Free-Radical Reactions of Diazonium Salts with α,β-Unsaturated Carbonyl Compounds. A New Synthesis of 1,4-Diarylpyrazole Derivatives

Attilio Citterio, Massimo Ramperti and Elena Vismara*

Istituto di Chimica del Politecnico, P.za L. da Vinci 32, 20133 Milano, Italy

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Free-radical decomposition of diazonium salts catalyzed by titanous or titanous and ferrous salts in the presence of β-substituted α,β-unsaturated carbonyl compounds leads to 1,4-diarylpyrazole derivatives. The reaction occurs *via* an intermediate azo compound (**1**), which can be reduced by the metal salt or can be isolated and hydrogenated to pyrazole derivatives.

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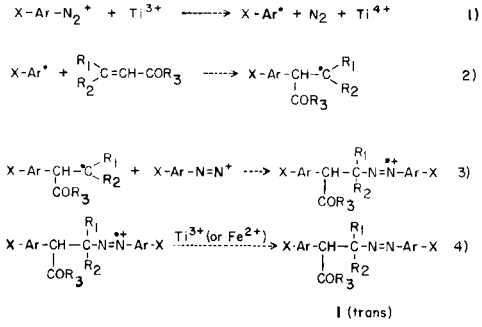
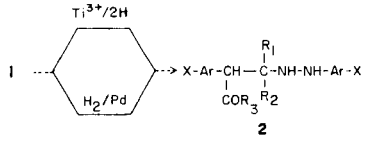
Recently, we have reported (1) an unusual reaction of diazonium salts and 4-methyl-3-penten-2-one in presence of mono electronic reducing agents. Now, we wish to report the application of this reaction for the synthesis of a variety of 1,4-diarylpyrazole derivatives starting from a β-substituted α,β-unsaturated carbonyl compound and a diazonium salt. This is a general reaction for the synthesis of these classes of compounds.

We suggest the following reaction mechanism (Scheme 1).



Scheme 1



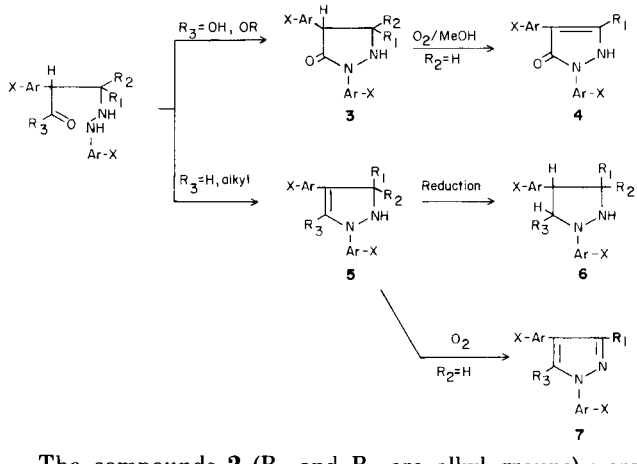
a; $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = OH$, X = *p*-Cl
b; $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = OH$, X = *p*-OCH_3
c; $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = OH$, X = H
d; $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = CH_3$, X = *p*-Cl
e; $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = CH_3$, X = H
f; $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = CH_3$, X = *p*-OCH_3
g; $R_1 = CH_3$, $R_2 = H$, $R_3 = OCH_3$, X = *p*-Cl
h; $R_1 = CH_3$, $R_2 = H$, $R_3 = OCH_3$, X = H
i; $R_1 = Ph$, $R_2 = H$, $R_3 = CH_3$, X = H
m; $R_1 = Ph$, $R_2 = H$, $R_3 = CH_3$, X = *p*-Br

Titanous(III) ions initiate the reaction by generating an aryl radical (equation 1), which adds to the α-position of α,β-unsaturated carbonyl compound (equation 2) (1). The resulting free-radical reacts with a second diazonium ion to produce an azo-radical cation (equation 3). The latter is then reduced by titanous or ferrous ions to *trans*-azo-derivative **1** (equation 4).

Compound **1** is the key intermediate in this type of synthesis and was isolated and subsequently reduced by catalytic hydrogenation (2) to arylhydrazine derivatives **2**, which in turn underwent cyclization to pyrazole derivatives. The reductive cyclization can also be carried out in one-step when there is an excess of titanous(III) salt (3,4).

