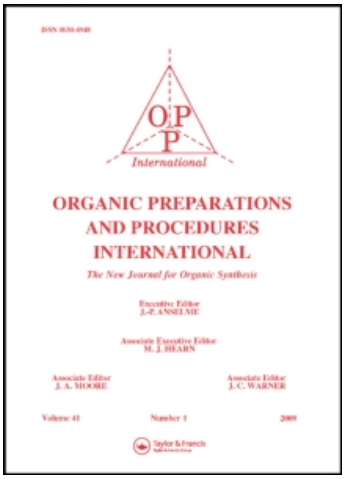

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SYNTHESIS OF PYRAZOLO[3,4-d]PYRIDAZINE, PYRAZOLO[3,4-d]PYRIMIDINE AND IMIDAZO[1,2-a]PYRIDINE DERIVATIVES USING HYDRAZONYL BROMIDES

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6. Reference 1a contains ^{1}H NMR and mass spectral data for both *E*-desmethyldoxepin (**3**) and *Z*-desmethyldoxepin (**5**).

7. The following reference contains ^{1}H NMR for 5,11-dihydro-5-[3,3-(dimethylamino)ethyl]-dibenz-[b,e][1,4]-oxazepine with a chemical shift of 5.24 for the O-CH_2 protons: H. L. Yale and F. A. Sowinski, *J. Med. Chem.*, **10**, 1022 (1967).

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SYNTHESIS OF PYRAZOLO[3,4-d]PYRIDAZINE, PYRAZOLO[3,4-d]PYRIMIDINE AND IMIDAZO[1,2-a]PYRIDINE DERIVATIVES USING HYDRAZONYL BROMIDES

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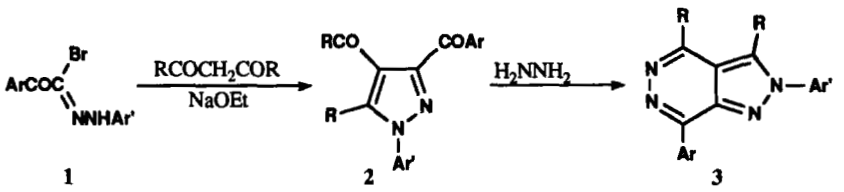
Although hydrazonyl bromides are interesting intermediates for heterocyclic synthesis,[1] very little attention was paid to the utility of hydrazonyl halides in the synthesis of the title compounds.[2] This paper describes the utility of hydrazonyl bromides in the synthesis of pyrazolo[3,4-d]pyridazine, pyrazolo[3,4-d]pyrimidine and imidazo[1,2-a]pyridine. For this purpose, we studied the reaction of hydrazonyl bromides (**1a-c**) with the sodium salt of dibenzoylmethane and of acetylacetone to give the previously unreported pyrazoles (**2**), which were converted to the pyrazolo[3,4-d]pyridazine (**3**) by condensation with hydrazine (Eq. 1).

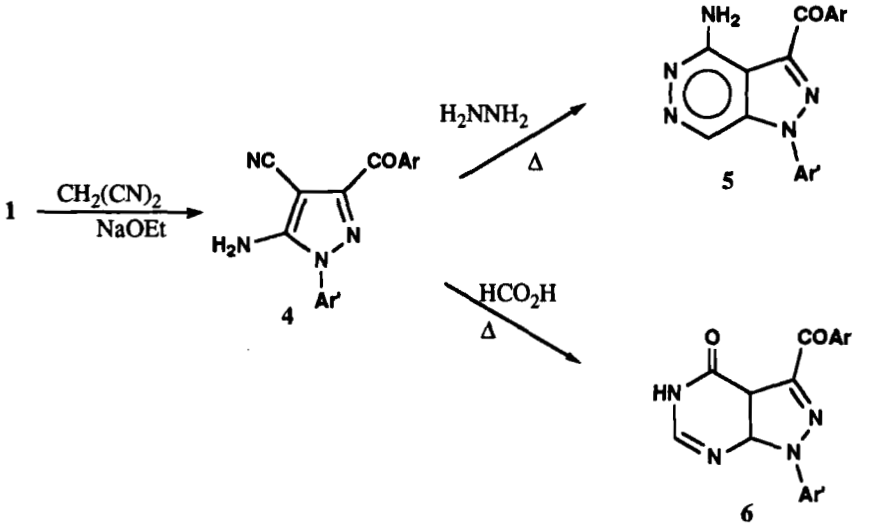
Treatment of (**1a-c**) with malononitrile in the presence of sodium ethoxide at room temperature afforded the 4-cyano-5-aminopyrazole derivatives (Eq. 2). The structure of the latter products were based on their elemental analysis, spectral data and their reactions described below. Refluxing of 4-cyano-5-aminopyrazoles (**4**) in formamide for 4 hrs gave 4-amino-1-aryl-3-(2-naphthoyl)-pyrazolo[3,4-d]pyrimidines (**5**); heating of **4** in formic acid afforded 1-aryl-3-(2-naphthoyl)pyra-



