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DIELS-ALDER REACTION OF UNACTIVATED 2-AZA-1,3-DIENES WITH DIETHYL KETOMALONATE: A CARBON DIOXIDE EQUIVALENT

José Barluenga,* Francisco J. González, and Santos Fustero

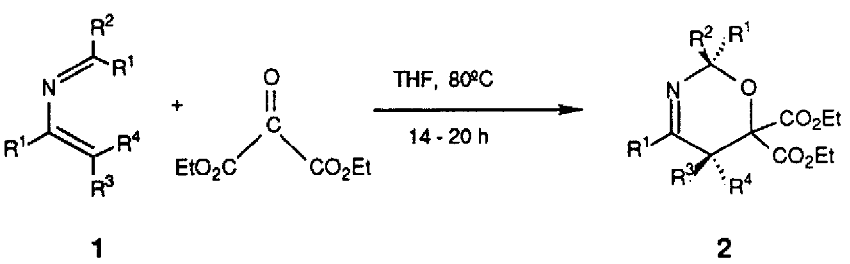
Departamento de Química Organometálica, Facultad de Química, Universidad de Oviedo, 33071-Oviedo, Spain

Summary: The [4+2] cycloaddition reaction of diethyl ketomalonate and butyl glyoxalate with unactivated 2-aza-1,3-dienes **1** is described for the first time.

The inability of the carbon dioxide to undergo [4+2] cycloaddition reactions with dienes is well known.[1] An alternative procedure is the use of diethylketomalonate as dienophile, because the diester groups attached to the carbonyl can be readily transformed in the carbon - oxygen double bond.[2] Moreover, the two diester groups are very effective in the polarization of the carbonyl in the Diels-Alder reaction with dienes.[3] In all previously reported cycloaddition reactions with diethylketomalonate only carbon dienes were employed.[2,3]

In this paper, we report the first example of a Diels-Alder reaction of unactivated 2-aza-1,3-dienes **1** with diethylketomalonate. In previous papers,[4] we have indicated the participation of unactivated 2-aza-1,3-dienes **1** in [4+2] cycloadditions with different heterodienophiles.

The reaction of **1** (10 mmol) with diethylketomalonate (10 mmol) (dry THF, 80ºC, 14 - 20 h), gave only the Diels-Alder adduct **2** when the solvents were removed (Scheme I, Table I).