Depending upon the nature of R_3 and workup conditions, different pyrazole derivatives were obtained: when R_3 was OH or OR, pyrazolinones **3** and pyrazolones **4** were obtained by working up the reaction mixture under nitrogen or oxygen atmosphere, respectively; whereas when R_3 was hydrogen or an alkyl group, pyrazolines **5** were obtained as intermediates which were either reduced to pyrazolidines **6**, or oxidized to pyrazoles **7** (Scheme 2).

Scheme 2



The compounds **2** (R_1 and R_2 are alkyl groups) were easily oxidized by atmospheric oxygen to azo compounds **1** and should be handled under nitrogen. In some cases the cyclized products were obtained under the reaction conditions along with low amounts of hydrazine **2** (for example in the preparation of the compound **7m** following

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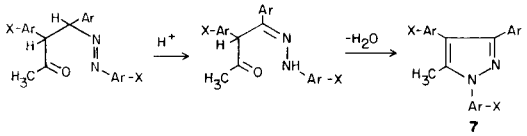
Table I

1,4-Diarylpyrazole Derivatives by Ti(III) Decomposition of Diazonium Salts ($X\text{-}ArN_2^+$) in the Presence of α,β-Unsaturated Carbonyl Compounds

Compound No.	Procedure	Yield %	Mp (°C)	Molecular Formula	Analyses Calcd./Found % C	H	N	Ir (cm^{-1}) ν max
3a	A	40	170	$C_{17}H_{16}N_2OCl_2$	60.91	4.81	8.36	3270 (NH), 1690 (C=O)
					61.00	4.90	8.40	
	B	53						
3b	A	30	129	$C_{19}H_{22}N_2O_3$	69.94	6.80	8.58	3200 (NH), 1695 (C=O)
					70.01	6.91	8.49	
	B	43						
3c	A	45	120	$C_{17}H_{16}N_2O$	76.66	6.81	10.52	3210 (NH), 1690 (C=O)
					76.75	6.90	10.48	
	B	41						
6d	A	45	84	$C_{18}H_{20}N_2Cl_2$	64.48	6.01	8.36	3260 (NH)
					64.60	6.08	8.35	
6e	A	45	79	$C_{20}H_{26}N_2O_2$	73.59	8.03	8.58	3250 (NH)
					73.61	8.09	8.55	
6f	A	38	72	$C_{18}H_{22}N_2$	81.16	8.33	10.52	3250 (NH)
					81.10	8.27	10.60	
4g	A	25	230	$C_{16}H_{12}N_2OCl_2$	60.21	3.79	8.78	1600-1630 (C=O)
					60.04	3.81	8.85	
4h	A	22	196	$C_{16}H_{14}N_2$	82.02	6.02	11.96	
					81.98	6.04	11.89	
	B	20						
7i	B	18	150	$C_{22}H_{18}N_2$	85.13	5.85	9.03	
					85.17	5.91	9.06	
7m	B	28	186	$C_{22}H_{16}N_2Br_2$	9.03	3.44	5.98	
	A	15			8.91	3.38	5.84	

the procedure B). The formation of these products may be explained by tautomerization of the azo compound **1** to hydrazone followed by cyclization (Scheme 3) in the acidic

Scheme 3



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medium used (5). Table I lists 1,4-diarylpyrazoles prepared in this study.

Although the yields ranged from moderate to good (20-80%), the method offers a new possibility for the synthesis of 1,4-diarylpyrazole derivatives, since the experimental conditions are simple and starting materials are inexpensive. The yields are higher when the β-position is disubstituted (*i.e.*, with 4-methyl-3-penten-2-one, 4-methyl-3-butenoic acid or its methyl ester, *etc.*) than when it was monosubstituted. The following reasons may be offered for such a behaviour: firstly, the addition of alkyl radical takes place predominantly at the α-position, due to steric hindrance, in the case of β-disubstituted olefins; whereas β-monosubstituted olefins are attacked on both α- and β-positions to give two products but only the α-adduct can give rise to pyrazole derivatives (6). Secondly, sterically hindered tertiary alkyl radicals appear to add to diazonium ions faster than primary and secondary alkyl radicals, owing to their greater nucleophilicity (7). No pyrazole derivatives are formed when the β-position is unsubstituted because the addition of the aryl radical takes place exclusively at the β-position [reductive arylation (8)].

Preliminary experiments indicate that a similar synthesis of the pyrazole nucleus can be obtained with other β-ketoalkyl radical sources (iodine abstraction from β-iodocarbonyl compounds, 1,4-dicarbonylperoxide decomposition, *etc.*).

