Unusual Reaction of 1,8-Diazabicyclo-[5.4.0]undec-7-ene with Diethyl Maleate

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Received January 19, 1993

Michael addition of DBU on diethyl maleate and subsequent cyclization of the adduct afforded a tricyclic derivative which was susceptible to react further with a second molecule of unsaturated diester.

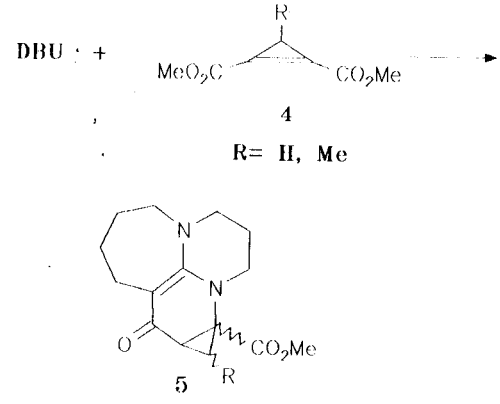
J. Heterocyclic Chem., **30**, 627 (1993).

During the course of our research on nucleophilic addition [1] of nucleobases (0.65 equivalent) on diethyl maleate (3 equivalents) in acetonitrile using DBU (1 equivalent) as a base (Scheme 1), we encountered in the case of unprotected guanine the formation of the unexpected tricyclic compounds **1** and **2a,2b** instead of the desired Michael addition product **3**.

The formation of such structures suggest clearly that nucleophilic properties of DBU are involved in this reaction. Numerous examples concerning the use of DBU in organic reactions have been recently reviewed [2], in particular: alkylations [3-6], opening of epoxides [7], addition on isocyanates and isothiocyanates [8-9] or on conjugated systems [10]. To our knowledge, only one example directly related to the tricyclic structure proposed above has been reported [11] during the reaction of DBU with methyl cyclopropene-1,2-dicarboxylate derivatives **4** (R = H, Me) which afforded the corresponding tetracyclic compounds **5** in 47-63% yield (Scheme 2).

From the results described in Scheme 1, it is clear that the yields of formation of **1** and **2** were low. In order to look at the mechanistic pathway for the formation of such a rather unusual by-products, we performed two additional experiments. These were conducted between diethyl maleate (3 and 15 equivalents) and DBU (1 equivalent) with the exclusion of any solvent for 2 days at room temperature.

Scheme 2

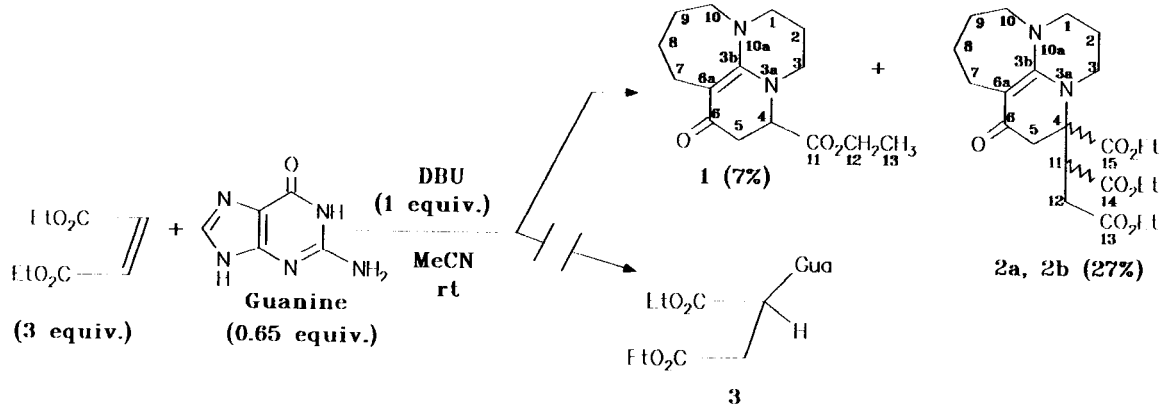


When diethyl maleate was used in a large excess (15 equivalents), compound **1** was isolated in a 13% yield accompanied by the diastereomeric mixture **2a,2b** (5%). Moreover, a three-fold excess of diethyl maleate afforded exclusively the diastereomeric mixture **2a,2b** (1:1) in a good yield (84%).

