An Improved Synthesis of Pyrazolo[3,4-*b*][1,5]benzoxazepine, -Benzothiazepine and -Benzodiazepine Derivatives *via* a Convenient One-Pot Synthesis

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An improved and simple method for the preparation of pyrazolo[3,4-*b*][1,5]benzoxazepine, -benzothiazepine and -benzodiazepine derivatives was established by the reaction of 5-chloro-1-phenylpyrazole-4-carbaldehydes, ethyl 3-(5-chloro-1,3-diphenylpyrazol-4-yl)-2-cyanoacrylate and 1,4-diacetyl-3-methyl-2-pyrazolin-5-one with o-aminophenol derivatives and o-phenylendiamine.

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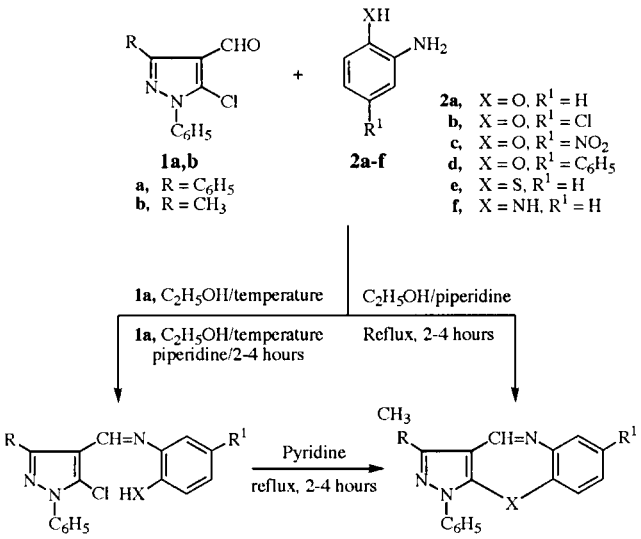
The analogues of pyrazolobenzazepine derivatives are a class of biological active compounds currently employed in the field of medicinal chemistry for their remarkable effects [1-3]. The condensation of compounds containing *o*-haloesters or *o*-haloaldehydes with *o*-aminophenols, *o*-aminothiophenol, and *o*-phenylenediamine has been widely applied as a synthetic auxiliary in their synthesis [3-5]. In the literature, the title compounds were prepared from the reaction of 5-chloro-3-methyl-1-phenylpyrazole-4-carbaldehyde (**1b**) with *o*-aminophenol derivatives **2a-f** in boiling toluene and then reducing the dihydro products with sodium borohydride, but no yields have been reported [6]. However, in continuation of our interest to develop a convenient and mild synthetic procedure for the synthesis of new heterocycle fused pyrazoles of pharmaceutical interest [7,8], we have now accomplished an improved synthesis of compounds **5** and **6**. This is achieved by replacing the toluene and sodium borohydride [6] by boiling the carbaldehydes **1a,b** with **2a-f** in ethanol containing few drops of piperidine at reflux. On the other hand, the carbaldehydes **1a,b** reacted easily with **2a-f** in ethanol at room temperature to give the new Schiff compounds **3a-f** and **4a-f** in 65-90% yield. The Schiff bases **3** and **4** were subsequently cyclized under reflux in ethanolic piperidine or pyridine solution to yield the corresponding target compounds **5** and **6** in 55-70% yields (Scheme 1). The chemical yields of **5** and **6** obtained directly from the reaction of **1a,b** with **2a-f** is higher than that from the cyclization of the corresponding Schiff bases. Similarly, 1,4-diacetyl-3-methyl-2-pyrazolin-5-one **1c** condensed readily with **2a-f** under reflux in ethanolic piperidine to give **8a-f** in 44-80% yields. The spectral and elemental analytical data of **8a-f** showed that the *N*-acetyl group was hydrolyzed under the reaction conditions shown in Scheme 2.