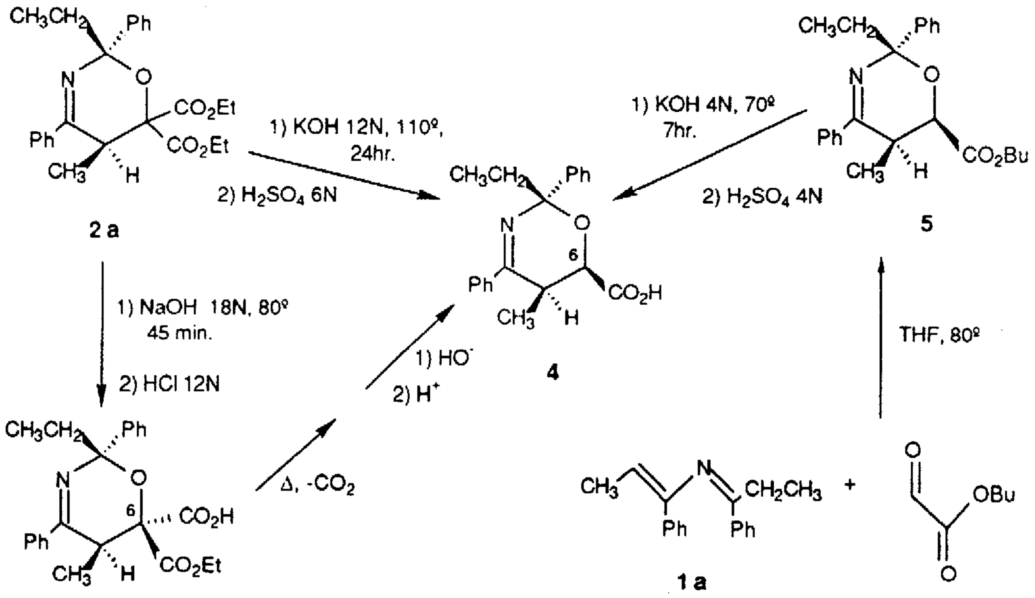


Scheme I

The reaction is rather general as can be seen from the results shown in Table I. Compounds **2** were characterized on the basis of their spectroscopic data and mass spectrometry;[5] this spectroscopic data indicates that a sole stereoisomer was identified in the crude reaction mixture.[6] The stereochemistry of the adduct **2** was tentatively assigned by comparison with other results previously obtained in the cycloaddition reactions of **1** with other dienophiles.

Table I. 6,6-Bis (ethoxycarbonyl)-5,6-dihydro-2*H*-1,3-oxazines, **2**.

Compd.	R^1	R^2	R^3	R^4	Yield(%)	m.p.(ºC)
a	Ph	Et	Me	H	90	105-7
b	Ph	Pr	Et	H	80	100-2
c	*p*-CH_3-C_6H_5	Et	Me	H	85	82-4
d	H	*i*-Pr	Me	Me	70	oil
e	Pr	Pr	Et	H	70	oil
f	C_6H_{11}	Et	Me	H	75	oil
g	Ph	Bu	Pr	H	80	93-5



Scheme II

However, in order to confirm the stereochemistry of **2**, the following reactions were carried out. When **2** (for example **2a**) was treated with KOH 12N (H_2O, 110ºC, 24 h), only the carboxylic acid **4** was isolated,[7] (70% yield) after the acid treatment of the reaction mixture (H_2SO_4 6 N / ice) (Scheme II). The ^1H NMR spectrum of **4** shows a doublet at 4.15 ppm (J = 3.1 Hz) that can be assigned to the hydrogen in C-6 in *cis* with the adjacent hydrogen.

On the other hand, the reaction of **1a** (R^1=Ph, R^2=Et, R^3=Me, R^4=H) (10 mmol) with butyl glyoxalate (10 mmol) (dry THF, 80ºC, 20hr.) gave the Diels-Alder adduct **5** (80% yield) after the solvents were removed[7] (Scheme II); the stereochemistry of the Diels-Alder adducts of 2-aza-1,3-dienes **1** with aldehydes is known.[4a] When the ester **5** was hydrolyzed with KOH 4N (THF, 70ºC, 7h), the compound obtained was the same monoacid **4** that was obtained from hydrolysis and descarboxylation of **2a** (Scheme II). This fact confirms the stereochemistry at C-6 in the acid **4**.

Furthermore, the partial hydrolysis of **2a** with NaOH 18N (THF, 80ºC, 45 min.) gave the monoester **3** (50% yield) (Scheme II), which by descarboxylation by heating at 120º during 14 h, and later hydrolysis gave the compound **4**. This correlation allows us to assign the stereochemistry of the C-6 in compound **3**, because the monoester **3** is an intermediate step in the transformation of **2a** into **4**.

In conclusion, we report here the first example of a [4+2] cycloaddition reaction of an unactivated 2-aza-1,3-diene with diethyl ketomalonate (a carbon dioxide equivalent) and with butyl glyoxalate. In addition, an example of a stereoselective descarboxylation in the 6,6-bis (ethoxycarbonyl)-5,6-dihydro-2*H*-1,3-oxazines, **2** is presented.