EXPERIMENTAL

Melting points were determined on a koffler apparatus, and are uncorrected. Infrared spectra were obtained in Nujol on a Perkin Elmer E 177 spectrometer. Nmr spectra were run on a Varian A 90 instrument using TMS as internal standard in deuterochloroform or DMSO-d_6. Mass spectra (ms) were obtained on a Hitachi-Perkin Elmer RMU 6D spectrometer using an all glass inlet system operating at 200°.

All reactions were monitored by tlc using silica gel plates 60 F 254 (Merck). Column chromatographic separations were carried out with silica gel (0.06-0.04) from Merck.

Organic extracts were dried over sodium sulphate and evaporated *in vacuo*. All substituted anilines (Carlo Erba) were purified by distillation on zinc pellets or by crystallization.

Solutions of titanous(III) chloride (15% w/w in acidic water) were supplied from Carlo Erba and standardized against cerium(IV) 0.1*N* solution. Solutions or arenediazonium chloride (or sulphate) were prepared by dissolving the substituted aniline (0.01 mole) in 36% hydrogen chloride (7 ml) or 30% sulphuric acid (18 ml) at 80°, cooling at 0° and

adding under stirring a cold solution of sodium nitrite (0.76 g, 0.011 mole) in water (13 ml or 8 ml, respectively).

All unsaturated carbonyl compounds were supplied by Fluka and were used as received. All the solvents and the solutions used were flushed with nitrogen for 10 minutes before use.

1,4-Bis(4-chlorophenyl)-3,3-dimethyl-5-pyrazolinone (**3a**).

Procedure A.

A cold solution (0-5°) of *p*-chlorobenzenediazonium chloride (20 ml, 0.05*M*) was added slowly (1 hour) to a solution of titanous chloride (23 ml, 0.022 mole), 4-methyl-3-pentenoic acid (2.0 g, 0.021 mole) in methanol (30 ml) at 0° under a nitrogen atmosphere. The reaction mixture was stirred until the evolution of nitrogen ended. The solid **2a**, which separated during the reaction, was filtered, washed with water and dried (739 mg, 42%), mp 149-150° dec.; ir: ν max 2200-2900 cm^{-1} (broad, NH-NH), 1750 (C=O); nmr (deuteriochloroform): δ 1.3 (s, 3H, CH_3), 1.8 (s, 3H, CH_3), 4.72 (s, 1H, C*H*-CO), 7.3-7.6 (m, 8H, Ar), 11.0 (broad, 3H, deuterium oxide exchangeable); ms: m/e 334 ($M^{\cdot+}$, 2%), 182, 170, 126, 125, 99, 87 (spectra identical with those of the compound **3a**).

The compound **2a** was dissolved in methanol (20 ml) and refluxed under nitrogen for 1 hour with basic alumina (2 g) (in order to accelerate the cyclization). After filtration and cooling, the product **3a** was obtained (668 mg, 95% from **2a**, 40% based on starting amine); nmr: δ 0.85 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.7 (s, 1H, CH), 4.6 (broad, 1H, NH), 7.74 (m, 6H, Ar), 7.9 (d, 2H, aromatic ortho-hydrogens); ms: m/e 334 ($M^{\cdot+}$, 2%), 182, 170, 126, 125, 99, 89).

Procedure B.

Titanous chloride (6 ml, 6.3 mmoles) was added dropwise to a cold (0°) and stirred solution of *p*-chlorobenzenediazonium sulphate (20 ml, 0.05*M*), ferrous sulphate (6.1 g, 22 mmoles) and 4-methyl-3-pentenoic acid (2.0 g, 0.021 mole) in water (10 ml) and acetic acid (30 ml) solution at such a rate that only a small excess of titanous ion was present during the reaction. Yellow crystals were separated, washed with water, dried and recrystallized from water/methanol (0.946 mg, 53%), mp 129-130°; uv: ν max 1700 (C=O), 2400-3200 (broad, COOH), 1080 and 1110 (C-O-); nmr (deuteriochloroform): δ 1.28 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 4.08 (s, 1H, C*H*-N=N), 7.2-7.7 (m, 8H, Ar), 11.25 (broad, 1H, OH); ms: m/e 350 ($M^{\cdot+}$, 0.2%), 332, 211, 183, 165, 153, 139, 125, 111, 59; uv: ν max (log ϵ) 223 (4.35), 257 (3.8), 271 (4.17), 410 (2.3).

