2-Oxohydrazones, 4-Hydrazono-1*H*-pyrazol-5-ones, and Derived Products by Air Oxidation of 1,2-Hydrazino-hydrazones

Orazio A. Attanasi,† Lucia De Crescentini,† Paolino Filippone,*,† Elisabetta Foresti,‡ and Fabio Mantellini†

Istituto di Chimica Organica, Università di Urbino, Piazza della Repubblica 13, 61029 Urbino, Italy, and Dipartimento di Chimica "G. Ciamician", Università di Bologna, Via Selmi 2, 40126 Bologna, Italy

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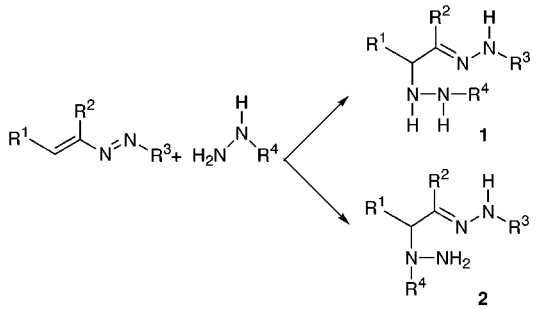
The azo-ene system of 1,2-diaza-1,3-butadienes can be influenced by the presence of electron-rich or electron-poor groups on terminal carbon and/or nitrogen.[1−5] Although the terminal carbon remains the preferential target of nucleophilic attacks, electron-donating groups reduce the electrophilic character of this atom, while electron-withdrawing ones enhance it.[5] Thus, a variety of α-substituted hydrazone derivatives can be obtained as a consequence of 1,4-conjugate addition (Michael-type) of carbon- and hetero-nucleophiles to the heterodiene system of these substrates. This formation of a carbon−carbon or carbon−heteroatom single bond is important both in itself and in view of several subsequent uses of these α-functionalized hydrazones as intermediates in organic chemistry.[1−5] Analogous electronic considerations may be made for monosubstituted hydrazines, which can be distinguished in electron-rich and electron-poor derivatives depending on electron-donating or electron-withdrawing groups bonded to the nitrogen atom, respectively. Although most reactions are due to the terminal NH_2 group, sometimes reactions by R−NH− nitrogen are reported in the literature. This is the case of the reactions between electron-rich 1,2-diaza-1,3-butadienes and electron-rich hydrazines, of which the two different 1,4-adducts **1** and **2** were reported (Scheme 1). In addition, even osazone species were frequently detected, especially in the presence of arylhydrazine reagent in excess.[1,2,6,7]

Scheme 1



Considering these findings, we decided to investigate the unexplored reactions of electron-poor 1,2-diaza-1,3-butadienes with electron-poor hydrazines and the usefulness of the products obtained as tools in organic and medicinal chemistry. Furthermore, since the hydrazino group is easily removable, we preferred to use the simple and cheaper methyl or *tert*-butyl hydrazinocarboxylate in all of the reactions examined.[8]

1,2-Diaza-1,3-butadienes **1a**−**e** reacted in THF at room temperature with methyl **2a** or *tert*-butyl hydrazinocarboxylate **2b** to give 1,2-hydrazino-hydrazones **3a**−**h**, in good to excellent yields (Scheme 2, path *a*). This reaction proceeds with high chemo- and regioselectivity via nucleophilic attack of the NH_2 hydrazino group at the terminal carbon of the heterodiene system of **1** to afford **3** by means of Michael-type 1,4-conjugate addition.

The reaction of adducts **3a**−**h** with MeONa in MeOH (30 wt %) at 0−5 °C and subsequent air bubbling produced 4-hydrazono-1*H*-pyrazol-5-ones **4a**−**f** in good yields (Scheme 2, path *b*). Under these basic and mild oxidative conditions, an internal nucleophilic attack of the NH hydrazone group at the carboxylate function in the δ position takes place, followed by the loss of an alcohol molecule, according to the formation of pyrazole rings from 1,2-diaza-1,3-butadienes previously reported.[3,4] The ^{1}H NMR spectra of compounds **4a**−**f** are consistent with both tautomeric forms shown in Scheme 2.