Furthermore, a convenient and simple route to prepare **5a-f** in good yield was achieved by the reaction of the readily

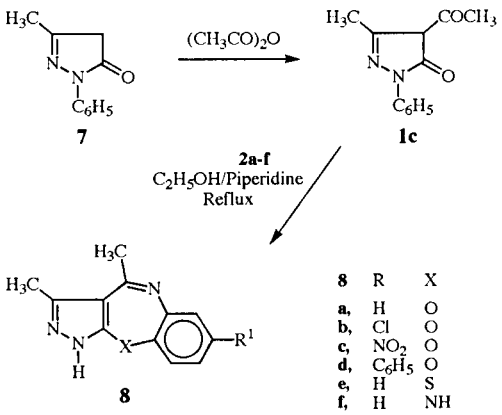
Scheme 1



	R	R^1	X
3a,	C_6H_5	H	O
b,	C_6H_5	Cl	O
c,	C_6H_5	NO_2	O
d,	C_6H_5	C_6H_5	O
e,	C_6H_5	H	S
f,	C_6H_5	H	NH
4a,	CH_3	H	O
b,	CH_3	Cl	O
c,	CH_3	NO_2	O
d,	CH_3	C_6H_5	O
e,	CH_3	H	S
f,	CH_3	H	NH

	R	R^1	X
5a,	C_6H_5	H	O
b,	C_6H_5	Cl	O
c,	C_6H_5	NO_2	O
d,	C_6H_5	C_6H_5	O
e,	C_6H_5	H	S
f,	C_6H_5	H	NH
6a,	CH_3	H	O
b,	CH_3	Cl	O
c,	CH_3	NO_2	O
d,	CH_3	C_6H_5	O
e,	CH_3	H	S
f,	CH_3	H	NH

