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Diels-Alder Reactions on 5-Acetyl-2-methyl-4-nitro-6-phenyl-pyridazin-3(2*H*)-one: a New Facet of the Pyridazine System

Vittorio Dal Piaz,* Maria P. Giovannoni, Giovanna Ciciani

Dipartimento di Scienze Farmaceutiche dell'Università, Via Gino Capponi 9, I-50121 Firenze, Italy

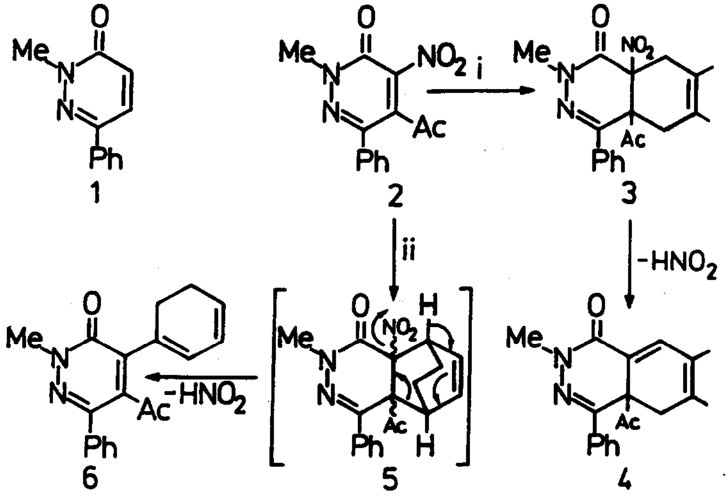
Donatella Giomi, Rodolfo Nesi

Dipartimento di Chimica Organica 'Ugo Schiff' dell'Università - Centro di Studio del C.N.R. sulla Chimica e la Struttura dei Composti Eterociclici e loro applicazioni, Via Gino Capponi 9, I- 50121 Firenze, Italy

Abstract: The title nitro ketone 2 was shown to react with 2,3-dimethylbuta-1,3-diene and cyclohexa-1,3-diene affording a mixture of the phthalazones 3 and 4 and the pyridazinone 6, respectively, through [2+4] cycloaddition processes.

After the first report on the reaction of 2-methyl-6-phenylpyridazin-3(2*H*)-one 1 with 2-diazopropane,[1] work carried out over the past decade has firmly demonstrated that the C(4)-C(5) double bond of variously substituted pyridazin-3(2*H*)-ones can enter as a 2π component in 1,3-dipolar cycloadditions both with diazoalkanes[2] and nitrile oxides.[3]

On the contrary, no attempt has been made, to our knowledge, to employ the same moiety as a dienophilic counterpart in [2+4] Diels-Alder reactions. Thus, we decided to explore this type of reactivity for the above compound 1 as well as the difunctionalized nitro derivative 2, that became recently available by oxidative ring opening of 3,6-dimethyl-4-phenylisoxazolo[3,4-*d*]pyridazin-7(6*H*)-one.[4]



Scheme. Reaction Conditions: i, DMB, toluene, 125-130°C; ii, cyclohexa-1,3-diene, toluene, 125-130°C.

No reaction was observed by prolonged heating of the former with 2,3-dimethylbuta-1,3-diene (DMB) and cyclohexa-1,3-diene (5 equiv.), respectively, in xylene at 155-160°C in a sealed tube; conversely, treatment of **2** with the same excess of DMB in a sealed tube under milder conditions (toluene, 125-130°C, 48h) afforded the phthalazine derivatives **3** and **4** that were isolated as pure products[5,6] by column chromatography in 25% and 28% yields, respectively, based on a little recovered starting material (ca. 10%).

These findings show the critical role of the nitro and/or acetyl for the activation of the latter substrate towards the Diels-Alder process with DMB; on the other hand, they also indicate that some of the primary cycloadduct **3** suffers from elimination of nitrous acid with formation of the corresponding dihydrophthalazin-1(2*H*)-one **4**.

When DMB was replaced with cyclohexa-1,3-diene, the pyridazinone **6**[5,6] was obtained in 75% yield under the same conditions. This result can be again accounted for on the basis of a [2 + 4] cycloaddition on **2** leading to a more crowded tricyclic system of the type **5** that now prefers to evolve into the final product **6** by loss of HNO_2 and concomitant ring opening; although **2** was also converted into **6** by treatment with the same diene at 85-90°C, attempts to isolate or detect the intermediate **5** under these milder conditions were unsuccessful.[7]

The Diels-Alder reactions of **2** appear attractive from a synthetic viewpoint since they can be regarded as a promising new strategy both for direct six-membered pyridazine annulations and preparation of peculiarly substituted pyridazinones.