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5. **2a**: ^{1}H NMR ($DCCl_3$) δ 0.80 (m,6H), 1.10 (d,3H), 1.20 (t,3H), 2.10 (m,2H), 2.65 (m,1H), 3.40 (m,1H), 3.50 (m,1H), 4.20 (m,2H), 7.10-7.90 (m,10H); ^{13}C NMR ($DCCl_3$) δ 167.85 (s), 167.28 (s), 164.10 (s), 142.65 (s), 137.20 (s), 130.11-126.66 (d), 93.30 (s), 79.92 (s), 61.43 (t), 61.05 (t), 38.56 (t), 31.68 (d), 13.96 (q), 13.61 (q), 13.17 (q), 8.68 (q); MS *m/z* , 394 (M^{+}-29). **2b**:^{1}H NMR ($DCCl_3$) δ 0.40 (t,3H), 0.70 (t,3H), 0.80 (m,6H), 1.20(m,8H), 1.60 (m,6H), 1.85 (m,4H), 2.10 (m,2H), 2.65 (m,2H), 3.40 (m,2H), 3.60 (m,2H), 4.20 (m,8H), 7.10-8.0 (m,20H); ^{13}C NMR ($DCCl_3$) δ 169.15 (s), 167.54 (s), 167.04 (s), 166.86 (s), 163.61 (s), 144.43 (s), 142.55 (s), 138.59 (s), 138.32 (s), 129.54-125.59 (m), 92.51 (s), 92.47 (s), 80.79 (s), 76.68 (s), 61.40 (t), 61.12 (t), 60.79 (t), 60.46 (t), 47.57 (t), 46.05 (t), 37.95 (d), 37.83 (d), 21.86 (t), 20.96 (t), 17.06 (t), 16.34 (t), 13.65 (q), 13.50 (q), 13.41 (q), 13.19 (q), 12.73 (q), 12.37 (q), 11.75 (q); MS *m/z* , 408 (M^{+}-43). **2c**: ^{1}H NMR ($DCCl_3$) δ 0.87 (m,6H), 1.15 (d,3H), 1.27 (t,3H), 2.10 (m,2H), 2.30 (s,3H), 2.40 (s,3H), 2.76 (m,1H), 3.51 (m,2H), 4.29 (m,2H), 7.0-8.0 (m,8H); ^{13}C NMR ($DCCl_3$) δ 167.59, 167.10, 163.44, 139.90, 139.63, 136.26, 134.34, 128.80, 127.46, 127.31, 126.36, 92.97, 79.65, 61.07, 60.69, 38.29, 31.31, 20.90, 20.58, 13.72, 13.47, 12.89, 8.49;MS *m/z* , 422 (M^{+}-29). **2d**: ^{1}H NMR ($DCCl_3$) δ 0.98 (d,3H), 1.02 (d,3H), 1.07 (s,3H), 1.27 (t,3H), 1.32 (t,3H), 1.42 (s,3H), 2.08 (m,1H), 4.27 (m,4H), 4.65 (dd,1H), 7.50 (d,1H); ^{13}C NMR ($DCCl_3$) δ 165.57 (s), 164.82 (s), 164.03 (d), 89.04 (d), 82.25 (s), 60.60 (t), 60.46 (t), 35.85 (s), 32.04 (d), 22.09 (q), 20.17 (q), 16.24 (q), 13.16 (q), 13.07 (q); MS *m/z* , 299 (M^{+}). **2e**: ^{1}H NMR ($DCCl_3$) δ 0.90 (m,12H), 1.30 (m,6H), 1.40 (m,6H), 1.67 (m,4H), 2.30 (m,4H), 2.60 (m,1H), 4.20 (m,4H); ^{13}C NMR ($DCCl_3$) δ 173.28 (s), 170.39 (s), 169.08 (s), 96.40 (s), 83.11 (s), 64.68 (t), 63.40 (t), 45.61 (t), 44.83 (t), 44.63 (d), 43.88 (t), 25.45 (t), 21.99 (t), 20.60 (t), 20.53 (t), 17.91 (q), 17.43 (q), 17.25 (q), 17.09 (q), 16.73 (q); MS *m/z* , 340 (M^{+}-43). **2f**: ^{1}H NMR ($DCCl_3$) δ 0.70 (t,3H), 0.90 (t,3H), 0.95 (d,3H), 1.20 (m,14H), 1.60 (m,12H), 2.10 (m,1H), 2.91 (q,1H), 4.10 (m,4H); ^{13}C NMR ($DCCl_3$) δ 171.77 (s), 171.17 (s), 168.70 (s), 95.95 (s), 80.75 (s), 62.82 (t), 62.47 (t), 47.91 (d), 44.70 (d), 34.09 (d), 33.60 (t), 31.79 (t), 30.43-28.41 (m), 16.03 (q), 15.58 (q), 15.21 (q), 9.98 (q); MS *m/z* , 406 (M^{+}-29). **2g**: ^{1}H NMR ($DCCl_3$) δ 0.70 (m,6H), 1.10 (m,8H), 1.50 (m,6H), 1.90 (m,1H), 2.10 (m,1H), 2.60 (m,1H), 3.40 (m,2H), 4.10 (m,1H), 4.30 (m,1H), 6.90-8.0 (m,10H); ^{13}C NMR ($DCCl_3$) δ 167.8 (s), 167.1 (s), 164.0 (s), 142.6 (s), 138.4 (s), 129.7-126.6 (m), 92.78 (s), 79.81 (s), 61.07 (t), 60.75 (t), 45.16 (t), 36.73 (d), 31.15 (t), 26.09 (t), 22.39 (t), 21.10 (t), 14.02 (q), 13.61 (q), 12.94 (q); MS *m/z* , 479 (M^{+}).

