

## A Convenient One-Pot Synthesis of 4-Amino-3-arylpyrazoles from $\alpha$ -Phthaloylaminoacetophenones

Chen Chen\*, Keith Wilcoxon, James R. McCarthy

Department of Medicinal Chemistry, Neurocrine Biosciences, Inc.

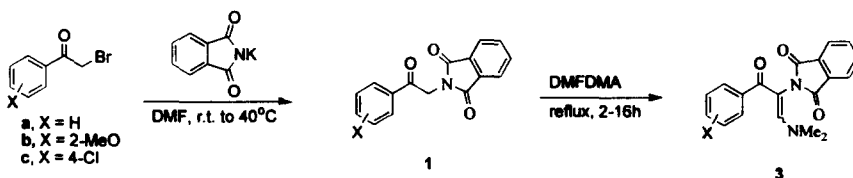
10555 Science Center Drive, San Diego, CA 92121, USA

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**Abstract.** Condensation of  $\alpha$ -phthaloylaminoacetophenones **1a–c** with N,N-dimethylformamide dimethyl acetal afforded the novel enamines **3a–c**. Cyclization of **3** with hydrazine, alkylhydrazine or phenylhydrazine salts (**4a–d**) gave 4-phthaloylamino-3-arylpyrazoles **7–9** in high yields. Deprotection of **7–9** was accomplished with hydrazine to provide 4-amino-3-arylpyrazoles **5** in good yields. © 1998 Elsevier Science Ltd. All rights reserved.

We required a general and convenient method to 4-amino-3-aryl-1-alkylpyrazoles that would be amenable to the rapid preparation of large numbers of analogs for biological testing. Surprisingly, there are few reports on the synthesis of 4-aminopyrazoles in the literature. The most promising method is a 4-step synthesis via the cyclization of an ethyl 3-benzoyl-3-nitroso-2-oxo-carboxylate with an alkyl hydrazine, followed by decarboxylation, but the overall yield is low.<sup>1a</sup> Other methods include nitration of the 3-arylpyrazoles, followed by reduction of the nitro group,<sup>1b–d</sup> and the recent report by Penning and coworkers on the condensation of benzoylnitromethane with N,N-dimethylformamide dimethyl acetal, followed by cyclization with (4-sulfamoylphenyl)hydrazine and hydrogenation to give a 4-aminopyrazole in 38%.<sup>1e</sup> We wish to report the development of a new and convenient method for the synthesis of 4-amino-3-arylpyrazoles that met our requirement for rapid analog preparation.

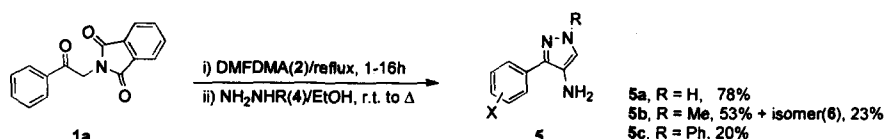
Scheme 1



$\alpha$ -Phthaloylaminoacetophenone derivatives **1a–c** were readily obtained by the reaction of  $\alpha$ -bromo- or  $\alpha$ -chloroacetophenones with phthalimide potassium salt in DMF.<sup>2,3</sup> Reaction of **1a** with 1.2 equivalents of neat dimethylformamide dimethyl acetal (DMFDMA, **2**) at reflux gave the enamine **3a** in quantitative yield (Scheme 1). To our knowledge, this is the first example of this transformation on an  $\alpha$ -phthaloyl-aminoketone.

Significantly, **3** was envisioned as a pivotal intermediate for a new synthesis of heterocycles bearing an amino group. Reaction of **3a**, obtained from **1a** and DMFDMA, with 2.5 equivalents of hydrazine (**4a**) in ethanol at room temperature for one hour followed by refluxing the mixture for one hour gave 4-amino-3-phenylpyrazole **5a** in 78% yield (two steps from **1a**) (Scheme 2). This simplified one-pot process provides the first general and facile synthetic route to a variety of multi-substituted aminopyrazoles.<sup>4</sup>