Irradiation of CH_3 in position 3 of the pyrazole ring (δ ∼2 ppm) did not show any NOE enhancement of NH at δ ∼12 ppm, and by irradiation of NH no NOE enhancement of CH_3 was observed. These results suggest that the proton at δ ∼12 ppm is not bonded at the heteroatom in position 2 (form 2) but at the nitrogen of the hydrazonic residue (form 1).

4-Hydrazono-1*H*-pyrazol-5-ones **4a**−**f** with BH_4^- on Amberlyst A-26 in MeOH at room temperature afforded 4-hydrazino-1,4*H*-pyrazol-5-ones **5a**−**f** in good yields

† Università di Urbino.
‡ Università di Bologna.

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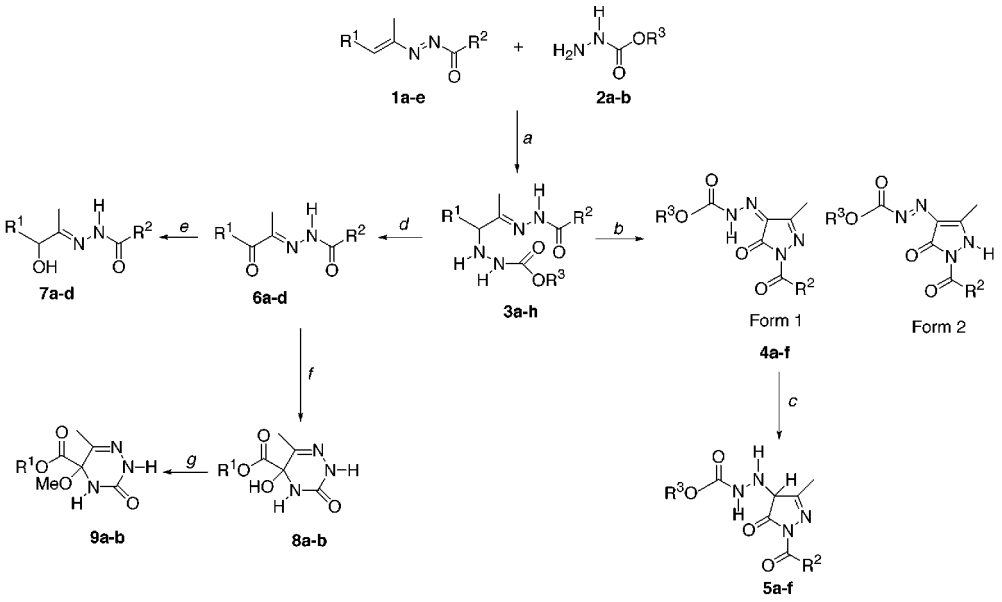
Scheme 2[a]



1a: $R^1 = CO_2Me$, $R^2 = NH_2$
1b: $R^1 = CO_2Et$, $R^2 = NH_2$
1c: $R^1 = CO_2Me$, $R^2 = NHPh$
1d: $R^1 = CO_2Et$, $R^2 = NHPh$
1e: $R^1 = CO_2Et$, $R^2 = O$*t*-Bu

2a : $R^3 = Me$
2b: $R^3 = t$-Bu

3a: $R^1 = CO_2Me$, $R^2 = NH_2$, $R^3 = Me$ (24 h, 78%)
3b: $R^1 = CO_2Et$, $R^2 = NH_2$, $R^3 = Me$ (17 h, 83%)
3c: $R^1 = CO_2Me$, $R^2 = NHPh$, $R^3 = Me$ (24 h, 86%)
3d: $R^1 = CO_2Et$, $R^2 = NHPh$, $R^3 = Me$ (27 h, 68%)
3e: $R^1 = CO_2Et$, $R^2 = O$*t*-Bu, $R^3 = Me$ (27 h, 79%)
3f: $R^1 = CO_2Et$, $R^2 = NH_2$, $R^3 = t$-Bu (48 h, 97%)
3g: $R^1 = CO_2Et$, $R^2 = NHPh$, $R^3 = t$-Bu (16 h, 86%)
3h: $R^1 = CO_2Et$, $R^2 = O$*t*-Bu, $R^3 = t$-Bu (8 h, 85%)

