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A Convenient One-Pot Synthesis of 4-Amino-3-arylpyrazoles from α-Phthaloylaminoacetophenones

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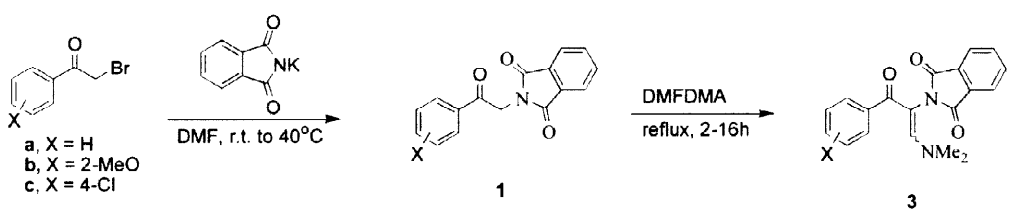
Abstract. Condensation of α-phthaloylaminoacetophenones **1a-c** with N,N-dimethylformamide dimethyl acetal afforded the novel enamines **3a-c**. Cyclization of **3** with hydrazine, alkylhydrazine or phenylhydrazine salts (**4a-d**) gave 4-phthaloylamino-3-arylpyrazoles **7-9** in high yields. Deprotection of **7-9** was accomplished with hydrazine to provide 4-amino-3-arylpyrazoles **5** in good yields.

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.[1a] Other methods include nitration of the 3-arylpyrazoles, followed by reduction of the nitro group,[1b-d] 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%.[1e] 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



a, X = H
b, X = 2-MeO
c, X = 4-Cl

1

3

α-Phthaloylaminoacetophenone derivatives **1a-c** were readily obtained by the reaction of α-bromo- or α-chloroacetophenones with phthalimide potassium salt in DMF.[2,3] 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 α-phthaloyl-aminoketone.

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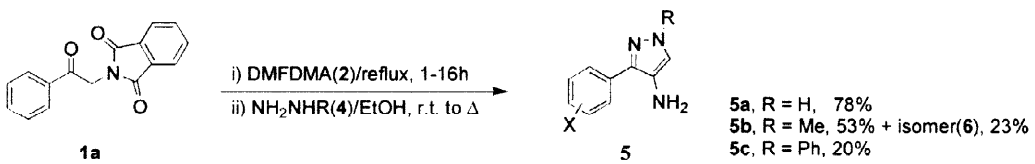
Significantly, **3** was envisioned as a pivotal intermediate for a new synthesis of heterocycles bearing an amino group. Reaction of **3a**, obtained from **1a** and DMFDMA, with 2.5 equivalents of hydrazine (**4a**) in ethanol at room temperature for one hour followed by refluxing the mixture for one 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.[4]

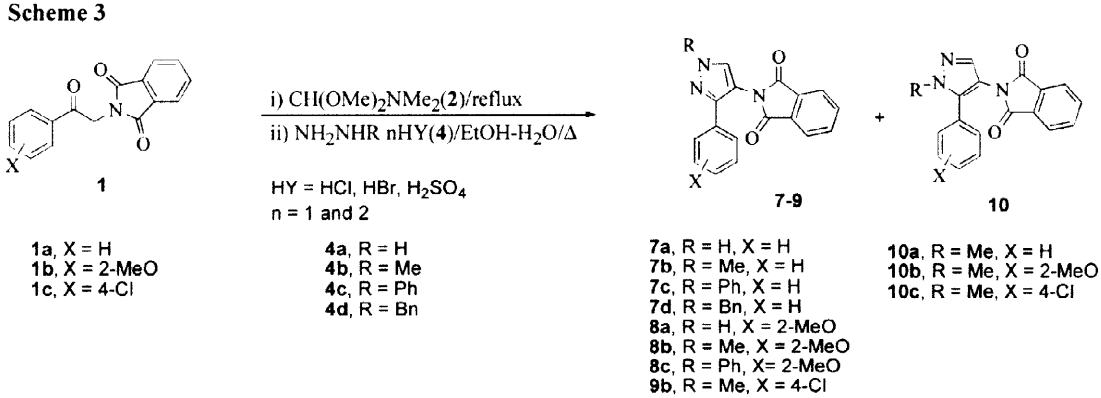
Scheme 2



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-phthaloylaminopyrazole (**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 a 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.[5] 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.[6,7]

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.

