboxy-1-phenyl (3-substituted) pyrazole derivatives with o-thioaminophenol, o-phenylenediamine, and o-aminophenol derivatives were realized. The influences of the polarizability of the heteroatoms on the reaction rates and chemical yields are discussed. © 1996 John Wiley & Sons, Inc.

INTRODUCTION

The azepinone derivatives are of importance in medicinal chemistry due to their antidepressant, antiallergic, and neurolepic actions [1–3]. The azepinones incorporating pyrazoline structures have been synthesized previously by different chemical sequences [4–6], but the syntheses starting from 5-chloro-4-carboxy-1-phenylpyrazole derivatives have not been exploited so far with the aim of modifying their antimicrobial activities. Hence, this article reports a convenient approach to synthesizing new pyrazolo-[3,4-b]-[1,5]-benzoazepinone derivatives.

A convenient route for the synthesis of precursors of the benzoazepinones has been developed by oxidation of 5-chloro-4-formyl-1-phenyl (3-substituted) pyrazoles (**2a,b**) with alkaline silver nitrate in ethanol to afford the corresponding 5-chloro-4-carboxy-1-phenyl (3-substituted) pyrazoles (**3a,b**) in 60–70% yield. However, the use of other oxidizing agents such as potassium permanganate or potassium bichromate was unsuccessful for this purpose. The IR spectra showed absorption bands at 1670 and 3400–3500 cm^{-1} due to the presence of –C=O and –OH groups. The mass spectra of 5-chloro-4-carboxy-3-methyl (or 3-phenyl)-1-phenylpyrazoles (**3a,b**) showed intense molecular ion peaks (base peaks) at m/z = 236 and 298, respectively. The ^{1}H-NMR spectra showed the disappearance of the formyl proton observed at δ 10.0.

Reactions of 5-chloro-4-carboxy-1-phenyl (3-substituted) pyrazoles (**3a,b**) with o-aminothiophenol, o-phenylenediamine, and 4-substituted o-aminophenol in xylene (140°C) afforded 1-phenyl-1H-pyrazolo-[3,4-b]-[1,5]-benzoazepinone derivatives (**4a–1**). However, the attempted reactions in ethanol catalyzed by piperidine afforded only trace amounts of the products after overnight refluxing.