4a: $R^2 = NH_2$, $R^3 = Me$ (0.1 h, 55% from **3a**, 57 % from **3b**)
4b: $R^2 = NHPh$, $R^3 = Me$ (0.1 h, 60% from **3c**, 59% from **3d**)
4c: $R^2 = O$*t*-Bu, $R^3 = Me$ (0.1 h, 42%)
4d: $R^2 = NH_2$, $R^3 = t$-Bu (0.1 h, 42%)
4e: $R^2 = NHPh$, $R^3 = t$-Bu (0.2 h, 74%)
4f: $R^2 = O$*t*-Bu, $R^3 = t$-Bu (0.1 h, 58%)

5a: $R^2 = NH_2$, $R^3 = Me$ (0.5 h, 71%)
5b: $R^2 = NHPh$, $R^3 = Me$ (1 h, 87%)
5c: $R^2 = O$*t*-Bu, $R^3 = Me$ (4 h, 61%)
5d: $R^2 = NH_2$, $R^3 = t$-Bu (4 h, 61%)
5e: $R^2 = NHPh$, $R^3 = t$-Bu (4 h, 67%)
5f: $R^2 = O$*t*-Bu, $R^3 = t$-Bu (6 h, 61%)

6a: $R^1 = CO_2Me$, $R^2 = NH_2$ (1 h, 78%)
6b: $R^1 = CO_2Et$, $R^2 = NH_2$ (1 h, 78%)
6c: $R^1 = CO_2Me$, $R^2 = NHPh$ (0.1 h, 88%)
6d: $R^1 = CO_2Me$, $R^2 = NHPh$ (0.1 h, 80%)

7a: $R^1 = CO_2Me$, $R^2 = NH_2$ (0.5 h, 61%)
7b: $R^1 = CO_2Et$, $R^2 = NH_2$ (0.5 h, 73%)
7c: $R^1 = CO_2Me$, $R^2 = NHPh$ (0.5 h, 90%)
7d: $R^1 = CO_2Et$, $R^2 = NHPh$ (0.5 h, 64%)

8a: $R^1 = CO_2Me$ (8 h, 79%)
8b: $R^1 = CO_2Et$ (12 h, 70%)

9a: $R^1 = CO_2Me$ (48 h, 68%)
9b: $R^1 = CO_2Et$ (8 h, 79%)

[a] Reagents and conditions: (*a*) THF, room temperature; (*b*) MeONa, MeOH−THF, air, 0−5 °C, TFA; (c) MeOH, BH_4^- on Amberlyst A-26, room temperature; (d) MeOH−THF, TFA, air, room temperature; (e) MeOH, BH_4^- on Amberlyst A-26, room temperature; (f) dioxane, reflux; (g) MeOH, reflux.

(Scheme 2, path *c*). The use of this supported reducing agent was more convenient than that of $NaBH_4$ or similar reagents because of higher yields and a simpler manipulation of the reaction mixture (only filtration). In addition to giving useful derivatives in organic chemistry, this reaction chemically confirmed the structures of **4** and **5**. Furthermore, the mild acidic−oxidative [MeOH−THF, TFA (trifluoroacetic acid) catalytic, air] conversion of **5** into **4** indirectly suggested that **5** was the intermediate in the formation of **4** from **3**. Indeed, the transformation of **3** into **4** was so fast (5−10 min) that the detection of any intermediate was not possible.

The reaction of compounds **3a**−**d** with TFA in THF and MeOH and bubbling air at room temperature led to 2-oxohydrazones **6a**−**d** in good yields[9] (Scheme 2, path *d*). The keto group of these compounds can be reduced to a hydroxy group by treatment with BH_4^- on Amberlyst A-26 in MeOH at room temperature giving 2-hydroxyhydrazones **7a**−**d** in good to excellent yields (Scheme 2, path *e*). It is noteworthy that **7** in MeOH−THF smoothly afforded **6** by reaction with bubbling air.

