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Tandem Dimerization and Double Annulation of 3,3,4,4-Tetracyanobutanal Acetal. Synthesis of a Bicyclic 2-Aminopyridine Derivative

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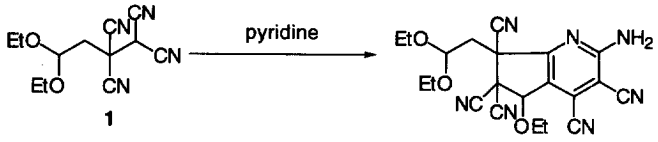
Abstract: 3,3,4,4-Tetracyanobutanal acetal **1**, which is easily obtained from tetracyanoethylene, ethyl vinyl ether, and ethanol, yielded 2-aminopyridine derivative **2** fused with cyclopentane in one pot in the presence of pyridine. On the basis of several experiments, the proposed mechanism involves the Michael reaction of **1** with the diene generated by the elimination of hydrogen cyanide and ethanol from **1**, followed by double intramolecular nucleophilic additions to the cyano groups. © 1999 Elsevier Science Ltd. All rights reserved.

We have reported the ring-opening polymerization of the cyclobutane adducts of strong acceptor olefins and vinyl ethers for the otherwise difficult synthesis of alternating copolymers of strong acceptor olefins and strong donor olefins.[1] When we studied the chain transfer reaction in the anionic polymerization of the cyclobutane adduct[2] of tetracyanoethylene (TCNE) and ethyl vinyl ether (EVE), we found an unprecedented annulation of acetal **1** that is easily obtained just by the addition of TCNE-EVE cyclobutane into ethanol.[3] We now report the tandem dimerization and double annulation of **1** catalyzed by pyridine yielding 2-aminopyridine derivative **2** fused with cyclopentane, and discuss the reaction mechanism.



1 **2**

Acetal **1** was reacted with equimolar pyridine[4] in CH_3CN at room temperature to yield a fluorescent compound, purple-colored in solution. On excitation at 302 nm in CH_3CN it emits fluorescence between 400 and 540 nm (maximum at 445 nm). The IR spectrum showed the characteristic absorptions of an amino group at

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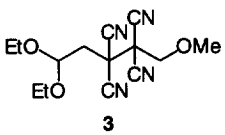
3436, 3346, and 1587 cm^{-1} and the absorptions attributable to a pyridine ring at 1644, 1569, 1485, and 1443 cm^{-1}. The ^1H NMR spectrum showed the signals of three ethoxy groups, one acetal methine and adjacent methylene group, and the broad signal of one amino group. In the ^{13}C NMR spectra, the characteristic signals assignable to the acetal carbon, cyano group, and ethoxy group were observed, but the signals of the quaternary carbon were not useful for the structure determination. Furthermore, several assignable signals appeared as a twin in ^1H and ^{13}C NMR spectra, implying that the product was a diastereomeric mixture.[5] The isomers were separated by recrystallization from the hexane-ethyl acetate solution, and the structure of **2** was unambiguously confirmed by a single-crystal X-ray analysis.[6] The result of X-ray crystallographic analysis is depicted in Figure 1.[7] The compound **2** is found to be a 2-aminopyridine derivative fused with a cyclopentane structure. The crystallized isomer was the anti-isomer regarding the cyano and ethoxy groups on the cyclopentyl ring, while the isomer in the mother liquid would be the syn-isomer.[8]

The compound **2** should be produced by the dimerization of **1** and the elimination of 1 equiv of ethanol and hydrogen cyanide. Some experiments were conducted in order to establish the reaction mechanism and the following results were obtained. (1) Compound **3**, in which the acidic proton on the dicyano methine group was replaced by the methoxy methyl group, was inert under the same conditions. (2) The reaction of **1** in MeOH yielded the product **4** in which the ethoxy group on the cyclopentyl group was replaced by the methoxy group. (3) Similar reaction was carried out in a large amount of methanol to give dienes **5**[9] and **6**[10] as well as **4**. (4) Compound **7**,[1f] in which two cyano groups were replaced by the methoxycarbonyl group, did not react under the same conditions.[11] (5) The Michael reaction of **1** with methyl vinyl ketone in the presence of pyridine afforded aminocyclopentene **8**[12] as well as the Michael adduct.