When performed with dimethyl glutaconate and dimethyl (*E*)-2-hexene-1,6-dioate, similar experiments failed in producing such a cyclic structure.

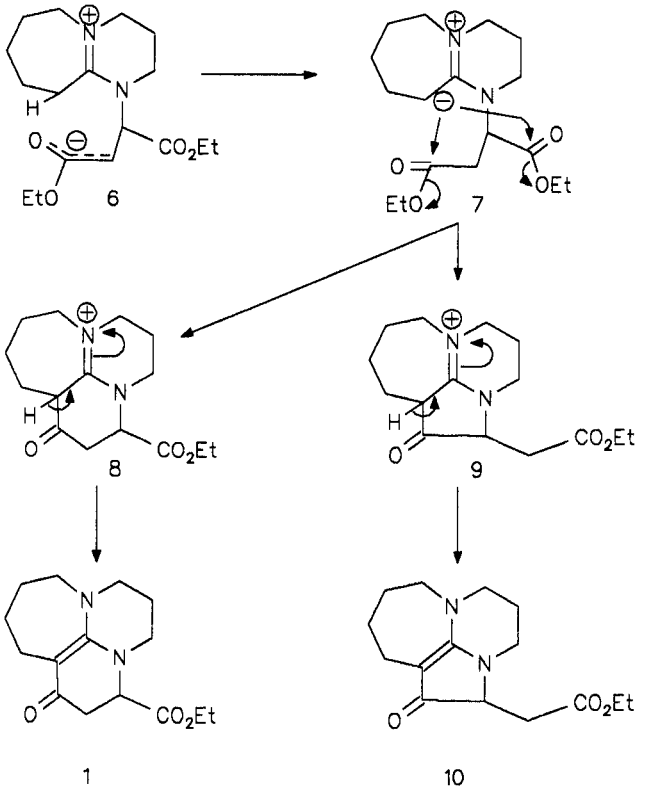
Thus, the mechanism concerning the formation of **1** could be rationalized as follows: DBU first added by a

Scheme 1



Michael addition on diethyl maleate *via* its N-8 nitrogen atom and afforded the quaternary ammonium salt **6** (Scheme 3). Subsequent abstraction of a H-6 proton by another molecule of DBU led to an intermediate ylide **7** which is susceptible to react with both ester functions to give either a six or a five-membered ring (**8** or **9**). Finally the acidic H-6 proton was abstracted and generated the incipient double bond conjugated with the carbonyl in order to produce the neutral tricyclic structure **1** or **10**.

Scheme 3



The ^{1}H-nmr spectra (COSY, NOESY) did not allow us to discriminate between these two structures. But, the ir spectra exhibited a carbonyl absorption at 1663 cm^{-1} strongly supporting a cyclohexenone *versus* a cyclopentenone ring structure [12]. Finally, the formation of a six-membered ring cyclenone was unambiguously determined by selective proton decoupling experiments of the proton coupled ^{13}C-nmr spectra. Thus, irradiation of the tertiary H-4 proton strongly modified the C-5, C-11, C-4, C-12 signals and left unchanged the C-6 signal, precluding the five-membered ring structure **10**.

Lastly, abstraction of the H-4 proton of **1** and conjugate addition of the resulting intermediate on a second molecule of diethyl maleate provided the diastereomeric equimolecular mixture **2a,2b**.

This report underscores the peculiar nucleophilic behaviour of DBU towards a 2-ethylenic-1,4-diester substrate to afford unusual tricyclic structures. It should be emphasized that such a reaction does not take place when applied generally to C5 and C6 conjugated ω-diester homologues.

EXPERIMENTAL

Diethyl maleate and DBU were used as received (Aldrich Chemical Co.). Melting points were obtained with a Büchi 510 (capillary) apparatus and are uncorrected. Elemental analyses were performed by the 'Service de Microanalyse du CNRS, Division de Vernaison'. The ^{1}H-nmr spectra were determined at 250.134 MHz on a Brüker AC250 and ^{13}C-nmr spectra at 50.32 MHz on a Brücher WP200. Mass spectra were obtained with a Jeol JMS-DX300 by the FAB ionization method.