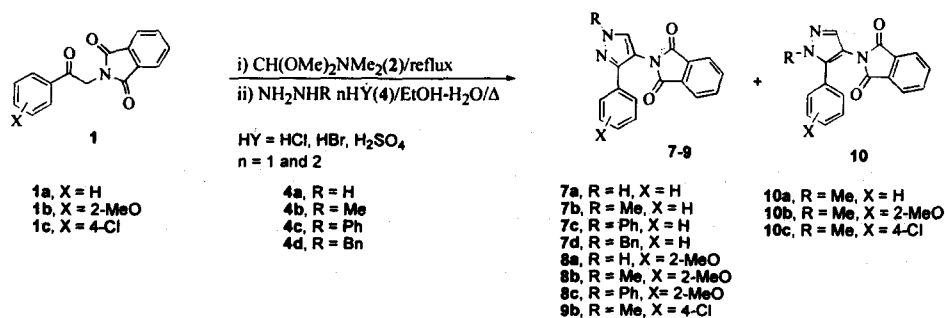
Scheme 2



When the reaction of **3a** and one equivalent of hydrazine (**4a**) was carried out at room temperature for one hour, the amino-protected product 3-phenyl-4-phthaloylamino-3-phenylpyrazole (**7a**) was isolated in 70% yield. If two equivalents of hydrazine (**4a**) were used and the reaction was carried out at room temperature overnight, 45% of **7a** was obtained along with 4-amino-3-phenylpyrazole (**5a**) in about 40%. When **3a** was treated with methylhydrazine (**4b**, 2.5 eq.) in ethanol at room temperature for one hour and at reflux for one additional hour, 4-amino-1-methyl-3-phenylpyrazole **5b** was isolated in 53%, along with an isomeric product, 4-amino-1-methyl-5-phenylpyrazole **6**, in 23% of yield. Under similar conditions, phenylhydrazine gave a very complex reaction mixture and only 20% of **5c** was isolated along with 35% of compound **7c**.

4-Aminopyrazoles **5a-c** darken slowly on standing in air, but the precursor 4-phthaloylamino-3-phenylpyrazoles **7** are white crystalline stable solids that can readily be isolated and subsequently converted to **5**. The isolation of **7** was accomplished by running the cyclization reactions with the corresponding hydrazine salts. Reaction of **3a** with 1.2 equivalents of hydrazine hydrobromide (**4a.HBr**) in refluxing aqueous ethanol afforded **7a** in 87% yield (Scheme 3). Removal of the phthaloyl group from **7a** with hydrazine to form **5a** proceeded cleanly in refluxing alcohol.<sup>5</sup> The use of hydrazine salts avoided the formation of **5a** even with a large excess of reagent or longer reaction times. Several hydrazine salts were used for the synthesis of **7-9** as summarized in Table 1.<sup>6,7</sup>

Scheme 3



The reaction of **3a** with hydrazine dihydrochloride (**4a.2HCl**) was slower than the corresponding hydrobromide or hydrochloride salt. An isomeric compound **10** was also obtained when methylhydrazine sulfate was used. Cyclization of **3a** with phenylhydrazine hydrochloride (**4c.HCl**) and benzylhydrazine dihydrochloride (**4d.2HCl**) gave only the major isomer **7c** and **7d**, respectively.

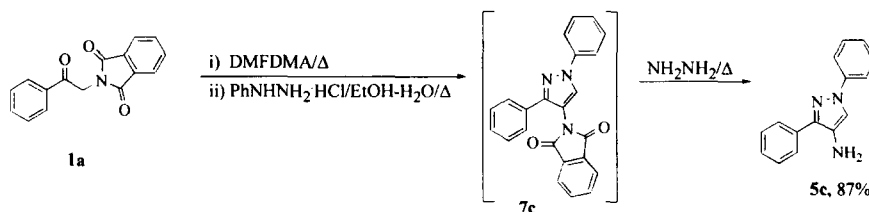
**Table 1.** Syntheses of 4-Aminopyrazoles **7-9** and **10** from **1a-c** and Hydrazine Salts **4**.

No.	Acetophenone		Hydrazine		Salt	Conditions	Yield (%) <sup>a</sup>	
	<b>1</b>	X	<b>4</b>	R			<b>7-9</b>	<b>10</b>
1	<b>a</b>	H	<b>a</b>	H	<b>HBr</b>	reflux, 2h	87 ( <b>7a</b> )	
2			<b>a</b>	H	<b>HCl</b>	reflux, 2h	86 ( <b>7a</b> )	
3			<b>a</b>	H	<b>2HCl</b>	reflux, 4h	82 ( <b>7a</b> )	
4			<b>b</b>	Me	<b>H<sub>2</sub>SO<sub>4</sub></b>	reflux, 1h	62 <sup>b</sup> ( <b>7b</b> )	26 <sup>b</sup> ( <b>10a</b> )
5			<b>c</b>	Ph	<b>HCl</b>	reflux, 2h	90 ( <b>7c</b> )	0
6			<b>d</b>	Bn	<b>2 HCl</b>	reflux, 3h	88 ( <b>7d</b> )	trace <sup>c</sup>
7	<b>b</b>	2-MeO	<b>a</b>	H	<b>HBr</b>	reflux, 1h	73 ( <b>8a</b> )	
8			<b>b</b>	Me	<b>H<sub>2</sub>SO<sub>4</sub></b>	reflux, 16h	40 ( <b>8b</b> )	39 ( <b>10b</b> )
9			<b>c</b>	Ph	<b>HCl</b>	reflux, 16h	83 ( <b>8c</b> )	0
10	<b>c</b>	4-Cl	<b>b</b>	Me	<b>H<sub>2</sub>SO<sub>4</sub></b>	reflux, 1h	61 ( <b>9b</b> )	20 ( <b>10c</b> )

a) Isolated yield; b) Ratio was determined by <sup>1</sup>H NMR; c) Tentatively assigned based on <sup>1</sup>H NMR of the crude reaction mixture.

