SHORT PAPER

The [3+2] cycloaddition of diphenyldiazomethane and ethyl diazoacetate with itaconic anhydride. A new access to spiranic cyclopropane derivatives†

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The reaction of itaconic anhydride **1** with ethyl diazoacetate **2** or diphenyldiazomethane **5** gave the expected spiro-derivatives, which spontaneously rearranged; specifically, the adduct from **1** and **5** loses a dinitrogen molecule, yielding a spirocyclopropane related to the known 5-azaspiro[2.4]heptane-4,6-diones or 5-azaspiro[2.4]heptanes.

**Keywords:** spiro compounds, diazoalkanes, itaconic anhydride, cycloadditions

The recurrent interest in bicyclic molecules with a spiran junction has led us to investigate the reactivity of some γ-methylene-γ-butyrolactones with selected 1,3-dipoles.[1–3] In a previous paper, we have shown that some 4-substituted arylcarbonitrile oxides undergo 1,3-dipolar cycloadditions with 5-methylenefuran-2(5*H*)-one with formation of spiroisoxazolines, which subsequently open to (2*E*)-3-(3′-arylisoxazol-5′-yl)-propenoic acids.[3] Some derivatives of these acids, bearing a halogen or hydroxy substituent on the 3′ position, are known as synthetic intermediates in the preparation of natural products related to ibotenic acid [(*R,S*)-α-amino-3-hydroxyisoxazole-5-acetic acid].

We report here the results of our study of the 1,3-dipolar cycloaddition reaction of itaconic anhydride (**1**) (2-methylenesuccinic anhydride) with ethyl diazoacetate (**2**) and diphenyldiazomethane (**5**). In particular, we present a new method for the preparation of 5-oxaspiro[2.4]heptane-4,6-diones **7** at room temperature, in a good-yielding one step [3+2] cycloaddition, using commercial itaconic anhydride and diphenyldiazomethane **4** as starting reagents. A three-step arduous synthesis of cyclopropane **7** has been described in a previous work,[5] the author using methyl 3-methoxycarbonyl-but-3-enoate (dimethyl itaconate) as starting material. This last paper also reported the preparation of 5-azaspiro[2.4]heptane-4,6-diones, used as diuretics, and of 5-azaspiro[2.4]heptanes known as antidepressants, whose structures are closely related to **7**.

Results and discussion

The [3+2] cycloaddition of itaconic anhydride **1** with ethyl diazoacetate **2** gave the Δ²-pyrazoline **4** *via* the prototropic rearrangement of the expected, first-formed Δ¹-pyrazoline **3** (Scheme 1). This rearrangement might be explained by the favoured formation of the conjugated structure **4**.

