# Methoxide Ion Mediated Reactions of Methyl Azidoacetate with 4- and 2-Cyanobenzaldehyde. An Unexpected Cyclization of the *ortho* Isomer to a 2(1*H*)-Benzazepine Derivative



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A condensation reaction of 4-cyanobenzaldehyde (**1**) with methyl azidoacetate (**2**) in the presence of sodium methoxide produces a mixture of geometrical isomers of azidocinnamates **3** which undergoes thermolysis to give an indole **4**. By contrast, the treatment of 2-cyanobenzaldehyde (**5**) with **2** in the presence of sodium methoxide and followed by the usual workup furnishes an azepine derivative **6**.

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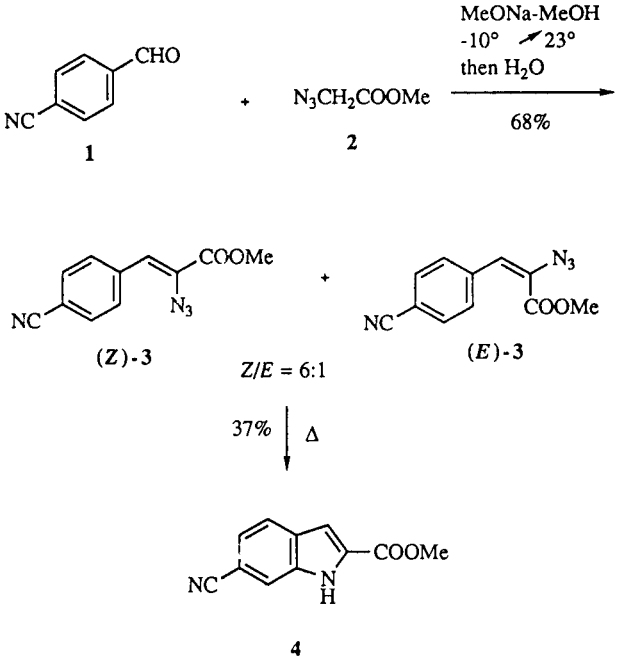
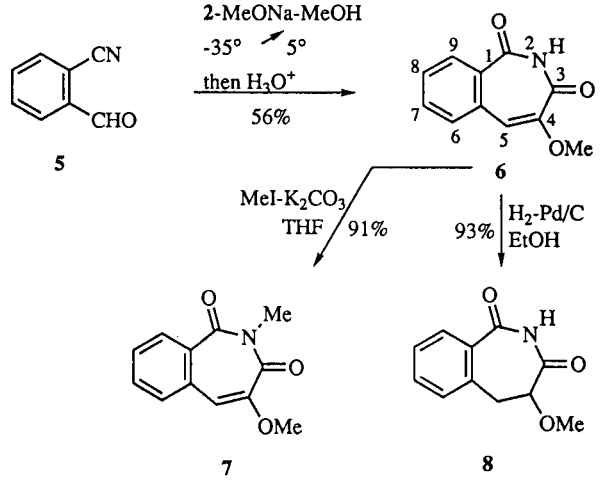
Methyl azidoacetate (**2**) is a recognized building block in heterocyclic synthesis. The reagent **2** readily undergoes a condensation reaction with aromatic aldehydes [1] to give precursors to a variety of heterocyclic systems [2-8]. This is exemplified in Scheme I by our previously unpublished preparation of an indole **4**. Under optimized conditions reported for similar reactions [1-5] the condensation of 4-cyanobenzaldehyde (**1**) with **2** in the presence of sodium methoxide furnished the expected azidocinnamate **3** as a mixture of geometrical isomers. Since the high resolution $^1$H nmr spectrum of the mixture gave clearly separated signals for individual components it was possible to use nOe experiments for configurational assignments.

Scheme I



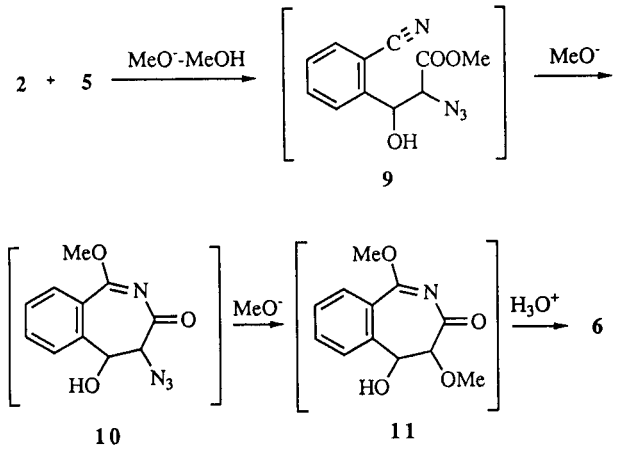

The *Z*-stereochemistry of the major isomer of **3** was assigned on the basis of the observed magnetization transfer between the vinyl and methyl protons. This mixture of isomers was heated, again under the general conditions reported for other azidocinnamates [2-6], to give the expected indole **4**. Physical data for this compound were virtually identical with those reported for **4** obtained by an independent route [7]. Mechanistically, the thermal decomposition of azidocinnamates involves elimination of molecular nitrogen. The resultant intermediate nitrene is believed to be in equilibrium with an azirine formed by interaction of the nitrene with the adjacent vinyl moiety. The azirines can be isolated under controlled conditions [3]. In general, however, thermal decomposition of the azidocinnamates gives indoles when there is an unsubstituted ortho position [2-6], and dihydroisoquinolines when there is an *ortho*-methyl or methylene group [2]. Several