When 2-oxohydrazones **6a,b** were heated in dioxane under reflux, alkyl 5-hydroxy-3-oxo-2,3,4,5-tetrahydro-[1,2,4]triazine-5-carboxylates **8a,b** were obtained in good yields (Scheme 2, path *f*). The heteroring closure proceeds via an unusual intramolecular nucleophilic attack of the semicarbazide NH_2 group at the keto function. The same heterocyclization process was not observed with the NHPh group. X-ray diffraction analysis of methyl 5-hydroxy-6-methyl-3-oxo-2,3,4,5-tetrahydro[1,2,4]triazine-5-carboxylate **8a** unequivocally confirmed the structure assigned to these compounds.

In MeOH under reflux, compounds **8a,b** reacted to give 5-methoxy derivatives **9a,b** (Scheme 2, path *g*).

This paper reports the chemo- and regioselective high-yield synthesis of the key 1,2-hydrazino-hydrazones without the presence of osazone-type bishydrazone species by reaction of electron-poor 1,2-diaza-1,3-butadienes with electron-poor hydrazines.[1,2,6,7] *tert*-Butoxy-carbon-

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ylhydrazones are valuable building blocks in the synthesis of HIV-1 protease inhibitors.[10] The hydrazine and especially BOC-hydrazine group may be considered as protecting groups of carbonyl or methylene functions that can be easily regenerated by cleavage of C=N or C−NH bonds, affording functionalized products and intermediates useful in organic synthesis.[8] Furthermore, α-hydroxy acids are widely present in natural products and very important in enantioselective syntheses.[11] Several derivatives exhibit conjugated double bond systems suitable for 1,4-additions[12] or hetero Diels−Alder cycloadditions.[13] Pyrazoles are of interest in organic,[3,5,14] biological,[15] pharmaceutical,[16] analytical,[17] and agricultural chemistry.[5,18] In addition, heterocycles having carbonylhydrazine side chains possess valuable medicinal properties.[19] Finally, this investigation permits a simple and high-yield entry to new 1,2,4-triazines.[20]

Experimental Section

General. 1,2-Diaza-1,3-butadienes **1a**−**e** were synthesized as standard *E*/*Z* isomeric mixtures according to previously reported procedures.[21,22] Starting materials and solvents were purchased from commercial sources and were used without further purification. Melting points were uncorrected. The products often decompose at their melting points. ^{1}H NMR spectra were recorded at 200 MHz, and ^{13}C NMR spectra were recorded at 50.32 MHz in DMSO-d_6. The multiplicities in ^{13}C NMR spectra were obtained by using 135 and 90° DEPT experiments. NOE enhancement factors were determined on degassed 0.01 M DMSO-d_6 solutions at 300 K, using the NOEDIFF pulse program. Generally, irradiation time was 2 s, with a power level of 31 low.

Preparation of 1,2-Hydrazino-hydrazones 3a−h. 1,2-Diaza-1,3-butadienes **1a**−**e** (1 mmol) and hydrazines **2a** and **2b** (1 mmol) were dissolved in THF (10 mL), and the mixture was magnetically stirred at room temperature for 2.0−78.0 h. Products **3a**−**h** were crystallized from ethyl acetate−cyclohexane. **3a:** mp 134−135 °C; ^{1}H NMR δ 1.78 (s, 3 H), 3.54 (s, 3 H), 3.66 (s, 3 H), 4.22 (d, 1 H, J = 3.0 Hz), 5.21 (m, 1 H), 6.31 (s, 2 H), 8.49 (brs, 1 H), 9.29 (s, 1 H); ^{13}C NMR δ 12.7, 51.5, 52.1, 68.4, 143.3, 156.9, 157.3, 169.8. Anal. Calcd for $C_8H_{15}N_5O_5$: C, 36.78; H, 5.79; N, 26.81. Found: C, 36.93; H, 5.71; N, 26.66.

