An unusual by-product from a non-synchronous reaction between ethyl 1,2,4-triazine-3-carboxylate and an enamine

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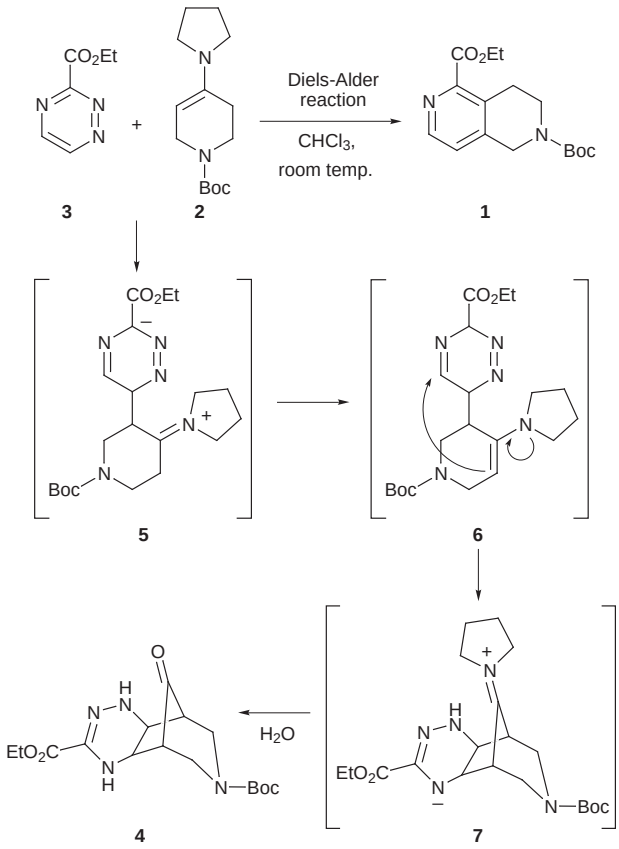
The main product from the reaction of ethyl 1,2,4-triazine-3-carboxylate 3 and the pyrrolidine enamine of *N-tert*-butoxycarbonylpiperidone 2 was an azabicyclo[3.2.1]octane 4 which resulted not from a Diels–Alder reaction, but from a series of non-synchronous steps, demonstrating a heretofore unknown reaction pathway for the electron-deficient diene 3 and electron-rich dienophile 2.

Utilization of 1,2,4-triazines as electron-deficient dienes in inverse electron demand Diels–Alder reactions with enamines has found extensive use for the synthesis of substituted pyridine derivatives. The work of Boger,[1] Taylor,[2] Snyder[3] and others have demonstrated the generality and utility of this approach to functionalized pyridines.

In a series of studies,[4] Boger and Panek examined the reaction of ethyl 1,2,4-triazine-3-carboxylate **3**[5] with a variety of enamines, and found those reactions to be relatively low yielding and complicated by uncharacterized side products. However, we desired the tetrahydronaphthyridine **1** (Scheme 1) for a medicinal chemistry study and believed that the inverse electron demand Diels–Alder reaction between **3**[5] and the enamine derived from *N-tert*-butoxycarbonyl-4-piperidone **2** would provide rapid access to the desired heterocycle **1** (Scheme 1). The necessary enamine **2** was directly available from the reaction of pyrrolidine and *N-tert*-butoxycarbonyl-4-piperidone in anhydrous Et_2O in the presence of anhydrous $MgSO_4$, and the 1,2,4-triazine **3** was available from previous studies.[5] Reaction of **2** and **3** in $CHCl_3$ at room temperature provided only a trace (8%) of the desired tetrahydronaphthyridine **1** (Scheme 1).[6] The major component of the reaction mixture (26%) was an unidentified product whose preliminary spectral data suggested the incorporation of both components **2** and **3** from the reaction without the elimination of nitrogen as would be seen in a Diels–Alder adduct. Extensive NMR studies and mass spectral data suggested that the compound was a tetrahydro-1,2,4-triazine fused to an azabicyclo[3.2.1]octane core (**4**, Scheme 1).[7] Crystals were prepared of this compound (ethyl acetate–benzene) of sufficient quality that X-ray diffraction studies could be performed, and this experiment confirmed the structure of the by-product as that depicted by **4** (Fig. 1).[8]