Scheme II



heterocyclic syntheses that involve elimination of molecular nitrogen from the *ortho*-substituted azidocinnamates but without an apparent intermediary of the nitrene have also been described [8,9].

Scheme III




In this paper we report a novel reaction of azidoacetate **2** with 2-cyanobenzaldehyde (**5**) and methoxide ion. The reaction proceeds under milder conditions than that for the previously discussed synthesis of azidocinnamates, and it involves the cyano group of **5**. The product 4-methoxy-2,3-dihydro-2(1*H*)-benzazepine-1,3-dione (**6**) was isolated in a 56% yield after acidic workup (Scheme II). The given structure was fully consistent with the elemental analysis results, ir, ms, $^{13}C$ nmr and $^{1}H$ nmr spectra. More specifically, the ir spectrum gave strong absorptions at 3311 $cm^{-1}$ for the imino function, at 1674 $cm^{-1}$ for the imide carbonyls, and at 1401 $cm^{-1}$ for the methoxy group. There were no ir absorptions for the cyano and ester groups. The mass spectrum gave a fragment ion peak at m/z 172 as the base peak corresponding to loss of the methoxy group from the molecular ion with a strong peak at m/z 203. The $^{13}C$ nmr spectrum consisted of eleven lines with all chemical shifts matching closely calculated values [10]. In particular the calculations strongly suggested the presence of the methoxy group at position 4 rather than at position 5 of the azepine ring. This suggestion was fully confirmed by proton nOe experiments which indicated a spatial closeness of the vinyl H5 and aromatic H6 protons. Thus, irradiation with the frequency for H-5 gave strong nOe signals for H-6 and OMe. In a similar way, irradiation at OMe gave an nOe signal at H-5 only. The presence of a substituent at C-4 is also consistent with the lack of coupling between the vinyl and imido protons. It has been reported that 2,3-dihydro-2(1*H*)-benzazepine-1,3-dione, a close analog of **6** lacking a methoxy group, shows a coupling constant J = 2.5 Hz between H2 and H4 [11,12].

In order to gain additional structural support the azepine **6** was methylated and hydrogenated to give the respective derivatives **7** and **8**. Compounds **7** and **8** were fully characterized. In particular, the $^{1}H$ nmr spectrum of **8** gave an ABX pattern for $H_2$5-H4 protons, as expected.

The proposed mechanism for **6** is given in Scheme III. We suggest that the initial adduct **9** undergoes addition of methoxide ion to the cyano group, which is followed by ring closure to give an intermediate product **10**. Although similar reactions with the involvement of the cyano group are rare, the known examples are well characterized [13,14]. A nucleophilic displacement at the azide in **10** by methoxide ion would give the final intermediate compound **11**. Treatment of **11** with acid during workup would give **6**, the observed product [15].

In summary, we have described an unusual but simple synthesis of a benzazepine derivative [16]. By using other alkoxide reagents it may be possible to prepare higher alkoxy homologs of **6**. Many benzazepine derivatives show potent biological activities such as central nervous system stimulant, bactericidal, fungicidal, anthelmintic, and muscle relaxing properties [17].

## EXPERIMENTAL

The $^{1}H$ nmr (400 MHz) and $^{13}C$ nmr spectra (100 MHz) were taken in deuteriochloroform solutions for compounds **3**, **7**, **8** and in a dimethyl sulfoxide $d_6$ solution for compound **6**, with tetramethylsilane as an internal reference. Mass spectra were obtained at 70 eV.

Methyl 2-Azido-3-(4-cyanophenyl)propenoates, **3**.

These compounds were obtained from aldehyde **1** and azidoacetate **2** [5] by using a general procedure [1-5], an oil, *E/Z*= 1:6 (by $^{1}H$ nmr), yield 68%; $^{1}H$ nmr: for (*Z*)-3, δ 3.94 (s, 3H), 6.85 (s, 1H), 7.66 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H); $^{1}H$ nmr: for (*E*)-3, δ 3.93 (s, 3H), 6.90 (s, 1H), 7.75 (d, J = 8 Hz, 2H), 7.85 (d, J = 8 Hz, 2H).