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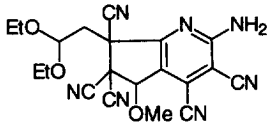

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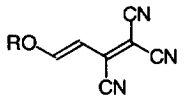
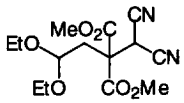


5: R = Et
6: R = Me



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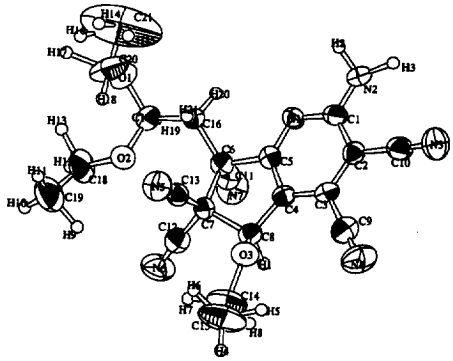
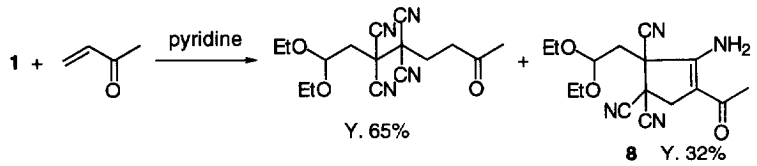


Figure 1. The X-ray crystal structure of **2**

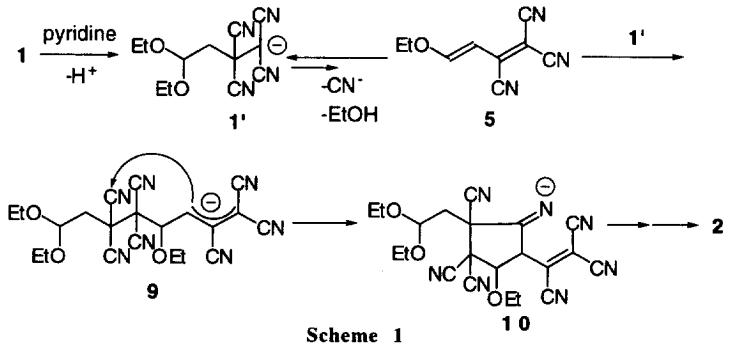


Y. 65%

8 Y. 32%

On the basis of the above results, we propose the mechanism depicted in Scheme 1 for this dimeric bicyclization. The dimerization involves the nucleophilic addition of carbanion **1'** to diene **5** that is generated by the elimination of hydrogen cyanide and ethanol from **1**. The dimer anion **9** undergoes intramolecular addition to the cyano group to form the cyclopentyl structure in a similar manner as the Michael reaction of **1** with methyl

vinyl ketone. The imino anion **10** attacks the terminal cyano group, followed by aromatization to construct the 2-aminopyridine structure.[13] To confirm this mechanism, the reaction of **1** with equimolar isolated **5** was carried out in the presence of pyridine to yield **2** in 77% yield based on **5**.[14] If **2** originated only from **1**, the yield of **2** should be less than 50% based on **5**. The higher yield of **2** certainly means that **1** reacted with **5** to give **2**.



Scheme 1

In summary, our results demonstrate that acetal **1**, easily obtained from TCNE, EVE, and ethanol, yields a bicyclic 2-aminopyridine derivative **2** in the presence of pyridine at room temperature, and reveal that this reaction is initiated by the addition of **1** to diene **5** generated from **1**. Such a highly efficient method for the synthesis of biologically important 2-aminopyridines is expected to have applications in the areas of pharmaceutical products and agricultural chemicals.

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References and Notes

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2. J. K. Williams, D. W. Wiley, B. C. McKusick, *J. Am. Chem. Soc.* **1962**, *84*, 2210-2215.
3. a) I. Karle, J. Flippen, R. Huisgen, R. Schug, *J. Am. Chem. Soc.* **1975**, *97*, 5285-5287; b) R. Huisgen, *Acc. Chem. Res.* **1977**, *10*, 117-124; c) *idem., ibid.* **1977**, *10*, 199-206.
4. The product **2** was also obtained in almost the same yields by using 2,6-lutidine or 4-dimethylaminopyridine.
5. **2**: To a solution of **1** (0.246 g, 1.0 mmol) in dry CH_3CN (1.0 mL) was added a solution of dry pyridine (0.087 g, 1.1 mmol) in CH_3CN (1.0 mL), and the mixture was stirred for 2.5 h. The reaction mixture was poured into sat. NH_4Cl solution and extracted with CH_2Cl_2, washed with water, followed by drying over $MgSO_4$. The solution was concentrated *in vacuo*, and the residue was purified by flash chromatography on

