Reaction between Conjugated Azoalkenes and Pyrazolinones: A Precious Entry to New Conjugated Azodiene and Asymmetric 4,4'-Bipyrazole Derivatives

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The first direct nucleophilic addition under mild reaction conditions of heterocyclic compounds to conjugated azoalkenes is reported. This reaction readily gives rise to new conjugated azodiene or asymmetric 4,4'-bipyrazole derivatives by means of two independent pathways.

In the wide scenarious of the azo-ene systems,[1–5] conjugated azodienes are relatively little investigated compounds, in spite of their potential usefulness in organic synthesis.[1–6] Furthermore, asymmetric 4,4'-bipyrazole derivatives are difficult to prepare by current synthetic methods reported in the literature.[7]

We now report the synthesis of new conjugated azodienes **4a–d** or asymmetric 4,4'-bipyrazol-4,4'-in-3,3'-ones **5a–b** by unprecedented[1–5] direct nucleophilic 1,4-addition of 1-methyl-3-*n*-propyl-2-pyrazolin-5-one **2a** or 1-phenyl-3-methyl-2-pyrazolin-5-one **2b** to the azo-ene system of conjugated azoalkenes **1a–c** in the presence of strong base anion exchanger resin Duolite® A102 (Rohm and Haas). This reaction affords firstly the intermediate CH-hydrazone adducts and then NH-hydrazone forms **3a–d** in tautomeric equilibrium with the relevant NH-hydrazino forms, as shown by the dissapearance in ^{1}H-NMR of the CH (4.37) signal and the appearance of a new NH (10.32) signal during few hours in the NMR tube.[4d,8]

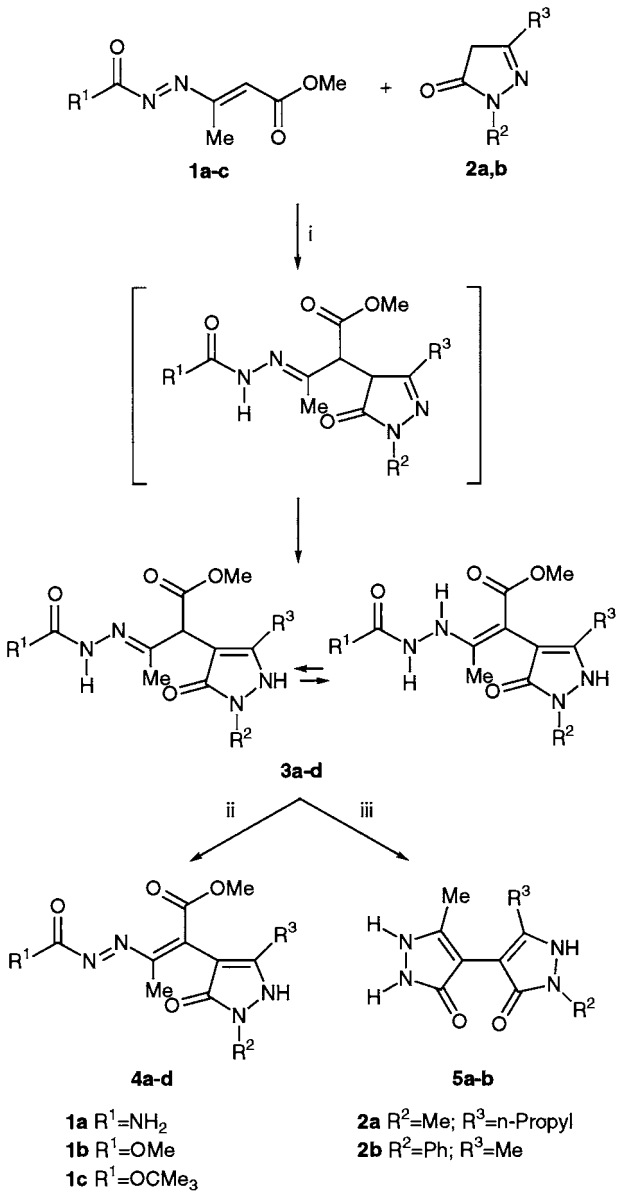
Subsequently, the above-mentioned products were obtained by two independent pathways. In fact, conjugated azodienes **4** having one of the two conjugated olefinic double bonds in the heterocycle ring arise by mild oxidation of the hydrazone derivatives **3** with selenium dioxide at room temperature. Asymmetric 4,4'-bipyrazol-4,4'-in-3,3'-ones derive by simple treatment of the same hydrazone adducts in methanol under reflux by means of the intramolecular cyclization of the hydrazone side-chain in position 4 of the pyrazolinone ring. The solvolytic cleavage of N-COR^1 bond was also observed (see Scheme 1 and Table 1).[8]

In conclusion we report here the first direct nucleophilic addition of heterocyclic compounds to the heterodiene system of conjugated azoalkenes. While the reaction of conjugated azoalkenes with activated methylene and methine compounds was extensively studied showing they are powerful tools in organic synthesis,[2–5] the present findings open a broad field of further innovative investigations on the chemistry of these versatile intermediates. Indeed, this reaction represents an unknown, mild and useful entry to a new class of conjugated azodienes in which one of two ene functions is located in the pyrazole ring. Moreover, the preparation of asymmetric 4,4'-bipyrazole derivatives difficult to obtain by other methods is also reported.