Preparation of 4-Hydrazono-1*H*-pyrazol-5-ones 4a−f. To a magnetically stirred solution of hydrazino-hydrazono 1,4-adducts **3a**−**h** (1 mmol) in a mixture of MeOH (5 mL) and THF (5 mL) at 0−5 °C was added a solution of MeONa (1 mmol) in MeOH (30 wt %), and the mixture was air-bubbled. The reaction was allowed to react for 0.1−0.2 h and then was acidified by addition of TFA (2 mmol). The residue was purified by chromatography on a silica gel column (cyclohexane−ethyl acetate mixtures) to yield pyrazoles **4a**−**f**, which were crystallized from ethyl ether−petroleum ether (40−60 °C). **4a:** mp 154−156 °C; ^{1}H NMR δ 2.17 (s, 3 H), 3.87 (s, 3 H), 7.17 and 7.64 (2 brs, 2 H), 12.17 (s, 1 H); ^{13}C NMR δ 11.7, 53.9, 134.6, 148.8, 149.1, 152.4, 156.8. Anal. Calcd for $C_7H_9N_5O_4$: C, 37.01; H, 3.99; N, 30.83. Found: C, 36.93; H, 3.71; N, 30.76. NOE enhancement factors: NH{CH_3} 0%; CH_3{NH} 0%.

Preparation of 4-Hydrazino-1,4*H*-pyrazol-5-ones 5a−f. To a magnetically stirred solution of pyrazoles **4a**−**f** (1 mmol) in MeOH (10 mL) at room temperature was added BH_4^- on Amberlyst A-26 (1 mmol). The reaction was left for 0.5−6.0 h and then was filtered. The residue was purified by chromatography on a silica gel column (cyclohexane−ethyl acetate mixtures) to yield pyrazoles **5a**−**f**, which were crystallized as follows: **5a** from ethyl ether−petroleum ether (40−60 °C), **5b** from methanol, **5c** from ethyl acetate−petroleum ether (40−60 °C), and **5d**−**f** from ethyl acetate−cyclohexane. **5a:** mp 150−152 °C; ^{1}H NMR δ 2.01 (s, 3 H), 3.73 (s, 3 H), 6.19 (d, 1 H, J = 8.0 Hz), 6.47 (s, 2 H), 6.57 (d, 1 H, J = 8.0 Hz), 10.49 (s, 1 H); ^{13}C NMR δ 11.1, 52.5, 73.9, 147.0, 150.8, 153.5, 153.6. Anal. Calcd for $C_7H_{11}N_5O_4$: C, 36.68; H, 4.84; N, 30.56. Found: C, 36.91; H, 4.72; N, 30.78.

Preparation of 2-Oxohydrazones 6a−d. To a magnetically stirred solution of hydrazino-hydrazono 1,4-adducts **3a**−**d** (1 mmol) in a mixture of MeOH (5 mL) and THF (5 mL) at room temperature was added TFA (1 mL), and the mixture was air-bubbled. The reaction was left for 0.1−1.0 h. Products **6a,b** were directly crystallized from the reaction medium, while **6c,d** were crystallized from ethyl ether−petroleum ether (40−60 °C). **6a:** mp 172−174 °C; ^{1}H NMR δ 1.96 (s, 3 H), 3.85 (s, 3 H), 6.23 and 6.95 (2 brs, 2 H), 10.63 (s, 1 H); ^{13}C NMR δ 9.2, 52.5, 140.7, 154.9, 165.6, 186.4. Anal. Calcd for $C_6H_9N_3O_4$: C, 38.51; H, 4.85; N, 22.45. Found: C, 38.65; H, 4.70; N, 22.63.

Preparation of 2-Hydroxyhydrazones 7a−d. To a magnetically stirred solution of 2-oxohydrazones **6a**−**d** (1 mmol) in a mixture of MeOH (5 mL) and THF (5 mL) at room temperature was added BH_4^- on Amberlyst A-26 (1 mmol). The reaction was left for 0.5 h and then was filtered. Products **7a,b** were crystallized from tetrahydrofuran, and **7c,d** were crystallized from ethyl acetate−petroleum ether (40−60 °C). **7a:** mp 124−125 °C; ^{1}H NMR δ 1.77 (s, 3 H), 3.66 (s, 3 H), 4.62 (d, 1 H, J = 7.0 Hz), 5.96 (d, 1 H, J = 7.0 Hz), 6.42 (s, 2 H), 9.32 (s, 1 H); ^{13}C NMR δ 12.4, 51.9, 74.6, 144.9, 157.2, 171.7. Anal. Calcd for $C_6H_{11}N_3O_4$: C, 38.10; H, 5.86; N, 22.21. Found: C, 38.25; H, 5.71; N, 22.43.

