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Aspects of the Chemistry of Functionalized 1-Phenylpyrazoles Available from 1,2-Diaza-1,3-butadienes and 2-Phenylazo-1,3-dicarbonyl Compounds

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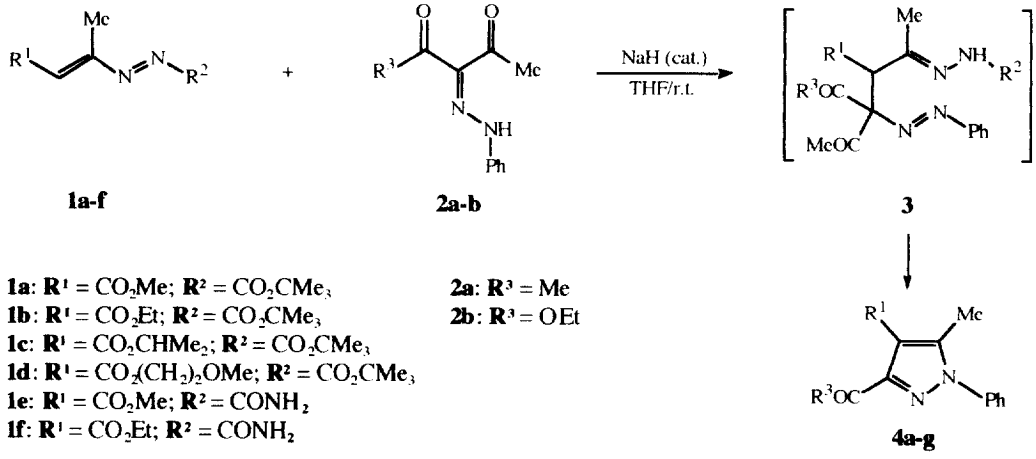
Abstract: In the presence of sodium hydride, treatment of 1,2-diaza-1,3-butadienes with 2-phenylazo-1,3-dicarbonyl compounds gave rise to functionalized 1-phenylpyrazole derivatives in good to excellent yields. Pyrazolo[3,4-*d*]1,6-dihydropyridazin-6(2*H*)-one derivatives were obtained by the reaction of 5-methyl-4-methoxycarbonyl-3-acetyl-1-phenylpyrazole with different hydrazines.

1,2-Diaza-1,3-butadienes are powerful tools in organic synthesis, particularly in the construction of heterocyclic rings.[1–4]

We report here the simple and high-yielding preparation of functionalized 1-phenylpyrazole derivatives from 1,2-diaza-1,3-butadienes and 2-phenylazo-1,3-dicarbonyl compounds. In the presence of sodium hydride in catalytic amount, 1,2-diaza-1,3-butadienes **1a-f** easily react in tetrahydrofuran at room temperature with 3-phenylazo-2,4-pentanedione (**2a**) or ethyl 2-phenylazoacetoacetate (**2b**) to afford directly 1-phenylpyrazole derivatives in good to excellent yields. Faster reactions and better yields were observed for 1-alkoxycarbonyl-1,2-diaza-1,3-butadienes **1a-d**, than for 1-aminocarbonyl-1,2-diaza-1,3-butadienes **1e-f** (see Scheme 1 and Table 1).[5]

In these reactions, the 1,2-diaza-1,3-butadienes provide the C(4)-C(5) part of the phenylpyrazoles with the 2-phenylazo-1,3-dicarbonyl compounds providing the N(1)-N(2)-C(3).[3] This reaction occurs probably by means of a preliminary 1,4-addition of the deprotonated phenylazodicarbonyl compounds to the 1,2-diaza-1,3-



1a: $R^1 = CO_2Me$; $R^2 = CO_2CMe_3$
1b: $R^1 = CO_2Et$; $R^2 = CO_2CMe_3$
1c: $R^1 = CO_2CHMe_2$; $R^2 = CO_2CMe_3$
1d: $R^1 = CO_2(CH_2)_2OMe$; $R^2 = CO_2CMe_3$
1e: $R^1 = CO_2Me$; $R^2 = CONH_2$
1f: $R^1 = CO_2Et$; $R^2 = CONH_2$

2a: $R^3 = Me$
2b: $R^3 = OEt$

Scheme 1

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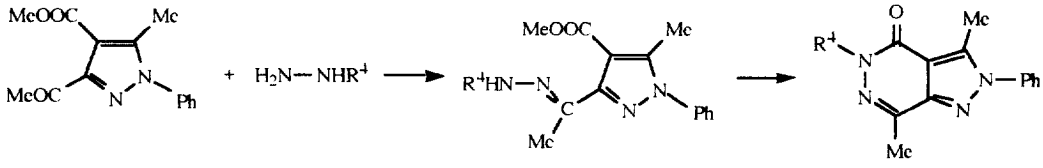
Table 1. Yields, melting points, and reaction times of 1-phenylpyrazoles **4a-g**.