1 2 3 (1)

Ar = 2-Naphthyl a) R = C_6H_5, Ar = C_6H_5; b) R = C_6H_5, Ar' = 4-$CH_3C_6H_4$
c) R = C_6H_5, Ar' = 4-ClC_6H_4; c) R = CH_3, Ar = 4-$CH_3C_6H_4$; e) R = CH_3, Ar' = 4-ClC_6H_4

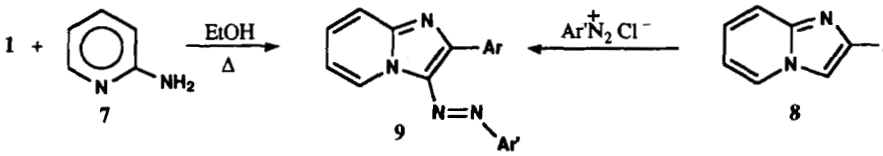
zolo[3,4-d]pyrimidinone **6**. The structures of **5** and **6** were based on their elemental analysis and spectral data (Table 1).



(2)

Ar = 2-Naphthyl a) Ar' = C_6H_5; b) Ar' = 4-$CH_3C_6H_4$; c) Ar' = 4-ClC_6H_4

The behavior of **1** is different from that of N-phenylsulfonylhydrazonyl chloride towards 2-aminopyridine (**7**). It was reported that N-phenylsulfonylbenzohydrazonyl chloride reacts with 7 to give triazolo[3,4-a]pyridine derivative.[3] Indeed, the reaction of **1a** with 1.2 equivalent of **7** in ethanol at reflux gave a single product (as evidenced by TLC) in 70% yield. On the basis of its elemental analysis, it was assigned the structure of 2-naphthyl-3-arylazoimidazo[1,2-a]pyridine (**9a**). Furthermore, coupling of 2-naphthylimidazo[1,2-a]pyridine (**8**) with N-nitrosoacetanilide or diazotized aniline in ethanol yielded a product identical in all respects (IR, ^1H NMR, mp.) with **9a**. Similarly, **1b** and **1c** react with **7** to give **9b** and **9c**, respectively (Eq. 3).



(3)