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References and Notes

1. Franck-Neumann, M.; Leclerc, G. *Tetrahedron Lett.*, **1969**, 106.
2. For a recent review, see: Stanovnik, B. *Tetrahedron Rep. N. 289*, **1991**, *47*, 2925 and references cited therein.
3. Srinivasan, T. N.; Sattur, P. B.; Rama Rao, K.; Bhanu Prasad, A. S.; Jemmis, E. D. *J. Heterocycl. Chem.*, **1989**, *26*, 553.
4. Dal Piaz, V.; Ciciani, G.; Turco, G. *Synthesis*, **1989**, 213.
5. Satisfactory analytical data were obtained for the new compounds.
6. Selected physical and spectral data for **3**: m.p. 154-156°C; IR (Nujol mull) ν 1725 ($\underline{CO}CH_3$), 1690 ($\underline{CO}NCH_3$), 1575 and 1360 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.40 (br s, 3H, 6-CH_3/7-CH_3), 1.67 (br s, 3H, 7-CH_3/6-CH_3), 2.21 (s, 3H, $COCH_3$), 2.46 (br s, 2H, 5-CH_2/8-CH_2), 3.03 (AB system, J = 18 Hz, 2H, 8-CH_2/5-CH_2), 3.51 (s, 3H, NCH_3), 7.15-7.23 (m, 2H, Ar-2H), 7.35-7.45 (m, 3H, Ar-3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 18.0 (q, 6-CH_3/7-CH_3), 18.4 (q, 7-CH_3/6-CH_3), 27.6 (q, $CO\underline{C}H_3$), 33.5 (t, C-5/C-8), 36.3 (t, C-8/C-5), 37.2 (q, NCH_3), 59.3 (s, C-4a), 89.8 (s, C-8a), 123.1 (s, C-6 and C-7), 127.5 (d), 128.6 (d), 129.9 (d), 134.4 (s) (Ph), 153.8 (s, C-4), 159.9 (s, 1-CO), 200.6 (s, $\underline{C}OCH_3$). **4**: m.p. 192-193°C; IR (Nujol mull) ν 1700 ($\underline{CO}CH_3$) and 1650 cm^{-1} ($\underline{CO}NCH_3$); ^1H NMR ($CDCl_3$) δ 1.22 (s, 3H, 6-CH_3/7-CH_3), 2.05 (d, J = 1.5 Hz, 3H, 7-CH_3/6-CH_3), 2.12 (s, 3H, $COCH_3$), 2.79 (AB system, J = 17 Hz, 2H, 5-CH_2), 3.83 (s, 3H, NCH_3), 6.85 (q, J = 1.5 Hz, 1H, H-8), 7.46 (br s, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 20.3 (q, 6-CH_3/7-CH_3), 20.6 (q, 7-CH_3/6-CH_3), 26.2 (q, $CO\underline{C}H_3$), 35.0 (t, C-5), 40.2 (q, NCH_3), 51.4 (s, C-4a), 119.6 (d, C-8), 128.5 (d), 128.6 (d), 128.7 (d), 130.8 (s) (Ph), 132.9 (s, C-8a/C-7), 135.2 (s, C-7/C-8a), 144.4 (s, C-6), 146.8 (s, C-4), 157.8 (s, 1-CO), 208.5 (s, $\underline{C}OCH_3$). **6**: m.p. 106-107°C; IR (Nujol mull) ν 1720 ($\underline{CO}CH_3$) and 1650 cm^{-1} ($\underline{CO}NCH_3$); ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H, $COCH_3$), 2.25-2.60 (m, 4H, 2 CH_2), 3.86 (s, 3H, NCH_3), 5.88-6.02 (m, 3H, olefinic protons), 7.35-7.45 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 31.8 (q, $CO\underline{C}H_3$), 40.7 (q, NCH_3), 143.0 (s, C-6), 159.0 (s, 3-CO), 200.5 (s, $\underline{C}OCH_3$).
7. Reaction was not observed at lower temperature.

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