3a,10a-Diaza-4-ethoxycarbonyl-1,2,3,7,8,9,10-heptahydrotricyclo[8.3.1.0^{3b,6a}]tetradecan 6-one (**1**).

To 20 ml (123 mmoles) of diethyl maleate was added 0.7 ml (4.7 mmoles) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature. The homogeneous solution was stirred at room temperature for 2 days. The brown solution was then chromatographed on a silica gel column using methanol (0 to 5%) in dichloromethane as the eluent to give the title compound **1** in 13% yield (0.17 g) as a solid, R_f 0.42 (dichloromethane:methanol 90:10), mp 82-83°; ^{1}H-nmr (deuteriochloroform): δ 1.17 (t, 3H, OCH_2CH_3, J = 7.09 Hz), 1.54 (m, 2H, 8'- and 8''-H), 1.76 (m, 2H, 9'- and 9''-H), 1.92 (m, 2H, 2'- and 2''-H), 2.13 (m, 1H, 7'-H), 2.19 (m, 1H, 7''-H), 2.39 (dd, 1H, 5'-H, J = 7.1, 15.8 Hz), 2.69 (dd, 1H, 5''-H, J = 4.51, 15.8 Hz), 3.08 (m, 2H, 3'- and 3''-H), 3.22 (t, 2H, 1'- and 1''-H, J = 5.5 Hz), 3.31 (m, 2H, 10'- and 10''-H), 3.66 (dd, 1H, 4'-H, J = 4.5, 7.1 Hz), 4.03 (q, 1H, OCH_2CH_3, J = 7.09 Hz), 4.04 (q, 1H, OCH_2CH_3, J = 7.09 Hz); ^{13}C-nmr (DMSO-d$_6$): δ 13.97 (1C, OCH_2CH_3), 20.62 (1C, 7-C), 21.56 (1C, 2-C), 25.64 (1C, 8-C), 28.17 (1C, 9-C), 35.49 (1C, 5-C), 40.12 (1C, 3-C), 48.07 (1C, 1-C), 52.68 (1C, 10-C), 59.95 (1C, OCH_2CH_3), 62.48 (1C, 4-C), 91.98 (1C, 6a-C), 168.35 (1C, 3b-C), 171.06 (1C, C(O)OEt), 188.08 (1C, 6-C); ms: 557 (1.7), 385 (1.25), 279 (100), 205 (10).

Anal. Calcd. for $C_{15}H_{22}N_2O_3$ (278.354): C, 64.72; H, 7.97; N, 10.07; O, 17.24. Found: C, 64.79; H, 7.91; N, 9.95; O, 17.45.

3a,10a-Diaza-4-ethoxycarbonyl-4-[11-ethoxycarbonylethylpropionate]-1,2,3,7,8,9,10-heptahydrotricyclo[8.3.1.0^{3b,6a}]tetradecan-6-one (**2a**) and (**2b**).

To 20 ml (123 mmoles) of diethyl maleate, was added 6 ml (40.12 mmoles) of DBU at room temperature. The homogeneous solution was stirred at room temperature for 2 days. The brown solution was then chromatographed on a silica gel column using methanol (0 to 5%) in dichloromethane as the eluent to give as an oil the mixture **2a,2b** (15.18 g) in 84% yield. Further purification of analytical samples was performed on preparative tlc (dichloromethane:methanol 95:5) to afford **2a** as an oil and **2b** as a solid. These compounds were stored under argon at −18° to avoid decomposition.