Reactants		Products	Yields[a] (%)	Mps[b] (°C)	Reaction times (h)
1a	**2a**	**4a**	82	71-73	0.5
1b	**2a**	**4b**	74	43-45	0.5
1c	**2a**	**4c**	61	58-60	0.5
1d	**2a**	**4d**	65	38-40	0.5
1a	**2b**	**4e**	84	oil	0.3
1b	**2b**	**4f**	89	oil	0.4
1d	**2b**	**4g**	73	oil	0.3
1e	**2a**	**4a**	44	71-73	15.0
1f	**2a**	**4b**	41	43-45	14.0
1e	**2b**	**4e**	45	oil	11.5
1f	**2b**	**4f**	47	oil	13.0

[a]Yield of pure isolated products. [b]Melting points are uncorrected.

butadiene substrates producing the hydrazone intermediate **3**. Intramolecular nucleophilic attack of the Ph-N nitrogen atom on to the carbon atom of the >C=N- hydrazonic function determines the closure of the five-membered heterocycle. The loss of the hydrazino residue and acyl group leads to the 1-phenylpyrazole derivatives **4a-g**.

In order to confirm their structures and to exemplify the synthetic usefulness of the 1-phenylpyrazoles **4a-g**, we treated 5-methyl-4-methoxycarbonyl-3-acetyl-1-phenylpyrazole **4a** with different hydrazine derivatives **5a-d** producing pyrazolo[3,4-*d*]1,6-dihydropyridazin-6(2*H*)-ones **7a-d**. In the case of the reaction between **4a** and *p*-toluensulfonylhydrazine **5d**, the hydrazone intermediate **6d** was isolated in a yield of 91%. This intermediate was converted into the corresponding pyrazolo[3,4-*d*]1,6-dihydropyridazin-6(2*H*)-one **7d** by treatment with potassium hydroxide in methanol under reflux. In the remaining cases, the pyrazolo[3,4-*d*]1,6-dihydropyridazin-6(2*H*)-ones **7a-c** were produced directly (see Scheme 2 and Table 2).[5]



4a **5a-d** **6d** **7a-d**

Scheme 2

In conclusion, this paper reports an unusual reaction of the azo-ene system of 1,2-diaza-1,3-butadienes, as well as a singular behaviour of 1,3-dicarbonyl compounds co-activated by an azo group. Furthermore, this

method offers a new, mild, simple, and convenient entry to 1-phenylpyrazole and pyrazolo[3,4-*d*]pyridazin-6(2*H*)-one derivatives which are of great interest both as products and intermediates in organic,[3,4,6] biological,[7] pharmaceutical,[8] analytical,[9] and agricultural chemistry.[4d,10]

Table 2. Yields, melting points, and reaction times of pyrazolo[3,4-*d*]1,6-dihydropyridazin-6(2*H*)-ones **7a-d**.

4	5	R^4	7	Yields[a] (%)	Mps[b] (°C)	Reaction times (h)
4a	**5a**	H	**7a**	77	185-187	10.0
4a	**5b**	$CH_2CH_2CH_3$	**7b**	72	110-112	6.0
4a	**5c**	4-$CH_3OC_6H_4$	**7c**	61	136-138	4.0
4a	**5d**	4-$CH_3C_6H_4SO_2$	**7d**	57	143-145	15.0

[a]Yield of pure isolated products. [b]Melting points are uncorrected.