Ar = 2-Naphthyl a) Ar' = C_6H_5; b) Ar' = 4-$CH_3C_6H_4$; c) Ar' = 4-ClC_6H_4

TABLE 1. Compounds **2-6, 9**

Comp.	mp. °C	Yield %	NMR ($CDCl_3$) δ ppm	Analysis Calcd (Found) C	H	N
2a	151	87	7.15-8.36 (m, 21H), 8.85 (s, 1H).	82.82 (82.63)	4.63 (4.44)	5.85 (5.81)
2b	167	85	2.43 (s, 3H), 7.12-8.35 (m, 20H), 8.86 (s, 1H).	82.90 (82.64)	4.91 (4.90)	5.68 (5.81)
2c	165	86	7.15-8.25 (m, 20H), 8.86 (s, 1H).	77.25 (77.15)	4.12 (4.03)	5.46 (5.43)
2d	116	90	2.23 (s, 3H), 2.27 (s, 3H), 7.20-8.22 (m, 10H), 8.85 (s, 1H).	78.23 (78.50)	4.47 (4.75)	7.60 (7.46)
2e	126	88	2.42 (s, 3H), 2.59 (s, 3H), 7.15-8.17 (m, 10H), 8.85 (s, 1H).	71.03 (70.94)	4.40 (4.61)	7.20 (7.04)
3a	255	90	7.25-8.53 (m, 21H), 8.90 (s, 1H).	83.52 (83.70)	4.67 (4.44)	11.80 (11.64)
3b	304	99	2.40 (s, 1H), 7.05-8.75 (m, 20H), 9.25 (s, 1H).	83.58 (83.70)	4.95 (4.91)	11.46 (11.07)
3c	292	86	7.15-8.25 (m, 20H), 9.05 (s, 1H).	83.32 (83.21)	4.44 (4.32)	13.77 (13.54)
3d	250	88	2.45 (s, 3H), 2.75 (s, 3H), 2.90 (s, 3H), 7.25-8.90 (m, 10H), 9.35 (s, 1H).	79.09 (79.00)	5.53 (5.21)	15.37 (15.14)
3e	288	85	2.75 (s, 3H), 2.85 (s, 3H), 7.25-8.75 (m, 10H), 9.25 (s, 1H).	71.74 (71.57)	4.45 (4.43)	14.55 (14.34)
4a	174	75	4.85 (s, 2H), 7.26-8.25 (m, 11H), 9.06 (s, 1H).	74.54 (74.28)	4.16 (4.10)	16.55 (16.51)
4b	216	73	2.46 (s, 3H), 4.78 (s, 2H), 7.26-8.38 (m. 10H), 9.05 (s, 1H).	74.98 (75.02)	4.57 (4.68)	15.89 (16.10)
4c	260	73	4.70 (s, 2110, 7.26-8.25 (m, 10H), 8.78 (s, 1H).	67.64 (67.60)	3.51 (3.74)	15.02 (15.13)
5a	250	70	6.05 (s, 2H), 7.25-8.26 (m, 12H), 9.07 (s, 1H).	72.31 (72.44)	4.13 (3.80)	19.16 (19.00)
5b	221	71	2.48 (s, 3H), 6.08 (s, 3H), 7.20-8.37 (m, 11H), 9.05 (s, 1H).	72.80 (73.20)	4.51 (4.60)	18.45 (18.30)
5c	264	70	5.77 (s, 2H), 7.20-8.26 (m, 11H). 9.04 (s, 1H)	66.07 (65.94)	3.53 (3.66)	17.51 (17.73)
6a	256	73	7.35-8.37 (m, 13H), 9.13 (s, 1H).	72.12 (72.50)	3.85 (3.76)	15.29 (15.11)
6b	274	71	2.40 (s, 3H), 7.36-8.35 (m, 12H), 8.79 (s, 1H).	72.61 (72.40)	4.23 (4.32)	14.72 (14.53)
9a	162	85	7.20-8.28 (m, 15H), 9.00 (s, 1H).	79.28 (78.98)	4.62 (4.81)	16.08 (16.22)

EXPERIMENTAL SECTION

Melting points were determined on MEL-TEMP II melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer. ^{1}H NMR spectra were measured in $CDCl_3$ with Varian T60-A spectrometer; chemical shifts are in ppm (δ) from internal TMS. Microanalysis were performed at the microanalytical unit of the University of Cairo, Giza, Egypt. 1-(2-Naphthoyl)methyl-2-dimethylsulfonium bromide[4] and N-aryl-C-(2-naphthoyl)methanohydrazonyl bromides were prepared as previously described.[4]

N-Aryl-C-(2-naphthoyl)methanohydrazonyl bromides (1a-c).- A solution of 1-(2-naphthoyl)-methyl-2-dimethylsulfonium bromide (3.1 g, 10 mmoles)[4] and the N-nitrosoacetanilide (15 mmoles) in ethanol (50 mL) was stirred for 24 hrs at room temperature. The mixture was diluted with water and the solid was collected and crystallized from N,N-dimethylformamide to give **1a-c**; **1a**, mp. 150°, lit.[4] mp. 150°, **1b**, 167°, lit.[4] mp. 167° and **1c**, mp. 210°, lit.[4] mp. 210°.