This reaction was regiospecific. The ^{13}C-NMR chemical shift of the spiro-carbon atom (69.9 ppm downfield from TMS) showed that this latter was deshielded because of the proximity of the nitrogen atom. The formation of the intermediate **3** has been proved by a ^{1}H NMR study. Indeed, when **1** and **2** were reacted for only one hour, a mixture of compounds **3** and **4** was obtained in a 40:60 ratio. After 48 hours, the isomerisation of **3** into **4** was complete. The presence of the intermediate **3** was evidenced by the X part of an AMX system positioned at 5.65 ppm (1H, dd, J_{AX} 6.6 Hz, J_{MX} 8.9 Hz) corresponding to the 3′-H proton. The product **4** was recognisable by the presence of a D$_2$O exchangeable proton situated at 9.10 ppm. We also noticed the transformation of the AM part of the AMX system of **3** (2.60 ppm, 1H$_M$, dd, J_{AM} 13.5 Hz, J_{MX} 8.9 Hz and 2.05 ppm, 1H$_A$, dd, J_{AM} 13.5 Hz, J_{AX} 6.6 Hz) into an AB system centred at 3.25 ppm. The ^{13}C NMR spectrum showed a signal at 137.8 ppm corresponding to a sp^2 carbon atom (C=N group). This was corroborated by the presence of a C=N bond at 1575 cm^{-1} in the infrared spectrum.
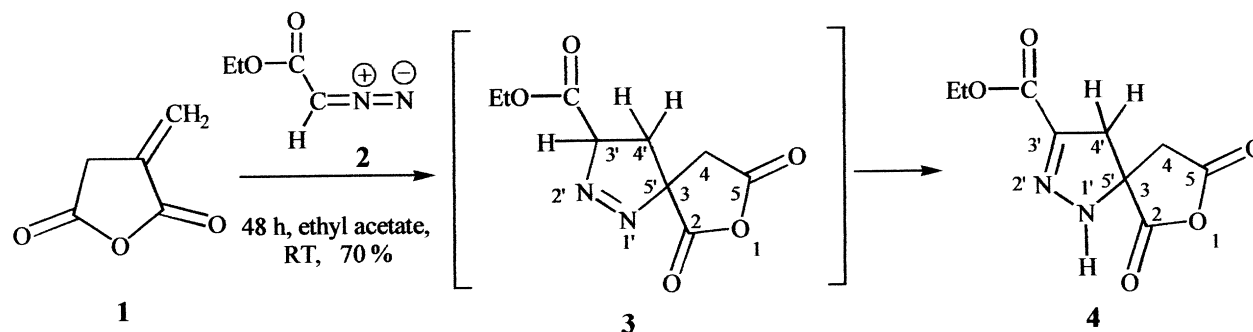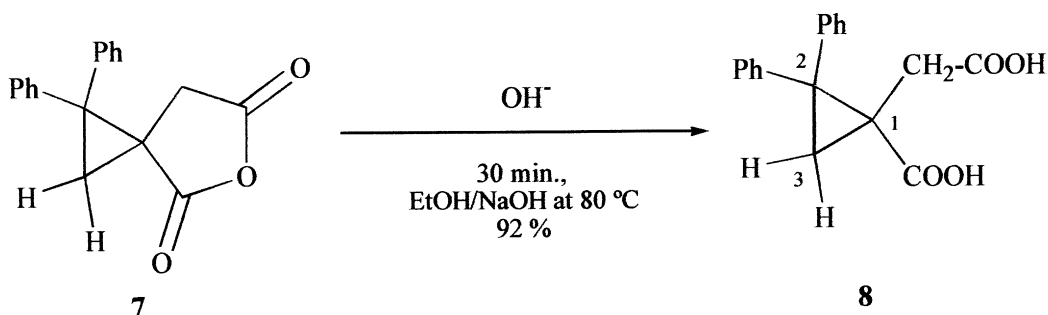

Scheme 1
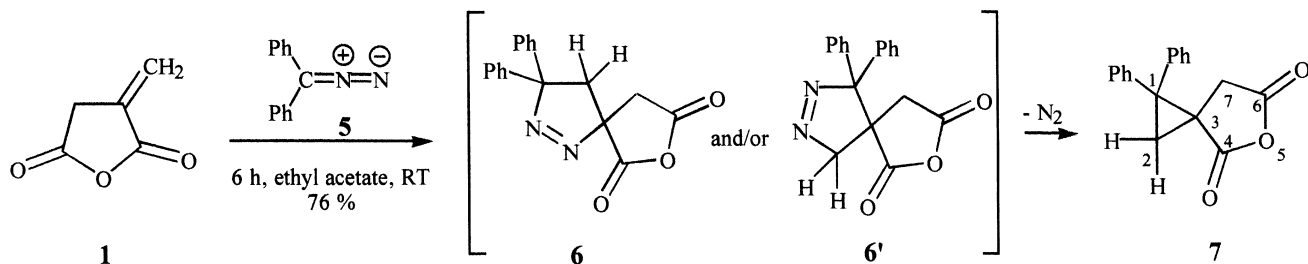
Scheme 2

Scheme 3
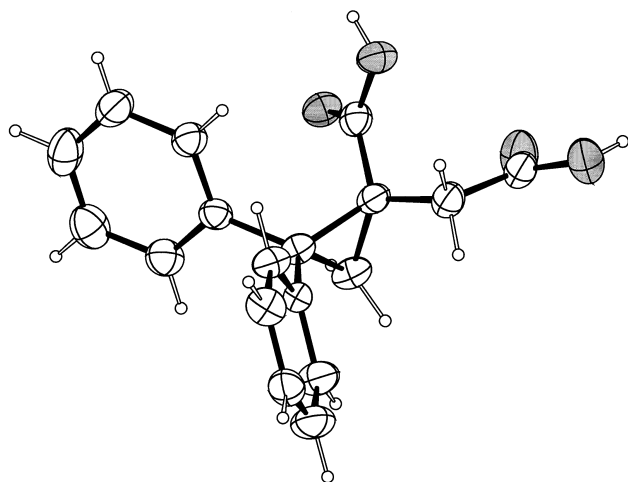
Fig. 1   ORTEP view of cyclopropane **8**.