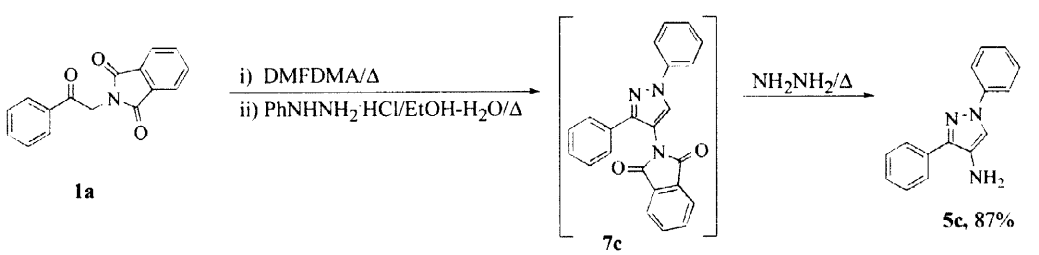
Table 1. Syntheses of 4-Aminopyrazoles **7-9** and **10** from **1a-c** and Hydrazine Salts **4**.

	Acetophenone		Hydrazine		Salt		Yield (%)[a]	
No.	**1**	X	**4**	R	**HY**	Conditions	**7-9**	**10**
1	**a**	H	**a**	H	**HBr**	reflux, 2h	87 **(7a)**	
2			**a**	H	**HCl**	reflux, 2h	86 **(7a)**	
3			**a**	H	**2HCl**	reflux, 4h	82 **(7a)**	
4			**b**	Me	**H_2SO_4**	reflux, 1h	62[b] **(7b)**	26[b] **(10a)**
5			**c**	Ph	**HCl**	reflux, 2h	90 **(7c)**	0
6			**d**	Bn	**2 HCl**	reflux, 3h	88 **(7d)**	trace [c]
7	**b**	2-MeO	**a**	H	**HBr**	reflux, 1h	73 **(8a)**	
8			**b**	Me	**H_2SO_4**	reflux, 16h	40 **(8b)**	39 **(10b)**
9			**c**	Ph	**HCl**	reflux, 16h	83 **(8c)**	0
10	**c**	4-Cl	**b**	Me	**H_2SO_4**	reflux, 1h	61 **(9b)**	20 **(10c)**

a) Isolated yield; b) Ratio was determined by ^{1}H NMR; c) Tentatively assighed based on ^{1}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



1a **7c** **5c**, 87%

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).

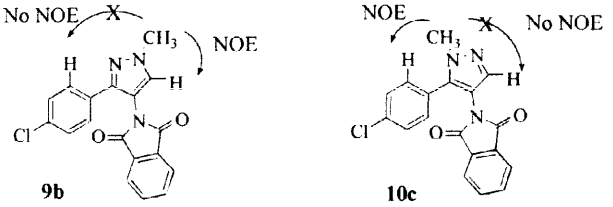


Chart 1. NOE of isomers **9b** and **10c**

In summary, condensation of α-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.

Acknowlegement: We thank Dr. Michael Schwaebe for the NOE experiments.

References and Notes

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2. a) Sheehan, J. C.; Bolhofer, W. A. *J. Am. Chem. Soc.* **1950**, *72*, 2786. b) Gabriel, S. *Chem. Ber.* **1908**, *41*, 1127.
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4. Synthsis of pyrazoles by condesation 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: α-Phthaloylaminoacetophenone (**1a**, 1.0 mmol) was heated with N,N-dimethylacetamide dimethyl acetal (**2**, 1.2 eq.)[8] at reflux overnight. (for characterization the reaction mixture was concentrated *in vacuo* to give α-phthaloylamino-α-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; ^{1}H NMR (TMS/$CDCl_3$): 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^++H); Anal. for $C_{23}H_{15}N_3O_2$ (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 ^{1}H NMR, ^{13}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*.