1,5-Diaryl-3-(2-naphthoyl)-4-acylpyrazoles (2). General Procedure.- To an ethanolic sodium ethoxide solution [prepared from sodium metal (0.1 g, 0.005 g atom) and absolute ethanol (30 mL)], dibenzoylmethane or acetylacetone (5.0 mmoles) was added with stirring. To the resulting solution, the appropriate hydrazonyl bromide (5.0 mmoles) was added at room temperature.The mixture was stirred for 6 hrs, during which the bromide dissolved and the crude pyrazoles precipitated. The latter were collected, washed with water, dried and crystallized from acetic acid. The pyrazole derivatives **2** formed together with their physical constants are given in Table 1.

3-(2-Naphthyl)pyrazolo[3,4-d]pyridazine derivatives (3). General Procedure.- The appropriate pyrazole derivative **3** (5.0 mmoles) in ethanol (30 ml) and hydrazine hydrate (0.75 mL, 15.0 mmoles) were refluxed for 4 hrs, during which the pyrazole dissolved and the corresponding pyrazolopyridazine derivative **3** was precipitated. The latter products **3** were collected, washed with water and crystallized from dimethylformamide (Table 1).

1-Aryl-3-(2-naphthoyl)-4-cyano-5-aminopyrazoles (4).- These compounds were prepared by the same method described for the preparation of compounds **2** using malononitrile as active methylene compound. The crude products were collected, washed with water, dried and crystallized from acetic acid (Table I).

1-Aryl-4-amino-3-(2-naphthoyl)pyrazolo[3,4-d]pyrimidines (5).- A mixture of 1-aryl-3-(2-naphthoyl)-4-cyano-5-aminopyrazole (**4**) (5.0 mmoles) and formamide (15 mL) was refluxed for 4 hrs. The solution was cooled and poured on cold water. The solid that precipitated was collected, dried and crystallized from dimethylformamide to give **5** (Table 1).

1-Aryl-3-(2-naphthoyl)pyrazolo[3,4-d]pyrimidinones (6).- Amixture of **4** (5.0 mmoles) and formic acid (20 mL) was refluxed for 1 hr. The solution was cooled and poured on water. The solid that precipitated was collected and crystallized from dimethylformamide to give **6** (Table 1).

2-(2-Naphthyl)-3-arylazoimidazo[1,2-a]pyridines (9).- Method A.- A mixture of the appropriate hydrazonyl bromides **1** (5.0 mmoles) and 2-aminopyridine (**7**) (0.56 g, 6.0 mmoles) in ethanol (20 mL) was refluxed for 4 hrs and then cooled. The precipitated solid was collected, washed with water

and crystallized from ethanol to give **9** (Table 1).

Method B. Coupling of 8 with Diazonium Salts.- A solution of **8** (1.2 g, 5.0 mmoles) in ethanol was stirred with sodium acetate (0.9 g, 10.0 mmoles) and the mixture was stirred in an ice to 0-5°. A cold aqueous solution (0-5°) of the diazonium salt[6] (5.0 mmoles) was added dropwise with stirring over 45 min. After addition, the mixture was stirred for further 30 min and then left for 2 hrs in an ice box. The precipitated product was collected, washed with water and crystallized from ethanol to afford compounds identical in all respects (IR, ^{1}H NMR, mp.) with compounds **9**.

Method B. Coupling of 8 with N-Nitrosoarylacetamides.- To a solution of **8** (1.2 g, 5.0 mmoles) in ethanol (50 mL) was added the appropriate N-nitrosoarylacetamides[7] (5.0 mmoles). The reaction mixture was warmed slightly and shaken to effect complete dissolution of the reactants, then stirred for 2 hrs. The precipitated crystalline product was collected, washed with methanol and crystallized from ethanol to afford compounds identical in all respects (IR, ^{1}H NMR, mp.) with compounds **9**.

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