*Anal.* Calcd. for $C_{11}H_8N_4O_2$ (a mixture of geometrical isomers): C, 57.89; H, 3.53; N, 24.55. Found: C, 57.80; H, 3.58; N, 24.30.

Methyl 4-Cyanoindole-2-carboxylate, **4**.

Thermolysis of a mixture of propenoates **3** by using a general procedure [2-6] gave an indole **4** in a 37% yield, mp 195-198°. The reported mp [7] was 198-199°.

4-Methoxy-2,3-dihydro-2(1*H*)-benzazepine-1,3-dione, **6**.

A solution of methyl azidoacetate (**2**, 1.4 g, 15 mmoles) and 2-cyanobenzaldehyde (**5**, 0.5 g, 3.8 mmoles) in methanol (5 ml) was added dropwise at -35° to a solution of sodium methoxide (3*M*, 5 ml). The mixture was stirred at 0° for 1 hour and then neutralized with acetic acid. Removal of methanol on a rotary evaporator was followed by flash chromatography of the residue

on a silica gel with dichloromethane as an eluent. Crystallization from methanol/ether (1:9) gave 0.43 g (yield 56%) of **6**, mp 123-124°; $^1$H nmr: δ 3.83 (s, 3H, $OCH_3$), 5.79 (s, 1H, H5), 7.61 (t, J = 8 Hz, 1H, H8), 7.65 (t, J = 8 Hz, 1H, H7), 7.70 (d, J = 8 Hz, 1H, H6), 7.88 (d, J = 8 Hz, 1H, H9), 9.65 (br s, exchangeable with deuterium oxide, NH); $^{13}$C nmr: δ 51.7 ($OCH_3$), 91.2 (C5), 121.0 (aromatic), 124.0 (aromatic), 129.5 (aromatic), 131.6 (aromatic), 132.8 (aromatic), 136.4 (aromatic), 147.5 (C4), 167.9 (C=O), 168.0 (C=O); ms: m/z 130 (43), 145 (25), 172 (100), 203 (67, $M^+$); ir (potassium bromide): 1401, 1674, 3311 cm$^{-1}$.

*Anal.* Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.13; H, 4.48; N, 6.80.

4-Methoxy-2-methyl-2,3-dihydro-2-(1*H*)-benzazepine-1,3-dione, **7**.

A mixture of an azepine **6** (142 mg, 0.7 mmole), iodomethane (0.35 ml, 5.6 mmoles), anhydrous potassium carbonate (386 mg, 2.8 mmoles), and anhydrous tetrahydrofurane (3.5 ml) was stirred at 23° for 7 days under a nitrogen atmosphere. The mixture was diluted with benzene and filtered through celite. Concentration on a rotary evaporator was followed by crystallization of the residue from ether to give 138 mg (yield 91%) of colorless crystals of **7**, mp 116-118°; $^1$H nmr: δ 3.45 (s, $NCH_3$), 3.68 (s, 3H, $OCH_3$), 5.73 (s, 1H, H5), 7.42 (t, J = 8 Hz, 1H, H8), 7.47 (t, J = 8 Hz, 1H, H7), 7.53 (d, J = 8 Hz, 1H, H6), 7.69 (d, J = 8 Hz, 1H, H9); $^{13}$C nmr: δ 27.2, 48.6. 90.4, 116.9, 120.5, 125.2, 127.8, 129.5, 134.5, 142.6, 162.2, 165.6; ms: m/z 158 (38), 159 (36), 186 (100), 217 (69, $M^+$); hrms Calcd. for $C_{12}H_{11}NO_3$: m/z 217.0739. Found: m/z 217.0738.

4-Methoxy-2,3,4,5-tetrahydro-2(1*H*)-benzazepine-1,3-dione, **8**.

A mixture of an azepine **6** (406 mg, 2 mmoles), a Pd/C catalyst (10%, 812 mg), and ethanol (5 ml) was stirred under an atmospheric pressure of hydrogen at 23° for 24 hours, and then filtered through celite. A solution was concentrated on a rotary evaporator, and the residue was crystallized from ether/acetone to give 382 mg (yield 93%) of **8**, mp 138-139°; $^1$H nmr: δ 2.52 (dd, J = 17 Hz, J = 10 Hz, 1H, H5), 3.01 (dd, J = 17 Hz, J = 3 Hz, 1H, H5), 3.79 (s, 3H, $OCH_3$), 4.96 (dd, J = 10 Hz, J = 3 Hz, 1H, H4), 7.25-7.75 (m, 4H, aromatic and NH), 7.87 (d, J = 8 Hz, 1H, H9); $^{13}$C nmr: δ 39.4, 52.2, 52.9, 122.4, 124.1, 128.7, 131.9, 132.1, 145.9, 170.3, 171.6; ms: m/z 132 (100), 145 (34), 146 (20), 177 (21), 205 (22, $M^+$), hrms Calcd. for $C_{11}H_{11}NO_3$: m/z 205.0739. Found: m/z 205.0741.

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