Anal. Calcd. for $C_{17}H_{16}Cl_2N_2O_2$: C, 58.13; H, 4.59; N, 7.98. Found: C, 58.21; H, 4.65; N, 8.05.

The compound **1a** (1 g), dissolved in diethyl ether (60 ml), was hydrogenated with 0.150 g of 10% palladium on carbon at room temperature and atmospheric pressure. Filtration of palladium on carbon and evaporation of the solvent give 0.940 g (98%) of **3a**.

1,4-Bis(4-methoxyphenyl)-3,3-dimethyl-5-pyrazolinone (**3b**).

This compound was prepared as described for **3a** following procedure A. The solution was maintained at 10° and the reaction was run for 3 hours; nmr (deuteriochloroform): δ 0.82 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 3.64 (s, 1H, CH), 3.8 (s, 6H, OCH_3), 4.5 (broad, 1H, NH), 6.8-7.3 (m, 6H, Ar), 7.85 (d, 2H, Ar); ms: m/e 326 ($M^{\cdot+}$, 64%), 270 (31), 251 (58), 226 (21), 178 (100), 166 (10), 163 (17), 162 (23), 148 (13), 147 (13), 142 (8), 135 (20), 122 (54), 121 (88), 108 (25), 91 (25).

1,4-Diphenyl-3,3-dimethyl-5-pyrazolinone (**3c**).

Compound **3c** had nmr (deuteriochloroform): δ 0.9 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 3.68 (s, 1H, CH), 4.7 (broad, 1H, NH), 7.0-7.5 (m, 8H, Ar), 7.95 (d, 2H, Ar); ms: m/e 266 ($M^{\cdot+}$, 76%), 251 (5), 210 (7), 181 (7), 182 (9), 148 (100), 147 (12), 133 (23), 132 (21), 117 (13), 107 (21), 106 (16), 99 (9), 92 (15), 91 (23), 77 (19).

1,4-Bis(4-chlorophenyl)-3,3,5-trimethylpyrazolidine (**6d**).

A cold solution of *p*-chlorobenzenediazonium chloride (20 ml, 1.0*M*) was added to a stirred solution of titanous chloride (40 ml, 42 mmoles) and 4-methyl-3-penten-2-one (7 ml) in methanol (45 ml) under nitrogen at 0°. Evolution of nitrogen gas started immediately and completed in 0.5 hour. The yellow crystals of **1d**, were collected by suction, washed with water and crystallized from methanol/water, giving **1d** (1.78 g, 51%), mp 97-98°; uv: ν max (cm^{-1}) 1705, 1680 (C=O); nmr (deuteriochloroform): δ 1.2 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.1 (s, 3H, $COCH_3$), 4.4 (s, 1H, C_h), 7.2-7.7 (m, 8H, Ar); ms: m/e 348 ($M^{\cdot+}$, small), 209, 166, 139, 122, 89, 75, 43; uv: ν max (log ϵ) 223 (4.36), 271 (4.18), 410 (2.3).

The intermediate **1d** was hydrogenated in ethylacetate (50 ml) with 5% palladium on carbon (200 mg) at room temperature and atmospheric pressure for 9 hours. The catalyst was filtered and the solvent was removed. The residue was chromatographed on silica gel (hexane-ethyl acetate (9:1) under nitrogen giving **6d** (1.58 g, 88%) as white needles; nmr (deuteriochloroform): δ 0.82 (s, 3H, CH_3), 1.1 (s, 3H, CH_3), 1.24 (d, 3H, CH-C*H*$_3$), J = 6 Hz), 3.5 (d, 1H, C*H*-Ar), 4.28 (m, 1H, C*H*-CH_3), 5.5 (broad, 1H, NH), 7.2-7.5 (m, 8H, Ar); ms: m/e 334 ($M^{\cdot+}$, 42%), 316 (18), 182 (100), 168 (41), 12 (15), 42 (38).

1,4-Bis(4-methoxyphenyl)-3,3,5-trimethylpyrazolidine (**6e**).

This compound was prepared as described for **6d** by adding the diazonium salt to the solution maintained at 15°; nmr (deuteriochloroform): δ 0.8 (s, 3H, CH_3), 1.1 (s, 3H, CH_3), 1.25 (d, 3H, CH-C*H*$_3$), 3.7 (d, 1H, C*H*-Ar), 4.28 (m, 1H, C*H*-CH_3), 5.4 (broad, 1H, NH), 6.8-7.3 (m, 8H, Ar), 3.8 (s, 6H, OCH_3); ms: m/e 326 ($M^{\cdot+}$), 308, 296, 176, 108, 42.

