SHORT PAPER

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Cyclizations of 2-(*o*-bromomethyl)benzylidene-1, 3-indandione initiated by 1-benzyl-1, 4-dihydronicotinamide and KCN: selectivity of O-alkylation and C-alkylation†

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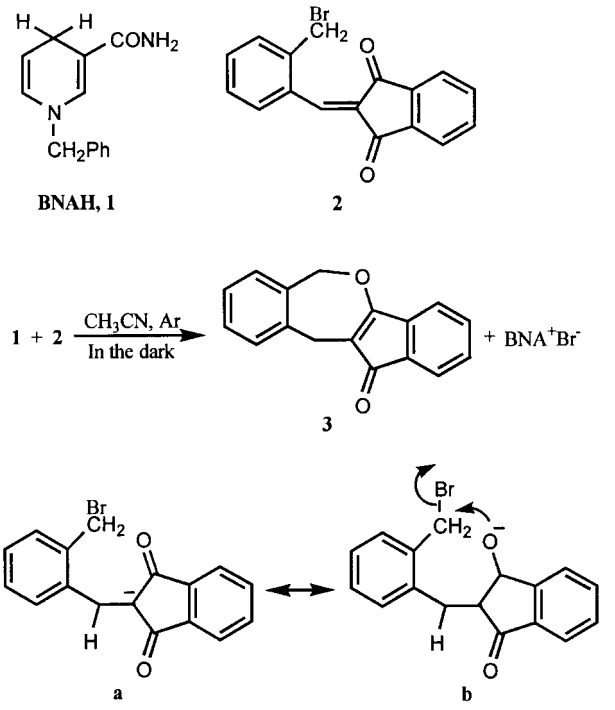
1-Benzyl-1, 4-dihydronicotinamide (**1**) and KCN reacted with 2-(*o*-bromomethyl)-benzylidene-1, 3-indandione (**2**) to give 7, 12-dihydro-1-oxoindeno[3, 2-c][2]benzooxepine (**3**) and 1′-cyano-3′-hydro-2, 2′-spirobi[2H-indene]-1, 3-dione (**4**), respectively, and the selectivity of O-alkylation and C-alkylation is discussed.

Cyclization is one of the most important and interesting aspects of organic chemistry.[1] Novel reductive cyclizations initiated by an NAD(P)H model,[2] 1-benzyl-1, 4-dihydronicotinamide (**1**, BNAH), which have been reported from this laboratory,[3] include the facile preparation of 2-phenyl-1, 2-cyclopropanedicarbonitrile, ethyl (*E*)-1-cyano-2-phenylcyclopropane-1-carboxylate and 2, 2-disubstituted indanes from 2-bromo-1-phenylethylidene malononitrile, ethyl (*Z*)-α-cyano-β-bromomethyl-cinnamate, and 1-(*o*-bromomethylphenyl)-2, 2-disubstituted-ethylenes (electron-withdrawing substituents), respectively. These three- and five-membered cyclizations prompted us to seek other types of cyclizations initiated by BNAH. Herein we report the reductive cyclization of 2-(*o*-bromomethyl)benzylidene-1, 3-indandione (**2**) by BNAH (Scheme 1).



Scheme 1

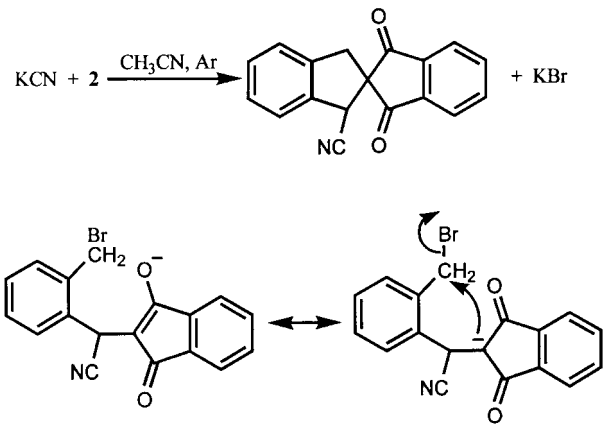
A mixture of **1** and **2** in dry acetonitrile was stirred for 4h at room temperature under argon. Conventional work-up gave 7, 12-dihydro-1-oxoindeno[3, 2-c][2]benzooxepine (**3**) in 86% yield (Scheme 1).