Preparation of Alkyl 5-Hydroxy-3-oxo-2,3,4,5-tetrahydro-[1,2,4]triazine-5-carboxylates 8a,b. A solution of 2-oxohydrazones **6a,b** (1 mmol) in dioxane (10 mL) was heated under reflux for 8−12 h. The residue was purified by chromatography on a silica gel column (cyclohexane−ethyl acetate mixtures) to yield **8a,b**, which were crystallized from ethyl acetate−petroleum ether (40−60 °C). **8a:** mp 136−138 °C; ^{1}H NMR δ 1.80 (s, 3 H), 3.71 (s, 3 H), 7.04 (s, 1 H), 8.26 (s, 1 H), 10.18 (s, 1 H); ^{13}C NMR δ 16.8, 52.9, 80.2, 140.4, 148.8, 168.8. Anal. Calcd for $C_6H_9N_3O_4$: C, 38.51; H, 4.85; N, 22.45. Found: C, 38.42; H, 4.69; N, 22.53.

Preparation of Alkyl 5-Methoxy-3-oxo-2,3,4,5-tetrahydro-[1,2,4]triazine-5-carboxylates 9a,b. A solution of **8a,b** (1 mmol) in MeOH (10 mL) was heated under reflux for 8−48 h. Product **9a** was crystallized from ethyl acetate−petroleum ether (40−60 °C), and **9b** was crystallized from ethyl ether−petroleum ether (40−60 °C). **9a:** mp 114−116 °C; ^{1}H NMR δ 1.78 (s, 3 H), 3.07 (s, 3 H), 3.74 (s, 3 H), 8.50 (s, 1 H), 10.46 (s, 1 H); ^{13}C NMR δ 16.8, 49.2, 53.1, 85.2, 137.1, 148.9, 167.0. Anal. Calcd for $C_7H_{11}N_3O_4$: C, 41.79; H, 5.51; N, 20.89. Found: C, 41.86; H, 5.73; N, 20.71.

Crystal Data. $C_6H_9N_3O_4$, MW = 187.2, monoclinic, space group $P2_1/n$, a = 8.070(4), b = 5.079(4), c = 18.060(6) Å, β = 91.45(5)°, U = 831.8(8) Å^3, Z = 4, D_c = 1.50 Mg m^{-3}, F(000) =

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392, $\lambda = 0.71069$ Å, $T = 298$ K, (Mo Kα) $\mu = 0.127$ mm^{-1}, crystal dimensions 0.20 mm × 0.30 mm × 0.50 mm. A total of 1572 reflections were collected (1462 unique, $R_{int} = 0.0663$).

Data Collection and Processing. Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer using graphite monochromated Mo Kα radiation, $\omega/2\theta$ scan mode, range $2.26° < \theta < 24.97°$. The unit cell parameters were determined by least-squares refinement on diffractometer angles for 25 automatically centered reflections, $3.31° < \theta < 6.91°$.

Structure Analysis and Refinement. The structure was solved by direct method and refined by full-matrix least-squares on F^2, using the SHELX program packages.[23,24] In the final refinement cycles 740 reflections having $I > 2\sigma(I)$ were used, with 83 parameters varied. In refinements weights were used in accordance with the scheme $w = 1/[\sigma^2(F_o^2) + (0.1130P)^2 + 1.2471P]$ where $P = (F_o^2 + 2F_c^2)/3$. The hydrogen atoms were located by geometrical calculation and refined using a "riding" model. The final agreement indices were $R_1 = 0.0660$ and $wR_2 = 0.1735$. Goodness of fit on $F^2 = 1.05$. The largest difference peak and hole were 0.419 and −0.292 e Å^{-3}.

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Supporting Information Available: Yields and reaction times of products **3a**−**h**, **4a**−**f**, **5a**−**f**, **6a**−**d**, **7a**−**d**, **8a,b**, and **9a,b**; complete procedures for the synthesis and isolation of all compounds; complete spectral data of all compounds (IR and ^{1}H and ^{13}C NMR assignments, MS); X-ray molecular structure of compound **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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