The azabicyclo[3.2.1]octane clearly was not the result of a Diels–Alder reaction. A likely mechanism for its formation is shown in Scheme 1. The electron-rich β-position on enamine **2** attacked the electron-deficient C6 position of 1,2,4-triazine **3** in a vinylogous Michael reaction fashion. The negative charge introduced into the 1,2,4-triazine ring was stabilized by the electron-delocalizing carboxylate located at C3 of the heterocycle. Probably because of this stabilized zwitterionic species **5**, the ammonium moiety that resulted from the vinylogous Michael attack of the enamine underwent a proton transfer reaction which protonated the enolate and reformed the enamine, leading to **6**. The enamine **6** then attacked the proximate imine (Scheme 1) forming intermediate ammonium species **7** which yielded **4** upon hydrolysis.

These results, coupled with evidence from the literature,[4,9,10] suggest that the presence of an electron-delocalizing substituent at C3 of the 1,2,4-triazine can shift the balance of reactivity from a concerted Diels–Alder reaction to a stepwise, non-synchronous reaction which gives rise to the observed by-



Scheme 1

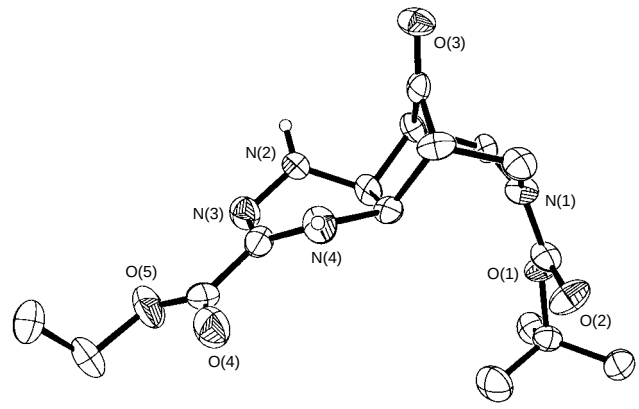


Fig. 1 Crystal structure of **4**

product **4**, especially if the C6 position is unsubstituted. The presence of the ethoxycarbonyl group provided resonance stabilization of the negative charge introduced into the 1,2,4-triazine ring from the attack of the enamine. This and possibly the steric hindrance of the ethoxycarbonyl group discouraged further reaction of C3 of the 1,2,4-triazine with the electrophilic iminium species in **5**, leading to the creation of the second enamine moiety. This newly formed enamine could then react in a relatively unhindered fashion, leading to the 7-azabicyclo[3.2.1]octane moiety found in **4**.

The result of this reaction might have general implications for the reactions of enamines (and other electron-rich dienophiles) with 1,2,4-triazines (or other electron-poor dienes) in attempted inverse electron demand Diels–Alder reactions. Previous examples of enamines reacting with azadienes with electron-delocalizing substituents on *both* carbon atoms involved with the Diels–Alder reaction (*i.e*. diethyl 1,2,4,5-tetrazine-3,6-dicarboxylate[9] and triethyl 1,2,4-triazine-3,5,6-tricarboxylate[4b]) are generally high yielding, suggesting that non-synchronous side reactions are either minimal or nonexistent. For example, triethyl 1,2,4-triazine- 3,5,6-tricarboxylate reacted with the pyrrolidine enamine derived from phenyl *n*-propyl ketone to afford the expected pyridine in 73% yield, whereas ethyl 1,2,4-triazine-3-carboxylate afforded only 10% of its expected pyridine when reacted with the same enamine.[4b] Also, when 3-(dimethoxymethyl)-1,2,4-triazine was used in place of ethyl 1,2,4-triazine-3-carboxylate, the Diels–Alder reactions of the acetal with enamines proceeded in higher yield.[4a] Therefore, it would appear that only in those cases where a resonance delocalizing group exists on one of the carbon atoms involved with the Diels–Alder reaction and the other, *para* carbon atom on the azadiene is unsubstituted, the balance of reactivity may be sufficiently altered to allow for, or favor, non-synchronous reactions such as vinylogous Michael reactions which would limit the amount of Diels–Alder product seen from these reactions. The result of these reactions would be products analogous to **4**. We are presently attempting to examine the generality of this hypothesis, and the implications for inverse electron demand Diels–Alder reactions.