The synthesis of **5c** from **1a** could be readily be accomplished in one pot in high yield (87%, Scheme 4). Intermediate **3a** (obtained from **1a** by treatment with 1.1 equivalent of DMFDMA neat) was treated with phenylhydrazine hydrochloride (**4c.HCl**) in refluxing aqueous ethanol for two hours, followed by the addition of two equivalents of hydrazine (**4a**) and refluxing for one additional hour.

**Scheme 4**



The assignment of the two isomeric structures **7-9** and **10** was confirmed by NOE NMR experiments on **9b** and **10c**. Thus when the 1-methyl group of the pyrazole **9b** was irradiated a NOE was observed on the pyrazole ring. Irradiation of the 1-methyl group on **10c** led to a NOE for the proton on the phenyl proton ortho to the pyrazole ring (see Chart 1).

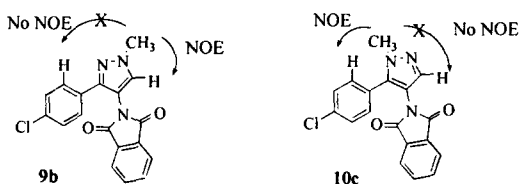


Chart 1. NOE of isomers **9b** and **10c**

In summary, condensation of  $\alpha$ -phthaloylaminoacetophenone derivatives **1** with *N,N*-dimethylformamide dimethyl acetal provided a pivotal intermediate enamines **3**. Cyclization of **3** with hydrazine salts (**4**) gave 4-phthaloylamino-3-arylpyrazoles **7-9** bearing three different substituents in good yields. The corresponding 4-amino-3-arylpyrazoles **5** were obtained by reaction of **3** with hydrazine free bases or simply by reaction of intermediates **7-9** with hydrazine. Thus a convenient synthetic route to 4-amino-3-arylpyrazoles via a simple procedure from readily available starting materials is now available. Studies on the syntheses of other heterocyclic rings from **3** are in progress.

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## References and Notes

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4. Synthesis of pyrazoles by condensation of substituted acetophenones with *N,N*-dimethylformamide dimethyl acetal followed by cyclization with hydrazine is reported: a) Lin, Y.; Lang, S. A. *J. Heterocycl. Chem.* **1977**, *14*, 345. b) Harper, R. W.; Jackson, W. T.; Larry, L.; Boyd, R. J.; Aldridge, T. E.; Herron, D. K. *J. Med. Chem.* **1994**, *37*, 2411.
5. For an example of deprotecting phthaloylamide with hydrazine, see: Sheehan, J. C.; Frank, V. S. *J. Am. Chem. Soc.* **1949**, *71*, 1856.
6. A typical procedure that illustrates the efficiency of the new synthetic method is as follows:  $\alpha$ -Phthaloylaminoacetophenone (**1a**, 1.0 mmol) was heated with *N,N*-dimethylacetamide dimethyl acetal (**2**, 1.2 eq.)<sup>8</sup> at reflux overnight. (for characterization the reaction mixture was concentrated *in vacuo* to give  $\alpha$ -phthaloylamino- $\alpha$ -*N,N*-dimethylaminomethyleneacetophenone (**3a**) as a brownish oil in quantitative yield). The resultant oil was mixed with phenylhydrazine hydrochloride (**4c HCl**, 1.1 eq.) in ethanol (10 ml) and water (1 ml) and heated to reflux for two hours. The cooled reaction mixture was purified on silica gel column with ethyl acetate-hexanes (1:1) to provide 4-phthaloylamino-1,3-diphenylpyrazole **7c** as a white solid (90% yield), m.p = 233-5°C; <sup>1</sup>H NMR (TMS/CDCl<sub>3</sub>): 7.25 (m, 5H), 7.31 (m, 5H), 7.78 (m, 2H), 7.81 (s, 1H), 7.88 (m, 2H); MS (ion spray) *m/e* 366 (M<sup>+</sup>+H); Anal. for C<sub>23</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub> (365.39), calcd. C%, 75.60; H%, 4.14; N%, 11.50. found C%, 75.95; H%, 4.27; N%, 11.88.
7. All compounds were fully characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, mass spectra. New compounds were further analyzed by microanalyses or high resolution mass spectra.
8. For less reactive acetophenone derivatives excess of **2** was used and the excess reagent was removed by evaporation *in vacuo*.