Scheme 2



8	R	X
a,	H	O
b,	Cl	O
c,	NO_2	O
d,	C_6H_5	O
e,	H	S
f,	H	NH

Scheme 3

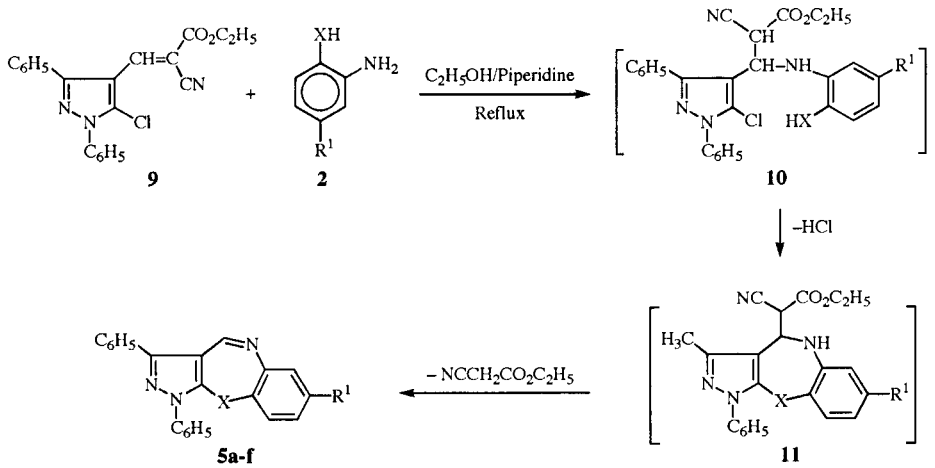


Table 1
The Physical, Analytical and Spectral Data of Compounds **3** and **4**

Compound No.	Mp (°C) Solvent	Yield %	M. Formula (M. Wt.)	Analysis% Calcd./Found C	H	N	Spectral ^{1}H NMR	MS, m/z [M$^+$]
3a	151-153 C_2H_5OH	80	$C_{22}H_{16}ClN_3O$ (373.84)	70.68 70.51	4.31 4.19	11.24 11.09	6.70 (s, 1H, CH=N), 7.2-7.7 (m, 14H, ArH), 8.40 (s, 1H, OH)	373
3b	291-293 C_2H_5OH	75	$C_{22}H_{15}Cl_2N_3O$ (408.28)	64.72 64.58	3.70 3.58	10.29 10.13	6.70 (s, 1H, CH=N), 7.2-7.8 (m, 13H, ArH), 8.50 (s, 1H, OH)	408
3c	304-305 CH_3OH	90	$C_{22}H_{15}ClN_4O_3$ (418.84)	63.09 63.23	3.61 3.47	13.38 13.25	6.80 (s, 1H, CH=N), 7.2-7.8 (m, 13H, ArH), 8.50 (s, 1H, OH)	418
3d	307-309 DMF	65	$C_{28}H_{20}ClN_3O$ (449.94)	74.75 74.61	4.48 4.36	9.34 9.18	6.80 (s, 1H, CH=N), 7.2-7.7 (m, 18H, ArH), 8.60 (s, 1H, OH)	449
3e	120-122 acetone	85	$C_{22}H_{16}ClN_3S$ (389.90)	67.77 67.61	4.14 4.01	10.78 10.62	5.50 (s, 1H, SH), 6.80 (s, 1H, CH=N), 7.1-7.7 (m, 14H, ArH)	389
3f	336-338 CH_3OH	75	$C_{22}H_{17}ClN_4$ (372.86)	70.87 70.72	4.60 4.48	15.03 14.95	5.80 (s, 2H, NH_2), 6.85 (s, 1H, CH=N), 7.1-7.7 (m, 14H, ArH)	372
4a	150-152 C_2H_5OH	80 (311.77)	$C_{17}H_{14}ClN_3O$	65.49 65.34	4.53 4.38	13.48 13.31	2.10 (s, 3H, CH_3), 7.1-7.9 (m, 10H, ArH + CH=N), 8.60 (s, 1H, OH)	311
4b	160-162 CH_3OH	70 (346.21)	$C_{17}H_{13}Cl_2N_3O$	58.98 58.81	3.78 3.65	12.14 12.01	2.11 (s, 3H, CH_3), 7.2-7.9 (m, 9H, ArH + CH=N), 8.55 (s, 1H, OH)	346
4c	300-302 CH_3OH	85 (356.77)	$C_{17}H_{13}ClN_4O_3$	57.23 57.10	3.67 3.52	15.70 15.52	2.10 (s, 3H, CH_3), 7.2-7.9 (m, 9H, ArH + CH=N), 8.60 (s, 1H, OH	356
4d	140-142 DMF	65 (387.87)	$C_{23}H_{18}ClN_3O$	71.22 71.05	4.68 4.52	10.83 10.65	1.98 (s, 3H, CH_3), 7.2-7.8 (m, 14H, ArH + CH=N), 8.50 (s, 1H, OH)	388
4e	110-112 C_2H_5OH	82 (327.83)	$C_{17}H_{14}ClN_3S$	62.28 62.10	4.30 4.14	12.82 12.65	2.10 (s, 3H, CH_3), 5.10 (s, 1H, SH), 7.2-7.8 (m, 10H, ArH + CH=N)	328
4f	130-132 CH_3OH	75 (310.79)	$C_{17}H_{15}ClN_4$	65.70 65.54	4.87 4.71	18.03 18.19	2.10 (s, 3H, CH_3), 5.80 (s, 2H, NH_2), 7.2-7.8 (m, 10H, ArH + CH=N)	311

obtainable acrylate compound **9** with **2a-f** in ethanolic piperidine solution at reflux. A possible rationale for the formation of **5** is shown in Scheme 3. Thus the amino function of **2** adds to the β- carbon of **9** to give the Michael intermediate **10**, which subsequently loses hydrogen chloride to afford intermediate **11**. The latter finally loses ethyl *cyanoacetate* to yield **5**. The structures of **5** were confirmed by means of spectroscopic analysis. It is worth mentioning that the yield of **5a-f** from the reaction of **9** with **2a-f** is higher than that from the corresponding reaction of **1a** with **2a-f**. The above simple one-pot reaction can be utilized easily to obtain such pharmaceutically important compounds in high yields using inexpensive and readily obtainable materials.

EXPERIMENTAL

Merck silica gel (pf_{254}) was used for chromatographic separation. All melting points were measured on a Gallen-Kamp melting point apparatus and are uncorrected. Mass spectra were taken on M-80 B Hitachi instrument. ^{1}H NMR spectra (deuterodimethylsulfoxide, δ = ppm) were recorded on Varian Spectrometer (90 MHz) and tetramethylsilane was used as internal standard. IR