In contrast to ethyl diazoacetate, the reaction of itaconic anhydride (**1**) and diphenyldiazomethane (**5**) produced a spiro-cyclopropane derivative (**7**) arising from the rearrangement of the primary cycloadducts **6** and/or **6′** after the loss of a dinitrogen molecule (Scheme 2).

No proton migration is possible in adduct **6**, although it could occur in adduct **6′**. However, such a prototropy would not give rise to a conjugated structure. Two hypotheses should be envisaged: either the formation of the single cycloadduct **6**, or the spontaneous denitrogenation of either of the intermediate pyrazolines. However, we did not succeed in isolating the transitory primary cycloadducts **6** and/or **6′**. Indeed, after reaction at room temperature and classical work-up, the elementary analysis of the residue revealed the absence of nitrogen. To try to find evidence for the spiro-intermediates **6** and/or **6′**, we performed the reaction at lower temperatures (*i.e.* 4°C, 0°C, –20°C). Nevertheless, we observed that, however low the temperature of the reaction medium was,

spontaneous gas evolution was noticed when we added the dipole **5** to a solution containing the dipolarophile **1**. As a result, we were unable to confirm the formation of either or both cycloadducts **6**/**6′**.

We did not succeed in obtaining suitable crystals of the anhydride (**7**) for an X-ray analysis. Fortunately, treatment of **7** in alkaline medium afforded, after acidification, the corresponding diacid **8** from which we obtained very clean monocrystals (Scheme 3).

The X-ray crystal structure[6] of **8** confirmed the presence of the cyclopropane ring (Figure 1).

Conclusion

The reaction of itaconic anhydride (**1**) with diazocompounds **2** and **5** furnished the expected unstable spirocycloadducts, which spontaneously rearranged through two different pathways. Prototropy occurred from the Δ^1-pyrazoline coming from ethyl diazoacetate (**2**), giving a more stable, conjugated structure. A cyclopropane derivative was directly obtained from diphenyldiazomethane (**5**), after denitrogenation of the unstable first-formed cycloadduct(s).

We have here a very simple and clean method for the synthesis of the known 5-oxaspiro[2.4]heptane-4,6-diones at room temperature. This last cyclopropane can also be related to the cyclic amino acid known as a promoter of the maturation of fruits.[6]

Experimental

Itaconic anhydride **1** and ethyl diazoacetate **2** were purchased from Aldrich. Diphenyldiazomethane **5** was synthesised according to the literature procedure.[4]

Reactions were carried out under a nitrogen atmosphere, using standard Schlenk techniques. Solvents were purified by standard methods and freshly distilled under nitrogen.

3′-Ethoxycarbonylspiro-Δ²-pyrazoline[5′,3]furan-2,5-dione (**4**): To a magnetically stirred solution of itaconic anhydride (**1**) (0.56 g, 5 mmol) in ethyl acetate (20 ml) was added ethyl diazoacetate (**2**) (0.57 g, 5 mmol) and 0.05 g of hydroquinone. The resulting mixture was stirred at room temperature under nitrogen for 48 hours. The solvent was evaporated under reduced pressure and the residual oil taken up in diethyl ether (20 ml). The slurry was subjected to ultrasonic irradiation, giving the crude crystalline product, which was then recrystallised in diethyl ether–CH_2Cl_2 (1:1).

Yield: 0.79 g (70%); white solid; m.p. 132–134°C. ν_{max} (KBr)/cm^{-1}: 3295 (N–H), 1875, 1790 (2 C=O anhydride), 1715 (C=O unsaturated ester), 1575 (C=N). δ_H: 1.30 (3H, t, J 7.3, CH_3), 2.95–3.50 (2H, AB system, J 18.6, 4′-H), 3.05–3.70 (2H, AB system, J 17.0, 4-H), 4.20 (2H, q, J 7.3, O-CH_2), 9.10 (1H, s, N-H). δ_C: 13.9 (CH_3), 43.0 (4′-C), 43.3 (4-C), 61.8 (CH_2-O), 69.9 (3,5′-C), 137.8 (3′-C), 161.8 (C=O), 167.5 (5-C), 172.8 (2-C). (Found: C, 47.70; H, 4.50; N, 12.40. $C_9H_{10}N_2O_5$ requires C, 47.77; H, 4.45; N, 12.38 %).

