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ONE-STEP CONSTRUCTION OF 6-AZA-2-THIABICYCLO[3.3.1]NONA-3,7-DIENE FRAMEWORK

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Abstract – The 6-aza-2-thiabicyclo[3.3.1]nona-3,7-diene framework was constructed upon treatment of dielectrophilic 3,5-dinitro-1-methyl-2-pyridone with *S*,*C*-dinucleophilic ethyl 3-thioxobutanoate, in which two moieties are connected by forming two bonds in the single manipulation.

The methods for constructing the 2-azabicyclo[3.3.1]nonane (ABCN) framework are relatively well-established[1] that are employed in syntheses of alkaloids. On the other hand, the similar framework having an additional sulfur atom has been rarely synthesized despite expectation of different properties. With regard to the 6-aza-2-thiabicyclo[3.3.1]nonane (ATBCN) framework, only a few descriptions are found in the literature.[2,3] Vedejs *et al*. isolated a ATBCN derivative by intramolecular Michael addition using α,β-unsaturated thiolactone, and it was then converted to eight membered ring products.[2] As another example, ATBCNs are also prepared by heating 2-(2-aminophenyl)benzothiopyran-4-one in ethanol with tin chloride, in which fused aromatic rings are necessary for stabilizing the ATBCN framework.[3] These procedures are effective for constructing the ATBCN framework, however, preparation of starting materials is somewhat troublesome. From this viewpoint, development of concise method for synthesizing the ATBCN framework is required. Meanwhile, 1-methyl-3,5-dinitro-2-pyridone (**1**)[4] serves as an excellent dielectrophile[5] to afford ABCN derivative upon treatment with 1,3-dicarbonyl compounds.[5a] This result prompted us to employ a combination of pyridone (**1**) and ethyl 3-thioxobutanoate (**2**)[6] as the source of *S*,*C*-dinucleophilic reagent for preparing the ATBCN derivative.

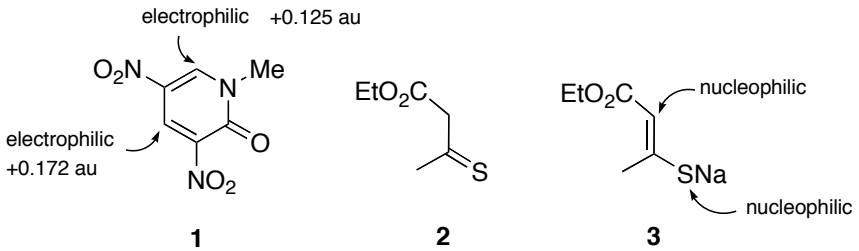
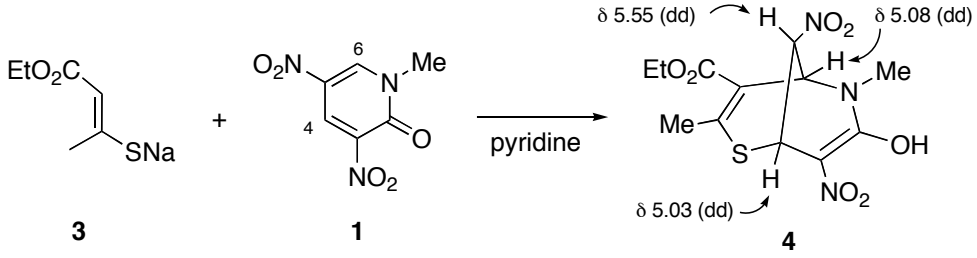


Figure 1. Substrates (**1-3**)



Conditions	Yield / %
70 °C, 2 h	13
50 °C, 2 h	63
rt, 2 d	83

Scheme 1. Reactions of dinitropyridone (**1**) with thioenolate (**3**) leading to **4**

When pyridone (**1**) was treated with sodium thioenolate (**3**) at 70 °C for 2 h, complicated reaction mixture was afforded. However, desired adduct (**4**) was isolated in 13% yield as a single isomer by simple recrystallization. Lower temperature was essential for the reaction to avoid side reactions, and the yield was increased up to 83%.