Table 2

The Physical, Analytical and Spectral Data of Compounds **5, 6** and **8**

Compound No.	Mp °C Solvent	Yield [a] %	M. Formula (M. Wt)	Analysis % Calcd./Found C	H	N	Spectral Data ^{1}H NMR	MS, m/z [M$^+$]
5a	150-152 CH_3OH	70	$C_{22}H_{15}N_3O$ (337.38)	78.32 78.14	4.48 4.32	12.46 12.31	7.1-7.9 (m, 15H, ArH + CH=N)	337
5b	210-212 C_2H_5OH	65	$C_{22}H_{14}ClN_3O$ (371.82)	71.70 71.21	3.80 3.65	11.30 11.14	7.1-7.8 (m, 14H, ArH + CH=N)	372
5c	240-242 C_2H_5OH	75	$C_{22}H_{14}N_4O_3$ (382.38)	69.10 68.92	3.69 3.52	14.65 14.51	7.2-7.8 (m, 14H, ArH + CH=N)	381
5d	115-117 CH_3OH	60	$C_{28}H_{19}N_3O$ (413.48)	81.34 81.18	4.63 4.47	10.16 10.02	7.1-7.8 (m, 19H, ArH + CH=N)	413
5e	80-82 C_2H_5OH	80	$C_{22}H_{15}N_3S$ (353.44)	74.75 74.58	4.28 4.12	11.89 11.73	7.2-7.9 (m, 15H, ArH + CH=N)	353
5f	110-112 C_2H_5OH	55	$C_{22}H_{16}N_4$ (336.40)	78.55 78.41	4.79 4.62	16.66 16.51	5.80 (s, 1H, NH), 7.2-7.8 (m, 15H, ArH + CH=N)	336
6a	108-110 C_2H_5OH	65	$C_{17}H_{13}N_3O$ (275.31)	74.17 74.01	4.76 4.61	15.26 15.08	2.10 (s, 3H, CH_3), 7.2-7.9 (m, 10H, ArH + CH=N)	275
6b	118-120 CH_3OH	60	$C_{17}H_{12}ClN_3O$ (309.75)	65.92 65.73	3.91 3.74	13.57 13.41	2.10 (s, 3H, CH_3), 7.2-7.8 (m, 9H, ArH + CH=N)	309
6c	250-252 DMF	74	$C_{17}H_{12}N_4O_3$ (320.31)	63.75 63.40	3.78 3.61	17.49 17.32	2.16 (s, 3H, CH_3), 7.1-7.9 (m, 9H, ArH + CH=N)	320
6d	110-112 CH_3OH	63	$C_{23}H_{17}N_3O$ (351.41)	78.61 78.43	4.88 4.72	11.96 11.80	2.12 (s, 3H, CH_3), 7.2-7.8 (m, 14H, ArH + CH=N)	351
6e	85-60 CH_3OH	65	$C_{17}H_{13}N_3S$ (291.37)	70.80 70.22	4.50 4.35	14.42 14.23	2.10 (s, 3H, CH_3), 7.2-7.8 (m, 10H, ArH + CH=N)	291
6f	112-114 C_2H_5OH	60	$C_{17}H_{14}N_4$ (274.33)	74.43 74.25	5.14 5.01	20.42 20.24	2.12 (s, 3H, CH_3), 2.25 (s, 1H, NH), 7.2-7.8 (m, 10H, ArH + CH=N)	274
8a	205-207 C_2H_5OH	52	$C_{12}H_{11}N_3O$ (213.24)	67.59 67.41	5.20 5.03	19.71 19.56	2.10 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.8 (s, 1H, NH), 7.2-7.8 (m, 4H, ArH)	213
8b	150-152 C_2H_5OH	44	$C_{12}H_{10}ClN_3O$ (247.68)	59.19 58.02	4.07 4.21	16.96 16.81	2.10 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.7 (s, 1H, NH), 7.2-7.8 (m, 3H, ArH)	248
8c	290-292 C_2H_5OH	80	$C_{12}H_{10}N_4O_3$ (258.24)	55.81 55.64	3.90 3.74	21.70 21.55	2.10 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.8 (s, 1H, NH), 7.1-7.7 (m, 3H, ArH)	258
8d	200-202 CH_3OH	55	$C_{18}H_{15}N_3O$ (289.34)	74.72 74.61	5.23 5.04	14.52 14.35	2.10 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.8 (s, 1H, NH), 7.1-7.8 (m, 8H, ArH)	288
8e	220-222 CH_3OH	70	$C_{12}H_{11}N_3S$ (229.30)	62.86 62.71	4.84 4.73	18.33 18.21	2.10 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 3.8 (s, 1H, NH), 7.2-7.7 (m, 4H, ArH)	229
8f	195-197 C_2H_5OH	50	$C_{12}H_{12}N_4$ (212.26)	67.90 67.71	5.70 5.53	26.40 26.24	2.10 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.5 (s, 1H, NH), 3.8 (s, 1H, NH), 7.2-7.7 (m, 4H, ArH)	212

[a] The chemical yield was determined based on the reaction of **1a-c** with **2a-f**.

spectra (potassium bromide, $\nu = cm^{-1}$) were run on Nicolet FT IR model 205 Spectrophotometer and all the Microanalysis were performed at Kyoto Institute of Technology, Kyoto, Japan and at the Microanalytical Center, Cairo University, Egypt.