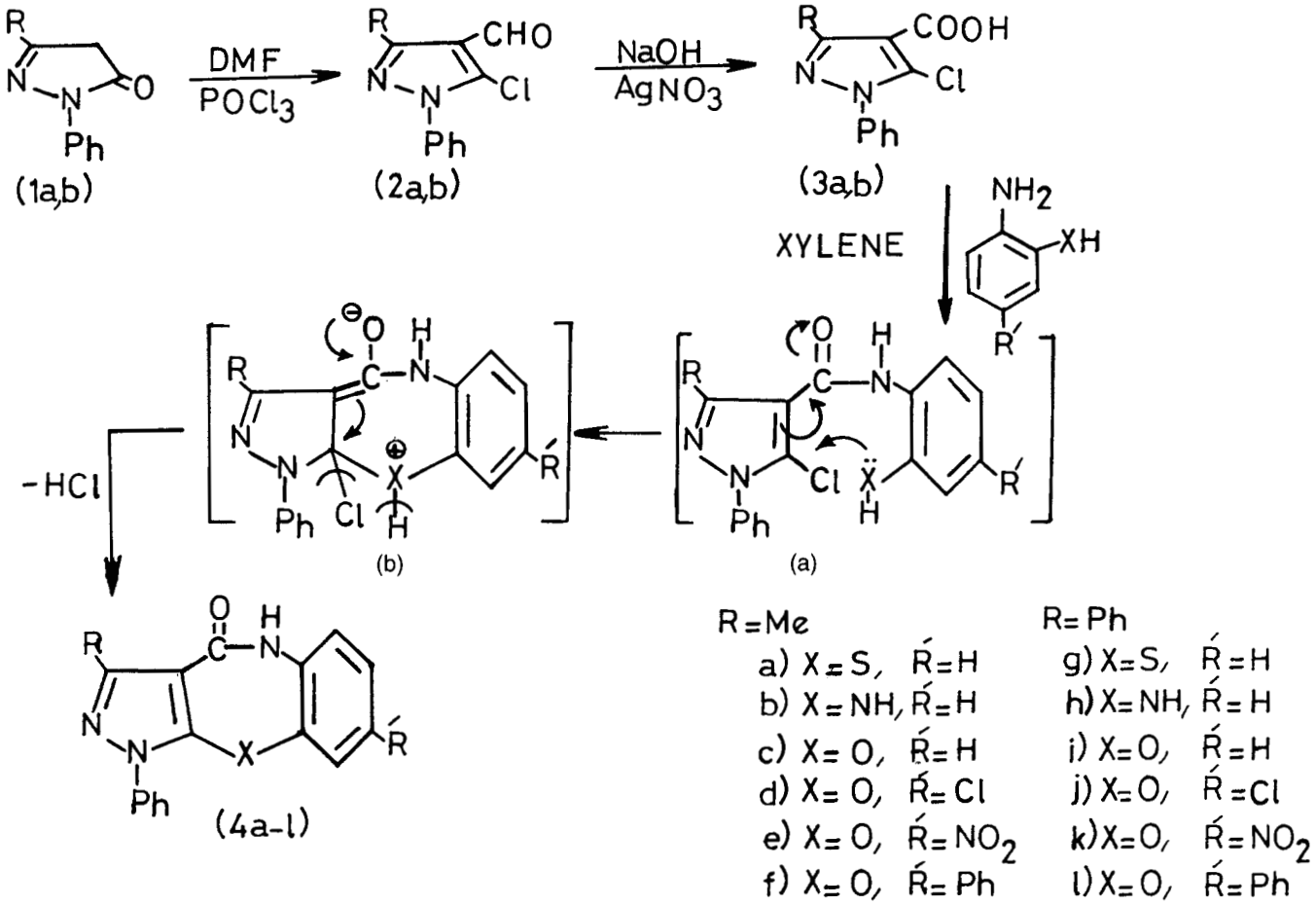
The formation of each azepinone (**4**) is believed to proceed in its first step by formation of an amido intermediate (A), followed by nucleophilic substitution of the chlorine anion as depicted in (B). Owing to the higher nucleophilic character of the sulfur atom when compared with oxygen or nitrogen, the thiazepinones were formed at a faster rate than the diazepinones or oxazepinones, the nucleophilic reactivity against C–Cl being in the order SH > NH > OH. IR spectra of the azepinones showed absorption bands characteristic for –NH–C=O at 3380–3300 and 1660 cm^{1-}, respectively. However, ^{1}H-NMR spectra taken in $CDCl_3$ revealed singlet signals around δ 7.5 assigned to –NH–C=O. Mass spectra were also confirmed the proposed structures which showed intense molecular ion peaks (base peaks), followed by the loss of the equivalent of HNCO from the molecular ion. The yields of the thiazepinones (**4a** and **4g**, X = S) are higher than those of the diazepinones (**4b** and **4h**, X = NH) or the oxazepinones (**4c** and **4i**, X = O).

© 1996 John Wiley & Sons, Inc.
1042-7163/96/060575-04

TABLE 1 5-Chloro-4-carboxy-1-phenyl(3-substituted)pyrazoles (**3a,b**)

No.	R	m.p. (°C)	Yield (%)	Formula (MWt)	Analysis (%) Calcd./Found C	H	N
3a	Me	225	60	$C_{11}H_9ClN_2O_2$(236.66)	55.83 55.72	3.83 3.71	11.84 11.69
3b	ph	203	70	$C_{16}H_{11}ClN_2O_2$(298.73)	64.33 64.19	3.71 3.57	09.38 09.27

3a: ^{1}H-nmr, 1.2 (S, 3H, Me), 7.2–7.8 (m, 5H, Ar–H). Mass sp.: 236 (100), 219 (30), 191 (10), 156 (25), 77 (70).
3b: ^{1}H-nmr: 7.2–7.8 (m, 10H, Ar–H), Mass sp.: 298 (100), 281 (25), 253 (30), 218 (30), 77 (50).