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(5) General procedure for the synthesis of 1-phenylpyrazoles **4a-g**: To a stirred solution of 3-phenylazo-2,4-pentanedione **2a** or ethyl 2-phenylazoacetoacetate **2b** (1.0 mmol) in tetrahydrofuran (10 ml) was added sodium hydride (0.3 mmol) and the suspension was allowed to react at room temperature for 10 min under magnetic stirring. A solution of 1,2-diaza-1,3-butadienes **1a-f** (2.8 mmol) in tetrahydrofuran (5 ml) was added dropwise and the reaction was allowed to react at room temperature for further 0.5-3.5 h under magnetic stirring. The solvent was evaporated under reduced pressure and the crude reaction product was purified by column chromatography (cyclohexane-ethyl acetate mixtures) affording the pure compounds **4a-g**. The products can be further purified by crystallization from diethyl ether-petroleum ether (30-60 °C).

General procedure for the synthesis of pyrazolo[3,4-*d*]1,6-dihydropyridazin-6(2*H*)-ones **7a-d**: To a stirred solution of 1-phenylpyrazole **4a** (1 mmol) in methanol (10 ml) was added the hydrazine derivatives **5a-d** (1 mmol) in methanol (10 ml) and the reaction was allowed to react at room temperature for 4 h under magnetic stirring. The solvent was evaporated under reduced pressure and the crude reaction product was purified by column chromatography (cyclohexane-ethyl acetate mixtures) affording the pure compounds **7a-c.** The products can be further purified by crystallization from ethyl acetate-petroleum ether (30-60 °C). In the case of the reaction between 1-phenylpyrazole **4a** and *p*-toluensulfonyldrazine **5d**, the hydrazone intermediate **6d** was isolated in 91% yield. To a solution of **6d** (1 mmol) in methanol (15

ml) was added KOH (1 mmol) in methanol (15 ml). The reaction mixture was heated under reflux for 20 h. The solvent was evaporated under reduced pressure and the crude reaction product was purified by column chromatography (cyclohexane-ethyl acetate mixtures) affording the pure compounds **7d**. The product can be further purified by crystallization from methanol-diethyl ether.

IR, MS, ^{1}H- and ^{13}C-NMR spectra, as well as elemental analysis data of all 1-phenylpyrazole **4a-g** and pyrazolo[3,4-*d*]1,6-dihydropyridazin-6(2*H*)-ones **7a-d** are in agreement with the structures reported. For **4a**: mp 71-73 °C; IR (nujol) 1717, 1696, 1596 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3 H, CH_3), 2.61 (s, 3 H, CH_3), 3.67 (s, 3 H, OCH_3), 7.30-7.55 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$) δ 11.6 (CH_3), 28.4 (CH_3), 51.8 (OCH_3), 112.3 (C4), 125.6, 129.2, 129.4 and 150.5 (Ph), 138.2 and 147.2 (C3 and C5), 164.0 (COO), 194.2 (CO); MS *m/e* (relative intensity) 258 (M^+, 80), 243 (100). **6d**: mp 136-138 °C; IR (nujol) 3140, 1717, 1594 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.17 (s, 3 H, CH_3), 2.38 (s, 6 H, 2 CH_3), 3.65 (s, 3 H, OCH_3), 7.38 (d, 2 H, *J*=8.1 Hz, Ar), 7.53 (m, 5 H, Ar), 7.73 (d, 2 H, *J*=8.1 Hz, Ar), 10.66 (b s, 1 H, NH, D_2O exch.); ^{13}C NMR (DMSO-d_6) δ 11.3 (CH_3), 16.0 (CH_3), 20.9 (CH_3), 51.2 (OCH_3), 111.1 (C4), 125.3, 127.4, 128.7, 129.2, 129.3, 136.3, 148.4 and 149.5 (Ar), 138.2 (C=N), 142.8 and 143.2 (C3 and C5), 163.9 (COO); MS *m/e* (relative intensity) 426 (M^+, 23), 271 (100). **7d**: mp 128-130 °C; IR (nujol) 1699, 1596 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.30 (s, 3 H, CH_3), 2.42 (s, 3 H, CH_3), 2.67 (s, 3 H, CH_3), 7.12 (d, 2 H, *J*=8.0 Hz, Ar), 7.50 (d, 2 H, *J*=8.0 Hz, Ar), 7.65 (m, 5 H, Ar); ^{13}C NMR (DMSO-d_6) δ 11.4 (CH_3), 16.6 (CH_3), 20.7 (CH_3), 112.1 (C of fused rings), 125.5, 126.9, 128.0, 128.9, 129.4, 137.5, 145.3 and 145.7 (Ar), 138.2, 139.0, 140.8 and 159.5 (C of fused rings); MS *m/e* (relative intensity) 394 (M^+, 3), 239 (100).

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