Table 1. Yields of products **3a-d**, **4a-d** and **5a,b**

1	2	3	Yield/%[a]	4	Yield/%[a]	5	Yield/%[a]
1a	**2a**	**3a**	75	**4a**	90	**5a**	81
1a	**2b**	**3b**	68	**4b**	81		
1b	**2b**	**3c**	71	**4c**	88		
1c	**2b**	**3d**	78	**4d**	92	**5b**	84

[a] Yields of isolated products.



Scheme 1. Reagents and conditions: i) Duolite® A102, THF, room temp.; ii) SeO_2, THF, room temp.; iii) MeOH, reflux.

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8 Typical experimental procedure for the synthesis of 1,4-adducts **3a–d**: To a stirred solution of conjugated azoalkenes **1a–c** (1 mmol) in THF (20 ml) was added 1-methyl-3-*n*-propyl-2-pyrazolin-5-one **2a** or 1-phenyl-3-methyl-2-pyrazolin-5-one **2b** (1 mmol) and Duolite® A102 (400 mg). The suspension was allowed to react at room temperature for 1 hr under magnetic stirring. The product was subsequentially isolated by column chromatography on silica gel with cyclohexane-ethyl acetate mixtures to give 1,4-adducts **3a–d**. **3d**: mp 118-120 °C; ^{1}H-NMR ($CDCl_3$): 1.51 (s, 9 H, CMe_3), 2.06 (s, 3 H, Me), 2.24 (s, 3 H, Me), 3.72 (s, 3 H, OMe), 4.37 (s, 1 H, CH), 7.10-7.81 (m, 5 H, Ph), 8.21 (bs, 1 H, NH, D_2O exch.), 10.96 (bs, 1 H, NH, D_2O exch.); ^{13}C-NMR ($CDCl_3$):12.6, 17.2, 26.1, 52.9, 82.8, 93.5, 119.3, 121.7, 126.5, 130.7, 138.6, 147.3, 150.1, 151.5, 153.0, 170.7; MS *m/z* (relative intensity) 402 (M^+, 14), 346 (74), 329 (9), 302 (15), 287 (22), 270 (100). Anal. Calcd for $C_{20}H_{26}0_5N_4$: C, 59.69; H, 6.51; N, 13.92; Found: C, 59.71; H, 6.50, N, 13.91.
Typical experimental procedure for the synthesis of conjugated azodienes **4a–d:** To a stirred solution of 1,4-adducts **3a-d** (1 mmol) in THF (20 ml) was added selenium dioxide (1 mmol). The suspension was allowed to react at room temperature for 15 min under magnetic stirring. The products was subsequentially isolated by column chromatography on silica gel with cyclohexane-ethyl acetate mixtures to give conjugated azodienes **4a–d. 4d**: mp 152-154 °C; ^{1}H-NMR ($CDCl_3$): 1.54 (s, 9 H, CMe_3), 2.03 (s, 3 H, Me), 2.26 (s, 3 H, Me), 3.96 (s, 3 H, OMe), 7.09-7.92 (m, 5 H, Ph), 8.67 (b s, 1 H, NH, D_2O exch.); ^{13}C-NMR ($CDCl_3$): 13.2, 17.9, 28.1, 53.3, 82.6, 116.7, 125.0, 127.0, 128.8, 137.6, 139.8, 144.7, 146.7, 152.2, 161.9, 166.4; MS *m/z* (relative intensity) 400 (M^+, 12), 344 (13), 300 (11), 295 (14), 272 (39), 259 (82), 240 (100). Anal. Calcd for $C_{20}H_{24}0_5N_4$: C, 59.99; H, 6.04; N, 13.99; Found: C, 59.97; H, 6.05, N, 14.00.
Typical experimental procedure for the synthesis of 4,4'-bipyrazol-4,4'-in-3,3'-ones **5a,b**: 1,4-Adduct **3a–d** (1 mmol) was dissolved in methanol (25 ml) and heated under reflux for 3 hr. The product was subsequently isolated by column chromatography on silica gel with ethyl acetate to give 4,4'-bipyrazol-5,4'-in-5,3'-ones **5a,b. 5b**: mp 284-286 °C; ^{1}H-NMR (DMSO): 2.09 (s, 6 H, 2 Me), 7.10-7.81 (m, 5 H, Ph), 10.92 (b s, 3 H, 3 NH, D_2O exch.); ^{13}C-NMR (DMSO): 11.3, 13.0, 93.9, 119.6, 124.7, 128.9, 138.2, 138.5, 147.3, 159.8; MS *m/z* (relative intensity) 270 (M^+, 100). Anal. Calcd for $C_{14}H_{14}0_2N_4$: C, 62.21; H, 5.22; N, 11.84; Found: C, 62.19; H, 5.23, N, 11.85.