SCHEME 1

EXPERIMENTAL

Merck silica gel was used for chromatographic separation. Melting points are uncorrected. IR spectra were recorded (KBr) with a FT IR Nicolet 205 instrument. ^{1}H-NMR spectra were measured in $CDCl_3$ on a Shimadzu NMR QE 300 MHz spectrophotometer. Mass spectra were taken on a M-80 B Hitachi instrument, and microanalysis data were obtained from the Kyoto Institute of Technology, Kyoto, Japan. 5-Chloro-4-formyl-1-phenyl (3-substituted) pyrazoles (**2a,b**) were prepared according to Ref. [7].

5-Chloro-4-carboxy-1-phenyl (3-substituted) Pyrazoles (**3a,b**)

General Procedure. A solution of silver nitrate (3.45 g, 0.04 mole) in ethanol (100 mL) was added dropwise to an ethanolic solution (100 mL) of each of the 5-chloro-4-formyl-1-phenyl (3-substituted) pyrazoles (**2a,b**, 0.025 mole) with stirring. After the addition, a solution of sodium hydroxide (2.5 g, 0.125 mole) in 80% ethanol (100 mL) was added dropwise with stirring, the mixture then being heated on a water bath for 4 hours. The mixture was

TABLE 2 Characterization of Pyrazolo-azepinones (**4a–l**)

No. 4	R	R'	X	m.p.[a] (°C)	Yield (%)	Formula (MWt)	Analysis (%) Calcd./Found C	H	N
a	Me	H	S	185	65	$C_{17}H_{13}N_3OS$ (307.37)	66.43 66.25	4.26 4.10	13.67 13.51
b	Me	H	NH	205	55	$C_{17}H_{14}N_4O$ (290.33)	70.33 70.16	4.86 4.75	19.30 19.17
c	Me	H	O	210	50	$C_{17}H_{13}N_3O_2$ (291.31)	70.09 70.16	4.50 4.36	14.42 14.27
d	Me	Cl	O	178	68	$C_{17}H_{12}ClN_3O_2$ (325.75)	62.68 62.56	3.71 3.55	12.90 12.78
e	Me	NO_2	O	207	55	$C_{17}H_{12}N_4O_4$ (336.31)	60.71 60.55	4.60 3.44	16.66 16.52
f	Me	ph	O	150	70	$C_{23}H_{17}N_3O_2$ (367.41)	75.19 75.31	4.66 34.52	11.44 11.28
g	ph	H	S	110	62	$C_{22}H_{15}N_3OS$ (369.44)	71.53 71.38	4.09 4.22	11.37 11.26
h	ph	H	NH	185	53	$C_{22}H_{16}N_4O$ (352.40)	74.98 74.86	4.58 4.45	15.90 15.85
i	ph	H	O	175	50	$C_{22}H_{15}N_3O_2$ (353.38)	74.78 74.66	4.28 4.17	11.89 1172
j	ph	Cl	O	145	70	$C_{22}H_{14}ClN_3O_2$ (387.82)	68.14 68.03	3.64 3.56	10.84 10.68
k	ph	NO_2	O	195	55	$C_{22}H_{14}N_4O_4$ (398.38)	66.33 66.17	3.54 3.42	14.06 14.17
l	ph	ph	O	165	75	$C_{28}H_{10}N_3O_2$ (429.48)	78.31 78.23	4.46 4.35	09.78 09.64

[a]General crystallization solvent is methanol except that **d**, **e**, **h**, **j** are from ethanol.