Compound **2a** had R_f 0.55 (dichloromethane:methanol 90:10); ^{1}H-nmr (DMSO-d$_6$): δ 1.15 (m, 9H, OCH_2CH_3), 1.57 (m, 2H, 8'- and 8''-H), 1.77 (m, 2H, 9'- and 9''-H), 1.92 (m, 2H, 2'- and 2''-H), 2.18 (m, 2H, 7'- and 7''-H), 2.36 (dd, 1H, 12'-H, J = 4.1, 16.76 Hz), 2.48 (dd, 1H, 12''-H, J = 11.14, 16.76 Hz), 2.75 (d, 1H, 5'-H, J = 14.6 Hz), 2.83 (d, 1H, 5''-H, J = 14.6 Hz), 3.1 (m, 1H, 3'-H), 3.23 (m, 2H, 3'- and 11'-H), 3.28 (m, 4H, 1'-, 1''-, 10'- and 10''-H), 4.02 (m, 6H, OCH_2CH_3); ^{13}C-nmr (DMSO-d$_6$): δ 13.68 (1C, OCH_2CH_3), 13.84 (2C, OCH_2CH_3), 19.96 (1C, 7-C), 21.18 (1C, 2-C), 25.4 (1C,

8-C), 27.77 (1C, 9-C), 30.51 (1C, 12-C), 37.26 (1C, 5-C), 40.12 (1C, 3-C), 44.73 (1C, 11-C), 47.69 (1C, 1-C), 51.98 (1C, 10-C), 59.63 (1C, OCH_2CH_3), 59.84 (1C, OCH_2CH_3), 59.93 (1C, OCH_2CH_3), 66.92 (1C, 4-C), 91.76 (1C, 6a-C), 166.95 (1C, 13-C), 168.99 (1C, 3b-C), 170.28 (1C, 14-C), 171.5 (1C, 15-C), 186.19 (1C, 6-C); ms: 451 (100), 423 (5), 377 (5), 277 (10), 205 (30).

Anal. Calcd. for $C_{23}H_{34}N_2O_7$ (450.536): C, 61.31; H, 7.61; N, 6.22; O, 24.86. Found: C, 61.11; H, 7.44; N, 6.01; O, 25.02.

Compound **2b** had R_f 0.5 (dichloromethane:methanol 90:10), mp 82-84°; ^{1}H-nmr (DMSO-d_6): δ 1.01 (m, 9H, OCH_2CH_3), 1.41 (m, 2H, 8′- and 8″-H), 1.63 (m, 2H, 9′- and 9″-H), 1.85 (m, 2H, 2′- and 2″-H), 2.05 (m, 3H, 11′-, 7′- and 7″-H), 2.55 (d, 1H, 5′-H, J = 13.94 Hz), 2.63 (d, 1H, 5″-H, J = 13.94 Hz), 2.78 (dd, 1H, 12′-H, J = 11.83, 17.03 Hz), 3.02 (dd, 1H, 12″-H, J = 11.83, 2.97 Hz), 3.15 (m, 2H, 3′- and 3″-H), 3.28 (m, 4H, 1′-, 1″-, 10′- and 10″-H), 3.88 (m, 6H, OCH_2CH_3); ^{13}C-nmr (DMSO-d_6): δ 13.85 (3C, OCH_2CH_3), 19.84 (1C, 7-C), 21.08 (1C, 2-C), 25.27 (1C, 8-C), 27.59 (1C, 9-C), 30.34 (1C, 12-C), 36.86 (1C, 5-C), 37.74 (1C, 3-C), 45.85 (1C, 11-C), 47.74 (1C, 1-C), 51.72 (1C, 10-C), 59.79 (1C, OCH_2CH_3), 60 (1C, OCH_2CH_3), 60.35 (1C, OCH_2CH_3), 61.01 (1C, 4-C), 91.8 (1C, 6a-C), 168.48 (1C, 13-C), 168.6 (1C, 3b-C), 171.42 (1C, 14-C), 171.44 (1C, 15-C), 186.2 (1C, 6-C); ms: 451 (100), 423 (10), 377 (8), 277 (20), 205 (40).

Anal. Calcd. for $C_{23}H_{34}N_2O_7$ (450.536): C, 61.31; H, 7.61; N, 6.22; O, 24.86. Found: C, 61.25; H, 7.63; N, 6.09; O, 25.12.

Acknowledgments.

The authors are deeply grateful to the "Ligue Nationale contre le Cancer" for a grant (to M. P.) and to A. N. R. S. (Agence Nationale de Recherche contre le Sida) for generous support.

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