For the new compound **3** the peak at δ_C 194.2 indicates one carbonyl group in **3**. The peak at δ_C 173.3 is attributed to the electron-deficient ethylenic carbon linked to an oxygen atom in the seven-membered ring. Furthermore, the reversal of the two peaks at δ_C 72.8 and 26.3 in the DEPT-135 spectrum due to CH_2O and benzylic CH_2, respectively, clearly indicates the skeleton of the seven-membered enol ether ring.

Based on the structure of **3**, it is reasonable to propose that a hydride from **1** attacks the benzylidene carbon of **2**, the resulting carbanion (**2a**) reacts as the enolate ion (**2b**), and undergoes nucleophilic substitution on the *o*-bromomethyl group to produce **3** (Scheme 1). This is an O-alkylation process.

Preparation of seven membered ring compounds a difficult process because of entropic factors that impede ring closure.[4] Illuminati and Mandolini[5] revealed that cyclization to 7-membered ring lactone was slower than that of 5-membered one by a factor of 10^{-4}. However, interest in the synthesis of seven-membered oxacycles has steadily increased and the general synthetic strategies have been reviewed recently.[6]

The facility of the above cyclization reaction enhances its potential usefulness in organic synthesis in the related areas. More important is the possibility that this efficient cyclization may open a new strategy to prepare such seven-membered oxacycles by taking advantage of ambident reactivity of enolates.[6]



Scheme 2

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Compund **2** was also reacted with KCN for comparison. A mixture of KCN and **2** in dry acetonitrile was stirred for 6h at room temperature under argon. Conventional work-up gave 1′-cyano-3′-hydro-2, 2′-spirobi[2H-indene]-1, 3-dione (**4**) in 88% yield (Scheme 2).

For new compound **4**, the peaks at δ_C 199.7 and 197.9 indicate two carbonyls in **4**. The low peak at δ_C 61.5 is attributed to the spiro centre carbon. The peaks at δ_C 40.9 and 40.3 reveal the presence of CH and CH2, respectively, which is further confirmed by the maintenance of the former and reversal of the latter in the DEPT-135 spectrum, and the maintenance of the former and disappearance of the latter in the DEPT-90 spectrum. These results confirm the spiro ring structure of **4**.

Since **4** is the sole product it is reasonable to propose that the cyanide anion attacks the benzylidene carbon of **2** and the resulting carbanion undergoes nucleophilic substitution on the *o*-bromomethyl group to produce **4** (Scheme 2). This is a C-alkylation process.

Spirocyclic compounds such as **4** have attracted great interest for their relationship to the core of the antitumor antibiotic fredericamycin.[7] Here a facile preparation is achieved with convenience and high yield, and it is important that this new route of cyclization may open a new strategy to synthesize this kind of spiro structures.[7c]

It is rather surprising to compare these two reactions: similar conditions lead to different results.

The investigation of the structure and reactivity of ambident intermediates such as enol anions has always posed a mechanistic challenge to the chemist.[8] Owing to the immense number of possible combinations of reactants, solvents, catalysts and temperature conditions, it is not easy to rationalize them in most cases.[9] It is characteristic of the title reaction that all the other conditions are the same except the corresponding cations of the anions. So we have presented a 'clean' model to investigate the effects of cations in C- or O-alkylation selectivity.

For ambifunctional anions the shielding of the atom with highest electron density by cations affects the reactivity of the whole resonance system. The electron density depends on the resonance of the system and on the radii of atoms taking part in the resonance.[9]

Both the title reactions proceed to give the corresponding anions. It is reasonable to propose that the cation K+ chelates well with the O-end and shields it to make the C-end more ready to undergo nucleophilic substitution to produce C-alkylation product **4**. On the contrary, the BNA+ cation is so bulky that it cannot chelate well with the anion, which makes the O-end more electron-rich (oxygen is more electronegative than carbon) and more ready to undergo nucleophilic substitution to give O-alkylation product.