TABLE 3 Spectral Data of Pyrazolo-azepinone Derivatives (**4a–l**)

Product 4	^{1}H-NMR (δ) (ppm)	Mass Fragments m/z (%)	
a	1.2 (S,3H,Me), 7.2–7.7 (m,9H,Ar), 7.5 (S,1H,NH).	307 264	(100), 279 (30), (25), 77 (40).
b	1.2 (S,3H,Me), 7.2–7.7 (m,9H,Ar), 7.6 (S,1H,NH), 9.6 (S,1H,NH).	290 247	(100), 262 (40), (30), 77 (50).
c	1.2 (S,3H,Me), 7.2–7.7 (m,9H,Ar), 7.6 (S,1H,NH).	291 248	(100), 263 (30), (30), 77 (50).
d	1.2 (S,3H,Me), 7.2–7.7 (m,8H,Ar), 7.7 (S,1H,NH).	325 282	(100), 297 (30), (40), 77 (50).
e	1.2 (S,3H,Me), 7.7 (m,8H,Ar), 7.5 (S,1H,NH).	336 293	(100), 308 (35), (30), 77 (55).
f	1.2 (S,3H,Me), 7.2–7.7 (m,13H,Ar), 7.4 (S,1H,NH).	367 324	(100), 339 (30), (20), 77 (50).
g	7.2–7.7 (m,14H,Ar), 7.5 (S,1H,NH).	369 326	(100), 341 (35), (40), 77 (60).
h	7.2–7.7 (m,14H,Ar), 7.3(S,1H,NH), 10.2 (S,1H,NH).	352 309	(100), 324 (30), (30), 77 (50).
i	7.2–7.7 (m,14H,Ar), 7.4 (S,1H,NH)	353 310	(100), 325 (35), (30), 77 (50).
j	7.2–7.7 (m,13H,Ar), 7.8 (S,1H,NH).	387 344	(100), 359 (30), (30), 77 (50).
k	7.2–7.7 (m,13H,Ar), 7.8 (S,1H,NH).	398 355	(100), 370 (40), (40), 77 (50).
l	7.2–7.7 (m,18H,Ar), 7.4 (S,1H,NH).	429 386	(100), 401 (45), (35), 77 (55).

filtered and the filtrate concentrated to dryness. The residue was dissolved in cold water and acidified with dilute hydrochloric acid (5 N). The colorless products were filtered off, washed with water, dried and recrystallized from methanol, and characterized as shown in Table 1.

3-Methyl (or 3-phenyl)-1-phenylpyrazolo-[3,4-b]-[1,5]-benzoazepinone derivatives (**4a–l**)

General Method. A mixture of equimolecular amounts of each of the 5-chloro-4-carboxy-1-phenyl (3-substituted) pyrazoles (**3a,b**, 0.01 mole) with o-aminothiophenol (1.3 g, 0.01 mole) for a period of 2 hours, o-phenylenediamine (1.08 g, 0.01 mole) for 4 hours, or o-aminophenol (1.09 g, 0.01 mole) for 5 hours, was refluxed in xylene (30 mL) at 140°C. Each mixture was cooled, washed with 10% sodium hydrogen carbonate, the organic solvent then being removed by steam distillation. The residue was subjected to chromatography on neutral silica gel using methylene chloride as eluent. The physical data of compounds **4** are presented in Table 2.

ACKNOWLEDGMENTS

The author express his appreciation and deep thanks to the ministry of Education, Culture, and Science (Monbusho) and to Profs. K. Hammanoue, T. Nakayama, and S. Miki, Kyoto Institute of Technology, Kyoto, Japan, for the Monbusho Scholarship and their kind help.

REFERENCES

[1] F. Hunziker, H. Leuner, J. Schmutz, *Arzniem. Forsch., 13*, 1963, 324.
[2] F. Hunziker, E. Fischer, J. Schmutz, *Helv. Chim. Acta., 50*, 1967, 1588.
[3] A. Wandre: Netherlands Patent, 6, 412, 380 (1965); *Chem. Abstr., 63*, (1965) 9971.
[4] I. Ito, T. Ueda, *Chem. Pharm. Bull., 18* (10), 1970, 1994.
[5] L. R. Swet, J. D. Ratajczyk, C. W. Nordeen, G. H. Aynilian, *J. Heterocyclic Chem., 12* (6), 1975, 1137.
[6] O. Migliara, A. Flugy, V. Novara, M. Gagliano, *Farmaco, 47*, 1991, 111.
[7] A. El Shekeil, A. Babaqi, M. Hassan, S. Shiba, *Heterocycles, 27*, 1988, 2577.