Ethyl 3-(5-chloro-1,3-diphenylpyrazol-4-yl)-2-cyanoacrylate (**9**) was prepared as reported in literature [**8**], and 5-Chloro-1-phenylpyrazole-4-carbaldehydes (**1a** and **1b**) were prepared as described in literature [**9**].

1,4-Diacetyl-3-methyl-2-pyrazolin-5-one (**1c**).

A mixture of 3-methyl-1*H*-pyrazolin-5-one **7** (2g, 20 mmoles) and acetic anhydride (30 g, 29 mmoles) was refluxed on a water bath for 2 hours. The solution was concentrated under vacuum and the residue was poured into ice - cold water (50 mL). The colourless crystals so formed were filtered and recrystallized from ethanol. mp: 46° (3g, 81%); ir (KBr): ν (cm^{-1}) 1676, 1670, 1665 (CO); ms, m/z: 182 (M$^+$, 100).

Anal. Calcd. for $C_8H_{10}N_2O_3$: C, 52.72; H, 5.53; N, 15.38. Found: C, 52.61; H, 5.36; N, 15.25.

Schiff Compounds (**3a-f** and **4a-f**).

General Procedure.

To an ethanolic solution (30 mL) of **1a** (2.8 g, 10 mmoles) an equimolar amount of *o*-aminophenol **2a** (1.1 g, 10 mmoles) was added and stirred at room temperature (30 °C) for 2 hours. The solid product so formed was collected by filtration, washed with cold ethanol and recrystallized from ethanol. Similarly, compound **1a** reacted with **2b-f** (10 mmoles each) under the same reaction conditions to give the Schiff bases **3b-f**. Compounds **1b** and **2a-f** were reacted (10 mmoles each) analogously in the presence of piperidine at room temperature to yield the Schiff compounds **4a-f**. The physical, analytical and spectral properties are listed in Table 1.

7-Substituted 1,3-Diphenylpyrazolo[3,4-*b*][1,5]benzoxazepines (**5a-d**), -Benzothiazepine (**5e**) and -Benzodiazepine (**5f**).

General Procedure.

A solution of compound **1a** (2.8 g, 10 mmoles) and *o*-aminophenols **2a** (1.1g, 10 mmoles) in 50 mL of ethanol in the presence of 0.1 mL of piperidine was refluxed for 2-4 hours. The reaction mixture was evaporated to dryness under vacuum to give crystals which were washed by 5 mL of acetic acid, dried and then dissolved in ether (3 × 20 mL). The combined ethereal solution was dried over anhydrous sodium sulfate, and then evaporated under vacuum to afford almost pure products. For spectral measurement the sample was subjected to plate chromatography using methylene chloride as eluent. Compound **1a** reacted similarly with **2b-f** (10 mmoles each) under the same reaction conditions to give the corresponding **5b-f**. Compounds **1b,c** and **2a-f** (10 mmoles each) were used analogously to give **6a-f** and **8a-f**, respectively. The physical, analytical and spectral data are listed in Table 2. The same compounds **5** and **6** were obtained *via* ring closure of the corresponding Schiff compounds **3** and **4** in refluxing ethanolic piperidine or pyridine solution for 2-4 hours.

Reaction of Ethyl 3-(5-chloro-1,3-diphenylpyrazol-4-yl)-2-cyanoacrylate (**9**) with *o*-Aminophenol (**2a**). Formation of **5a-f**.

General Procedure.

Equimolar amounts of **9** (0.38 g, 0.1 mmoles) and **2a** (0.1 g, 0.1 mmoles) was boiled in ethanol at reflux in the presence of 0.1 mL of piperidine for 3-5 hours. The reaction mixture was concentrated and the residue was triturated with a few drops of hydrochloric acid. The solid product so formed was filtered and washed with water (50 mL), dried and recrystallized to give **5a**. Analogously, compounds **9** and **2b-f** (0.1 mmoles each) were reacted under the same reaction conditions to yield **5b-f**. The structures of **5a-f** were confirmed on the basis of spectral, as well as melting and mixed melting points.

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