LeNoble[10] summarized his findings for salts of acetoacetic esters in a single sentence: The freer the anion, the larger the O/C ratio. As described above, the anion in BNAH reaction is freer because the BNA^+ is separated by virtue of its bulk, and the polar nonprotonic solvent is also responsible for enhanced chelation of BNA^+, making the anion freer.

Experimental

Melting points were uncorrected. IR spectra were measured on a Bruker Vector 20 IR spectrometer. ^1H NMR and ^{13}C NMR spectra were taken on a Bruker DMX-500 NMR spectrometer with $CDCl_3$ as solvent and TMS as internal reference. Mass spectra were determined on a VG analytical ZAB-HS mass spectrometer with an ionization potential of 70 eV. Elemental analyses were carried out with an Italian 1106 analyser.

BNAH was prepared according to the literature.[11] Compound **2** was prepared as described.[3] Acetonitrile was dried and distilled from CaH_2 before use.

Reaction of **1** *and* **2**: The bromide **2** (1 mmol) and BNAH (1 mmol) were dissolved in dry acetonitrile (10 ml) and the yellow solution was stirred under argon at room temperature in the dark for 5h. The mixture was evaporated to dryness and the residue subjected to column chromatography on silica gel with petroleum ether-ethyl acetate (40:1) as eluent to give 7, 12-dihydro-1-oxoindeno[3, 2-c][2]benzooxepine **3** (yield 86%), yellow crystal, mp 138–139 °C; ν_{max}/cm^{-1} (Nujol) 1693 (C=O), 1620, 1584, 1463, 1477, 1301, 1155;δ_H 7.36 (m, 8H), 5.61 (s, 2H, CH_2O), 3.80 (s, 2H, $ArCH_2$); δ_C 194.2 (C=O), 173.3 (ArC), 141.8, 139.7, 133.9, 132.2, 131.9, 130.3, 129.9, 129.6, 128.6, 127.2, 120.9, 118.0, 107.8, 72.8 (CH_2O), 26.3 ($ArCH_2$); *m/z* 248(M^+), 191, 189, 133, 115, 105, 104, 77, 76; (Found: C, 82.19; H, 4.91. $C_{17}H_{12}O_2$ requires C, 82.24; H, 4.88%).

Reaction of KCN and **2**: The bromide **2** (1 mmol) and KCN (1 mmol) were added to dry acetonitrile (10 ml) and the yellow solution was stirred under argon at room temperature for 6h. The mixture was evaporated to dryness and the residue subjected to chromatography on a silica column with petroleum ether-ethyl acetate (10:1) as eluent to give 1′-cyano-3′-hydro-2, 2′-spirobi[2H-indene]-1, 3-dione **4** (yield 88%), colorless crystal, mp 132–133 °C; ν_{max}/cm^{-1} (KBr) 2244 (C≡N), 1738 (C=O), 1705(C=O), 1589, 1282; δ_H 8.10–7.94 (m, 4H), 7.36-7.44 (m, 4H), 4.78(s, 1H, ArCH), 3.44 (d, 1H, *J* 16.1Hz, $ArCH_2$), 3.30 (d, 1H, *J* 16.1Hz, $ArCH_2$); δ_C.199.75 (C=O), 197.93 (C=O), 141.53, 141.43, 139.26, 137.13, 136.69, 135.36, 129.57, 128.53, 124.93, 124.71, 124.12, 124.08, 117.03, 61.48, 40.95 (ArCH), 40.27 ($ArCH_2$); *m/z* 273(M^+), 246, 189, 133, 104, 76; (Found: C, 79.07; H, 4.01; N, 5.17. $C_{18}H_{11}NO_2$ requires C, 79.11; H, 4.06; N, 5.13%).

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