6. In two cases , **2b** and **2f**, the ^{1}H NMR spectra of the crude products showed the presence of small amounts (10-15%) of the other isomer.

7. **3**: IR, (KBr) 3147, 1753, 1726; m.p., 122-5°C (d); ^{1}H NMR ($DCCl_3$) δ 0.75 (t,3H), 0.85 (t,3H), 1.10 (d,3H), 2.10 (m,2H), 2.75 (m,1H), 3.40 (m,1H), 3.60 (q,1H), 7.1-8.0 (m,10H), 9.0 (br. s,1H); ^{13}C NMR ($DCCl_3$) δ 171.1 (s), 167.8 (s), 165.0 (s), 142.3 (s), 137.0 (s), 130.2-126.0 (m), 93.9 (s), 79.9 (s), 61.4 (t), 38.2 (t), 31.7 (d), 13.6 (q), 13.5 (q), 8.7 (q); MS *m/z* , 395 (M^{+}). **4**: IR, (Nujol), $\nu_{máx.}$(cm^{-1}): 2600, 1700; ^{1}H NMR ($DCCl_3$) δ 0.90 (t,3H), 1.20 (d,3H), 2.10 (m,2H), 3.20 (m,1H), 4.15 (d, *J*=3.1 Hz,1H), 7.10-8.0 (m,10H); ^{13}C NMR ($DCCl_3$) δ 173.5 (s), 164.6 (s), 143.5 (s), 136.6 (s), 130.5-126.5 (d), 94.9 (s), 70.2 (d), 38.0 (t), 32.0 (d), 13.5 (q), 8.6 (q); MS *m/z* , 294 (M^{+}-29). **5**: ^{1}H NMR ($DCCl_3$) δ 0.88 (t,3H), 0.90 (t,3H), 1.12 (d,3H), 1.32 (m,2H),1.58 (m,2H), 2.08 (q,2H), 3.10 (m,1H), 4.10 (d,*J*= 3.1 Hz,1H), 4.16 (m,2H), 7.10-7.90 (m,10H); ^{13}C NMR ($DCCl_3$) δ 169.21 (s), 163.90 (s), 143.96 (s), 136.41 (s), 132.23-124.51 (m), 93.81 (s), 69.80 (d), 64.17 (t), 37.35 (t), 31.18 (d), 30.32 (t), 18.78 (t), 13.34 (q), 12.92 (q), 8.08 (q); MS *m/z* , 379 (M^{+}).

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