1,1-Diphenyl-4,6-dioxo-5-oxaspiro[2.4]heptane (**7**): To a magnetically stirred solution of itaconic anhydride (**1**) (0.56 g, 5 mmol) in ethyl acetate (20 ml) was added diphenyldiazomethane (**5**) (0.97 g, 5 mmol) and 0.05 g of hydroquinone. Immediate gas evolution was noted. The resulting mixture was stirred at room temperature under nitrogen for 6 hours. The solvent was evaporated under reduced pressure, and the residual oil taken up in diethyl ether (20 ml) and worked-up as detailed above. The crude product was recrystallised in diethyl ether-CH_2Cl_2 (1:1).

Yield: 1.055 g, 76%; white solid; m.p. 173–174°C. ν_{max} (KBr)/cm^{-1}: 1835, 1770 (2 C=O anhydride). δ_H: 2.20 (1H, d, J 5.4, 2-H), 2.45 (1H, d, J 5.4, 2-H), 2.70–2.95 (2H, AB system, J 20.1, 7-H), 7.30 (10H, s, arom-H). δ_C: 26.1 (2-C), 31.4 (1-C), 34.3 (7-C), 47.3 (3-C), 127.5–138.5 arom-C), 169.3 (6-C), 171.1 (4-C). (Found: C, 77.46; H, 5.10; N, 0.00 $C_{18}H_{14}O_3$ requires C, 77.68; H, 5.07; N, 0.00 %).

1-Carboxy-2,2-diphenyl-1-cyclopropaneethanoic acid (**8**): To a solution of anhydride **7** (69.5 mg, 0.25 mmol) in ethanol (4.1 ml) was added 0.9 ml of aqueous NaOH (2 M). The mixture was stirred and refluxed for 30 minutes. After cooling to room temperature, the solution was acidified (2M HCl). Filtration of the slurry afforded the diacid, which was recrystallised from water.

Yield: 68 mg, 92%; colourless solid; m.p.: 192–194°C. ν_{max} (KBr)/cm^{-1}: 3300–2815 (OH), 1720 (C=O acid). δ_H: 1.65 (1H, d, J 18.0, CH_2), 1.75 (1H, d, J 5.2, 3-H), 2.40 (1H, d, J 5.2, 3-H), 3.25 (1H, d, J 18.0, CH_2), 7.00–7.50 (10H, m, arom-H), 9.25 (2H, s, O–H). δ_C: 24.1 (2-C), 31.9 (3-C), 38.0 (1-C), 45.0 (CH_2), 126.7-141.5 (arom-C), 178.4 (COOH). (Found C, 73.05; H, 5.61. $C_{18}H_{16}O_4$ requires C, 72.96; H, 5.44 %).

Crystal data of cyclopropane **8**: X-Ray crystallographic analysis was caried out on a Nonius kappa CCD diffractometer. The diffraction data of MoKα radiation were collected and 4314 independent reflections were used to solve the structure with program SHELXS86[7] and refined with program SHELXL93.[8] A list of all crystallographic results have been deposited at the Cambridge Crystallographic Data Centre, UK, as Supplementary Material No CCDC 162054 (CIF File).

$C_{18}H_{16}O_4$, M 296, triclinic, $a = 9.641(2)$, $b = 9.669$ (2), $c = 19.334(4)$ Å, $\alpha = 95.54(2)°$, $\beta = 98.46$ (2)°, $\gamma = 115.82$ (2)°, $U = 1578.4(6)$ Å^3, T = 293(2) K, space group $P\text{-}1$, $Z = 4$, $\mu = 0.094$ mm^{-1}, R-values w$R_2 = 0.1313$, $R = 0.0652$ (2489 reflections with $I > 2\sigma(I)$), 43577 measured reflections, 4314 independent ($R_{int} = 0.0646$). C_1C_2 : 1542 (5) Å, C_1C_3 : 1500 (5) Å, C_2C_3 : 1499 (5) Å, $C_2C_1C_3$: 59,1 (2)°, $C_1C_2C_3$: 59,1 (3)°, $C_1C_3C_2$: 61,9 (3)°.

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