SiO_2 (hexane-ethyl acetate) then followed by preparative HPLC (chloroform) to give **2** (0.185 g, 88%); m.p. 168-174 °C; IR (KBr): 3436, 3346, 3232, 2980, 2932, 2896, 2224, 1644, 1569, 1587, 1485, 1443, 1228, 1122, 1035, 864 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.95 for the anti-isomer and 6.01 for the syn-isomer (2s, 2H), 5.61 for the anti-isomer and 5.39 for the syn-isomer (2s, 1H), 4.97 (dd, J = 7.3 and 3.1 Hz, 1H), 4.30-4.26 for the anti-isomer and 4.26-4.21 for the syn-isomer (2m, 1H), 4.15-4.09 for the anti-isomer and 4.03-4.00 for the syn-isomer (2m, 1H), 3.88-3.42 (m, 1H), 3.75-3.65 (m, 3H), 2.96 for the anti-isomer and 2.88 for the syn-isomer (2dd, J = 3.1 and 15.3 Hz, 1H), 2.46 for the anti-isomer and 2.38 for the syn-isomer (2dd, J = 7.3 and 15.3 Hz), 1.48 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.3, 158.0, 124.0, 121.3, 113.8, 112.5, 111.0, 108.8, 98.8, 95.7, 85.2, 70.0, 63.2, 62.0, 51.7, 51.4, 37.8, 15.1, 14.8, 14.6 for the anti-isomer, 161.5, 161.2, 124.3, 122.4, 113.9, 112.4, 111.6, 111.2, 110.3, 99.1, 95.0, 84.4, 70.6, 63.4, 62.1, 51.8, 51.6, 38.5, 15.3, 15.0, 14.7 for the syn-isomer; MS: [*m/z*]: 420 [MH^+], 419 [*M*], 374 [*M*-EtO]. Elemental analysis calcd for $C_{21}H_{21}N_7$: C 60.14, H 5.05, N 23.38; found: C, 60.00, H 5.18, N 23.24.

6. Texsan software was employed for the entire structure analysis.
7. Crystal data for **2**: colorless prism, crystal dimensions 0.20 × 0.20 × 0.30 mm, $C_{21}H_{21}O_3N_7$, M_r = 419.44, monoclinic, space group $P2_1/n$(no. 14), a = 11.231(8), b = 12.815(4), c = 16.525(3), β = 108.56(2) Å, V = 2254(1) $Å^3$, ρ_{calcd} = 1.235 gcm^{-3}, Z = 4, $F(000)$ = 880.00, $\mu(Mo_{K\alpha})$ = 0.87 cm^{-1}, $\lambda(Mo_{K\alpha})$ = 0.71069 Å; 4338 reflections measured, 1924 observed ($I>3.00\sigma(I)$); number of variables 281; $R1$ = 0.075; $wR2$ = 0.082.
8. The ratio of isomers was estimated to be anti/syn = 72/28 by ^1H NMR spectrum.
9. **5**: IR (KBr): 3058, 2998, 2224, 1590, 1260, 1005, 954, 900, 846 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.74 (t, J = 11.8 Hz, 1H), 6.27 (d, J = 11.8 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 167.7, 139.5, 111.5, 111.4, 110.7, 103.9, 83.7, 71.5, 14.7.
10. **6**: IR (KBr): 3058, 2224, 1596, 1269, 1005, 969, 846, 838 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.76 (t, J = 12.0 Hz, 1H), 6.24 (d, J = 12.0 Hz, 1H), 4.02 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.2, 139.3, 111.3, 111.2, 110.6, 103.0, 84.5, 60.8.
11. 4,4,3-Tricyano-3-methoxycarbonylbutanal diethyl acetal[1e] reacted with triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give a bicyclic 2-aminopyridine derivative similar to **2** in low yield.
12. **8**: IR (neat): 3400, 3292, 2980, 2932, 2896, 2254, 1659, 1614, 1125, 1062, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.83 (br, 2H), 4.94 (dd, J = 4.0 and 7.8 Hz, 1H), 3.96-3.90 (m, 3H), 3.79-3.65 (m, 1H), 3.51 (d, J = 13.7 Hz, 1H), 3.42 (d, J = 13.7 Hz, 1H), 2.53 (dd, J = 7.8 and 14.9 Hz, 1H), 2.39 (dd, J = 4.0 and 14.9 Hz, 1H), 2.15 (s, 3H), 1.31 and 1.27 (2t, J = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.7, 153.9, 113.9, 112.6, 111.9, 100.3, 100.2, 64.9, 52.5, 43.7, 38.9, 36.8, 28.5, 15.2, 14.8.
13. For the synthesis of cyano-substituted 2-aminopyridine from 2-alkoxy-1,1-dicyanoethylene and enamine, see: a) H. Kurihara, H. Mishima, *J. Heterocycl. Chem.* **1977**, *14*, 1077-1079; b) T. W. Bell, Z. Hou, S. C. Zimmerman, P. A. Thiessen, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2163-2165.
14. Into a solution of **1** (0.246 g, 1.0 mmol) and **5** (0.174 g, 1.0 mmol) in dry CH_3CN (2.0 mL) was added a solution of dry pyridine (0.08 mL, 1.0 mmol) in dry CH_3CN (2.0 mL), and the mixture was stirred for 14 h. After evaporation of the solvent, CH_2BrCl (0.127 g, 0.982 mmol) as an internal standard was added to the residue. The yield of **2** was determined by the signal intensity ratio of **2** to that of CH_2BrCl in the ^1H NMR spectrum in $CDCl_3$.