The MS spectrum and analytical data obviously indicated that **4** should be 1:1 adduct of **1** and **2**. In the ^{1}H NMR, three signals having two coupling constants were observed between 5-5.6 ppm, which shows the spins of the protons influence each other. One of the couplings is ascribed to an interaction between two bridgehead protons in the bicyclic system.[7] The structure of **4** was finally determined by X-ray crystal structure analysis (Figure 2) besides spectral data. The ATBCN (**4**) is a formal adduct resulted from stepwise additions of *S*-nucleophilic site of **2** at the 4-position of **1** and of *C*-nucleophilic site at the 6-position, respectively, thus two reaction paths are plausible as shown in Scheme 2. Semiempirical molecular orbital calculations (PM5)[8] indicate that C(4) of pyridone (**1**) is more positive than C(6) as shown in Figure 1 suggesting *S*-attack occurs prior to *C*-attack.[5c] However, the other mechanism initiated by *C*-attack cannot be excluded completely.

ATBCN (**4**) was stable to be recovered even though it was heated at 80 °C with *p*-toluenesulfonic acid or with sodium ethoxide in ethanol. Such stability of **4** would be advantageous for various biological assays. In summary, we demonstrated a new method for constructing the ATBCN framework with a single manipulation, in which two bonds are formed.

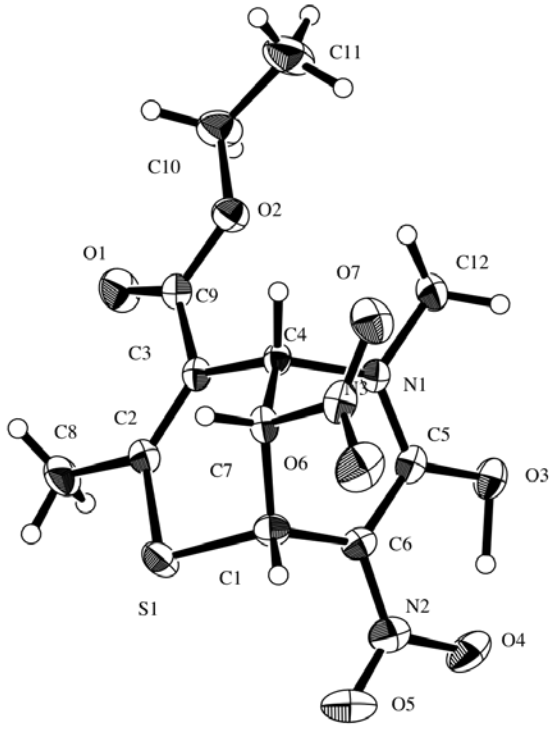
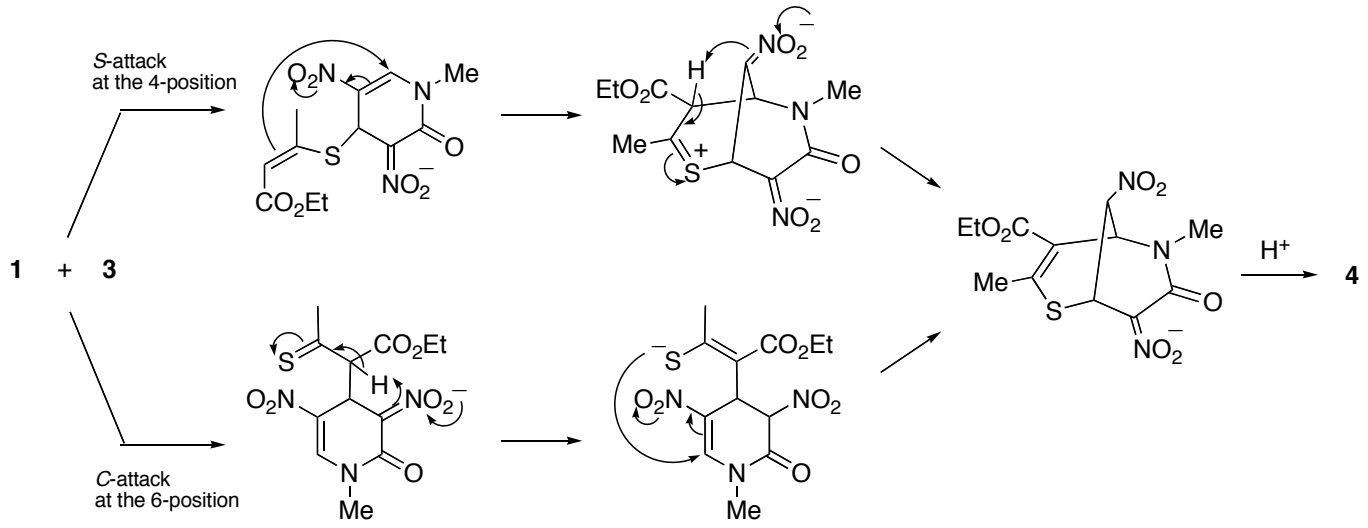