1,4-Diphenyl-3,3,5-trimethylpyrazolidine (**6f**).

Compound **6f** had nmr (deuteriochloroform): δ 0.8 (s, 3H, CH_3), 1.2 (s, 3H, CH_3), 1.26 (d, 3H, CH-C*H*$_3$), 3.6 (d, 1H, C*H*), 4.28 (m, 1H, C*H*-CH_3), 5.5 (broad, 1H, NH), 7.1-7.5 (m, 10H, Ar) ms: m/e 226 ($M^{\cdot+}$), 248, 146, 106, 77, 42.

1,4-Bis(4-chlorophenyl)-3-methyl-5-pyrazolone (**4g**).

The procedure A, described for the synthesis of **3a**, was followed using a double amount of reagents and methyl 2-butenoate (6 g, 52.6 mmoles). The reaction mixture was extracted with ethyl acetate (3 × 50 ml). The extract was washed with water, dried and evaporated. The residue allowed to stand for two days gives **4g** as white crystals (799 mg, 25% yield). A pure sample was obtained by crystallization from ethyl acetate; nmr (DMSO-d_6): δ 2.20 (s, 3H, CH_3), 7.2-7.9 (m, 8H, Ar), 11 (broad, 1H, NH); ms: m/e 318 ($M^{\cdot+}$, Cl_2 cluster), 289, 282, 255, 248, 179, 151, 113.

1,4-Diphenyl-3-methyl-5-pyrazolone (**4h**).

This compound was prepared as **4g**. The product (mp 195-196°) was identical with an authentic sample (mp 196°) prepared as described in the literature (9).

The compound **4h** was also prepared following the procedure B by isolation of **1h** by column chromatography (Silica gel-hexane) using a preparative liquid-liquid chromatograph Miniprep (Jobin-Ivon). The olefine used as methyl 2-butenoate, mp 162-164°; ir: ν max (cm^{-1}) 1728 (C=O), 1150; nmr (deuteriochloroform): δ 1.2 (d, 3H, CH_3), 3.7 (s, 3H, OCH_3), 4.2 (d, 1H, C*H*-CH, J = 7 Hz), 4.58 (m, 1H, C*H*-CH_3), 7.0-7.4 (m, 10H, Ar); ms: m/e 282 ($M^{\cdot+}$), 251, 177, 149, 105, 77, 59; uv: ν max (log ϵ) 265 (4.11), 415 (2.1).

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.97. Found: C, 72.45; H, 6.42; N, 9.92.

1,3,4-Triphenyl-5-methylpyrazole (**7i**).

A solution of titanous chloride (12 ml, 12 mmoles) was added slowly to a solution obtained by dissolving ferrous sulphate (6 g, 21.6 mmoles) in water (10 ml), adding diazonium sulphate (10 ml, 11 mmoles) and subsequently 4-phenyl-3-buten-2-one (3 g, 20.5 mmoles) in acetic acid (50 ml) at 10°. Nitrogen evolution was slow and the reaction mixture was stirred for 2 hours. The reaction was extracted with diethyl ether (3 × 60 ml). The extract was washed with water (2 × 50 ml) and 10% sodium carbonate solution (50 ml), dried and evaporated. The residue was chromatographed (silica gel, hexane-ethyl acetate 9:1) to give a fraction of pure **7i** (579 mg, 18%). The compound (mp 150°) appear to have similar properties with the compound prepared following the literature procedure (10).

1,4-Bis(4-bromophenyl)-3-phenyl-5-methylpyrazole (**7m**).

This compound was prepared as described for **7h** using 4-bromobenzenediazonium sulphate (9.1 ml, 10.9 mmoles). Column chromatography of the crude product gave **7m** (712 mg); nmr (deuteriochloroform): δ 2.28 (s, 3H, CH_3), 7.0-7.7 (m, 13H, Ar); ms: m/e 466 ($M^{\cdot+}$, Br_2 cluster), 385 ($M^{\cdot+}$ − Br), 370, 345, 306, 198 (M^{++}), 155, 115.

When the procedure A was used, the product was extracted with ethylacetate and the crude residue was chromatographed as before.

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