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Notes and References

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3 S. C. Benson, L. Lee and J. K. Snyder, *Tetrahedron Lett.*, 1996, **37**, 5061 and references cited therein; W.-H. Fan, M. Parikh and J. K. Snyder, *Tetrahedron Lett*., 1995, **36**, 6591 and references cited therein.
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6 *Selected data* for **1**: δ_H($CDCl_3$, 200 MHz) 8.50 (d, *J* 4.9, 1 H), 7.19 (d, *J* 4.9, 1 H), 4.63 (s, 2 H), 4.46 (q, *J* 7.1, 2 H), 3.66 (br t, *J* 5.9, 2 H), 3.17 (br t, *J* 5.9, 2 H), 1.50 (s, 9 H), 1.44 (t, *J* 7.1, 3 H); *m*/*z* (FAB LRMS) 308 (18%), 307 ([MH]$^+$, 96), 251 (100), 207 (8), 57 (71).
7 *Selected data* for **4**: white solid; mp 187.5–189.5 °C with effervescence; ν_{max}(KBr)/cm^{-1} 3359 (br), 1759, 1701, 1640; δ_H(DMSO, 500 MHz, 340 K) 6.66 (br m, NH), 6.48 (d, *J* 4.0, NH), 4.27 (br dd, *J* 12.7 and 12.9, 2 H), 4.19 (q, *J* 7.0, 2 H), 3.85 (t, *J* 5.0, 1 H), 3.39 (d, *J* 5.6, 1 H), 3.28 (d, *J* 12.7, 1 H), 3.19 (d, *J* 12.9, 1 H), 2.33 (s, 1 H), 2.26 (s, 1 H), 1.43 (s, 9 H), 1.24 (t, *J* 7.0, 3 H); δ_C(DMSO, 500 MHz, 340 K) 215.1, 161.3, 154.1, 137.4, 79.8, 60.7, 53.8, 53.2, 52.6, 52.4, 51.8, 50.3, 28.0, 14.0; *m*/*z* (FAB LRMS) 354 (19%), 353 ([MH]$^+$, 100), 297 (27). Calc. for $C_{16}H_{24}N_4O_5$: C 54.54; H, 6.87; N, 15.90. Found: C, 54.29; H, 6.93; N, 15.73%).
8 Crystals of **4** were grown in a concentrated EtOAc–benzene solution, and benzene was incorporated into the crystalline lattice in a ratio of 1 : 1 with **4**. A small single crystal was mounted on glass fiber under Paratone-8277 and placed on the X-ray diffractometer in a cold N_2ogen stream supplied by a Siemens LT-2A low temperature device. The X-ray intensity data were collected on a standard Siemens SMART CCD Area Detector System equipped with a normal focus molybdenum target X-ray tube operated at 2.0 kW (50 kV, 40 mA). A quadrant of data were collected using a narrow frame method with scan widths of 0.3° in *w*, and an exposure time of 30 s per frame. Frames were integrated to 40° with the Siemens SAINT program yielding a total of 3416 reflections, of which 1832 were independent reflections [*R*(int) = 0.0700]. The unit cell parameters were based upon the least-squares refinement of three dimensional centroids of 857 reflections at −80 °C, giving a monoclinic cell with *a* = 15.038(1), *b* = 13.967(1), *c* = 10.777(1) Å, β = 99.594(4)°, *V* = 2232.0(2) Å^3. The space group was assigned as $P2_1/c$ (*Z* = 4 and D_c = 1.281 g cm^{-3}) on the basis of systematic absences using the XPREP program (Siemens, SHELXTL 5.04). The absorption coefficient was 0.092 mm^{-1}. The structure was solved by direct methods and refined by full-matrix least-squares on F^2. All non-hydrogen atoms were refined with anisotropic thermal parameters, with H atoms included in idealized positions. The empirical formula is $C_{16}H_{24}N_4O_5{\cdot}C_6H_6$ giving a formula weight of 430.50 g mol^{-1}. Final *R* indices [1143 data having $I > 2\sigma(I)$]; R_1 (%) = 7.90 [R_1 = 0.0790; wR_2 = 0.1481]. CCDC 182/810.
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