Figure 2. An ORTEP drawing of **4** with 30% probability thermal ellipsoids



Scheme 2. Plausible mechanism

EXPERIMENTAL

Melting point was measured on a Yanaco micro melting point apparatus and uncorrected. The IR spectrum was recorded on a Horiba FT-200 IR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were measured on a Brucker DPX-400 at 400 MHz and on a JEOL-FT-NMR GSX at 68 MHz, respectively with TMS as an internal standard. MS spectrum was recorded on a Shimadzu GCMS-QP2000 mass spectrometer, and elemental microanalysis was performed using a Yanaco MT-3 CHN corder.

6-Aza-8,9-dinitro-4-ethoxycarbonyl-7-hydroxy-3-methyl-2-thiabicyclo[3.3.1]nona-3,7-diene (4a)

To a solution of ethyl 3-thioxobutanoate (**2**) (219 mg, 1.5 mmol) in dry EtOH (10 mL), 0.1 M EtONa solution in EtOH (15 mL) was added. After stirring at room temperature for 15 min, EtOH was removed under reduced pressure, and then the residue was dissolved in dry pyridine (15 mL). To the solution of **3**, a solution of dinitropyridone (**1**) (199 mg, 1 mmol) in pyridine (15 mL) was slowly added on an ice bath, and the resultant mixture was stirred at room temperature for 2 d. After removal of pyridine under reduced pressure, water (10 mL) was added and then acidified (about pH 3) with 0.5 M HCl. The aqueous layer was extracted with $CHCl_3$ (30 mL × 3), and the organic layer was dried over $MgSO_4$ and concentrated. The residue was subjected to recrystallization from EtOH to afford **4** (286 mg, 0.83 mmol, 83% yield) as colorless plates; mp 155-158 °C. IR (KBr) 1697, 1583, 1558, 1363 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (dd, *J* = 7.2, 7.2 Hz, 3H), 2.34 (s, 3H), 3.19 (s, 3H), 4.3-4.4 (m, 2H), 5.03 (dd, *J* = 2.8, 2.8 Hz, 1H), 5.08 (dd, *J* = 2.8, 2.8 Hz, 1H), 5.55 (dd, *J* = 2.8, 2.8 Hz, 1H), 18.6-19.0 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.3, 22.6, 35.5, 36.0, 54.8, 61.9, 79.4, 110.7, 118.0, 152.6, 163.6, 164.5; MS (EI) 345 (M^+, 53), 299 (81), 253 (69), 220 (100). Anal. Calcd for $C_{12}H_{15}N_3O_7S$: C 41.74, H 4.38, N 12.17. Found: C 41.77, H 4.41, N 12.13.

X-Ray crystallography

Colorless plate crystals were formed by recrystallization from ethanol. All measurements were made on a Rigaku AFC7R diffractometer with graphite monochromatized Mo-Kα radiation. Unit cell parameters were determined by least-squares refinement of 22 automatically centered reflections. Crystallographic data were as follows: $C_{12}H_{15}N_3O_7S$, M=345.33, orthorhombic, *Pbca* (No. 61), a = 12.984(4) Å, b = 17.872(5) Å, c = 12.884(5) Å, V = 2989.5(15) Å^3, Z = 8, D_{calcd} = 1.534 g/cm^3, μ = 2.582 cm^{-1}, F(000) = 1440.00, and $2\Theta_{max}$ = 55.0º. The data were corrected for Lorentz and polarization effects. Calculations were performed with the CrystalStructure 3.8 program.[9] The structure was solved by direct method (SIR2004)[10] and refined with full matrix least-squares method. The final *R1* and *wR2* were 0.0451 and 0.1298 for of 3435 unique reflections with I > 3.00σ(I), respectively.

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