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Reduction of *o*- and *p*-Bromomethylbenzylidenemalononitrile by 1-Benzyl-1,4-dihydronicotinamide

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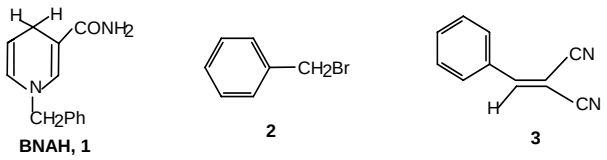
Abstract: o-Bromomethylbenzylidenemalononitrile **4** is reduced by 1-benzyl-1,4-dihydro-nicotinamide (BNAH, **1**) to give 2,2-indanedicarbonitrile **6** and *p*-bromomethylbenzylidene-malononitrile **5** is reduced by BNAH to give **7** and **8** by hydride transfer mechanism.

Keywords: *o*- and *p*-Bromomethylbenzylidenemalononitrile**,** 1-benzyl-1,4-dihydronicotinamide**,** hydride transfer mechanism.

NADH is an important coenzyme that plays a vital role in biological redox reactions[1]. 1-Benzyl-1,4-dihydronicotinamide (BNAH, **1**) is widely used as a model of NADH to mimic the reduction of unsaturated compounds such as ketones, imines, alkenes, *etc*[2]. Although most of the researches have been focused on mechanistic studies of the reduction, the use of BNAH as a mild reducing agent in synthetic organic chemistry is also of interest. It was recently reported from this laboratory that 2-bromo-1-phenylethylidenemalononitrile was reduced by BNAH in acetonitrile in the dark to give 2-phenyl cyclopropane-1,1-dicarbonitrile[3] and that ethyl (Z)-α-cyano-β-bromomethylcinnamate was reduced under similar conditions to give (E)-1-cyano-2-phenylcyclopropane-1-carboxylate[4]. These reactions provide a new route to synthesizing cyclopropane derivatives. As an extension of this work we have investigated the reduction of analogous compounds with the aim of seeking new reactions for use in organic synthesis and also of understanding the relationship between structure and reactivity in BNAH reduction. Herein we report the reduction of title compounds by BNAH.

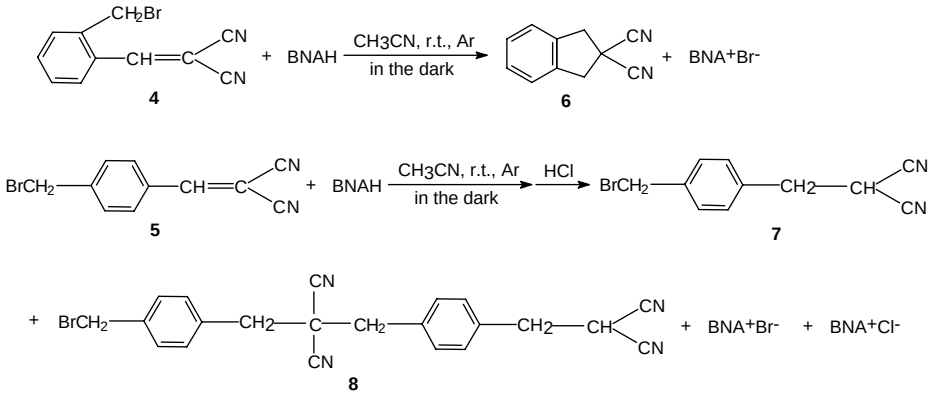
Fukuzumi *et al* reported that benzyl bromide **2** did not react with BNAH in the dark but was reduced by BNAH under irradiation with light to give toluene[5]. We have found that benzylidenemalononitrile **3** did not react with BNAH in the dark but was reduced by BNAH in the presence of Mg^{2+} to give benzylmalononitrile[6].

Scheme 1



o-Bromomethylbenzylidenemalononitrile **4**, which carries a bromomethyl and a 2,2-dicyanoethenyl group at the ortho position of the same molecule, reacted readily with BNAH in dry acetonitrile at room temperature in the dark and, after quenching with hydrochloric acid and the usual work-up, gave 2,2-indanedicarbonitrile **6**. *p*-Bromomethyl-benzylidenemalononitrile **5**, which carries a bromomethyl and a 2,2-dicyanoethenyl group at the para position of the same molecule, also reacted readily with BNAH under the same conditions to give *p*-bromomethylbenzylmalononitrile **7** and *p*-[2,2-dicyano-3-(4'-bromomethyl) phenyl] propylbenzylmalononitrile **8**. The structures of **6**, **7** and **8** were determined by spectroscopic methods. Both **7** and **8** are new compounds. The reactions can be represented as shown in **Scheme 2.**

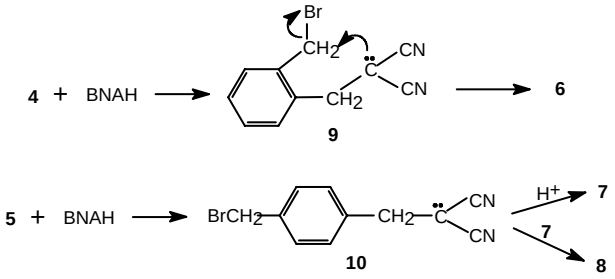
Scheme 2



$NaBH_4$, a typical hydride donor, was used to reduce **4** and **5** for comparison. When **4** was reduced with $NaBH_4$, the product **6** was obtained. When **5** was reduced by $NaBH_4$, **7** and **8** were obtained along with other complicated by-products which were not identified.

Based on the results described above, it is reasonable to propose that the reactions take place *via* a hydride transfer mechanism. Thus a hydride from BNAH adds to the β-methine carbon of the α, β-unsaturated malononitrile moiety in **4** and **5** and the resulting carbanions undergo, in the case of **9**, intramolecular displacement on the *o*-bromomethyl group to produce an indane structure and, in the case of **10**, proton transfer to give **7** or intermolecular displacement on the *o*-bromomethyl group of **7** to give **8**, respectively (**Scheme 3**).

Scheme 3



It is interesting to note that in the reactions described above the presence of both bromomethyl and 1,1-dicyanoethenyl group in **4** and **5** makes the compounds sufficiently electrophilic and renders the hydride attack from BNAH feasible in contrast to **2** and **3**.

Product **6** can be transformed to other indane derivatives by functional group interconversion. It was reported in the literature[7] that **6** was obtained by the condensation of *o*-dibromomethylbenzene and malononitrile in the presence of sodium hydride. Since indane structure occurs widely in natural products, the new reaction reported herein may be of potential use in related synthesis.

Experimental

Melting points were uncorrected. Elemental analysis were carried out with an Italian-1106 elemental analytical apparatus. ^{1}H NMR spectra were obtained on a Bruker DMX-500 spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference. Mass spectra were determined on a VG-ZAB-HS mass spectrometer (EI).

BNAH was prepared according to the literature[8]. *o*-Bromomethylbenzylidene-malononitrile **4** and *p*-bromomethyl-benzylidenemalononitrile **5** were prepared by Knoevenagel condensation of *o*- and *p*-tolualdehyde with malononitrile followed by bromination with NBS/AIBN, respectively[9]. HPLC grade acetonitrile was dried and distilled from calcium hydride before use.

Reduction of 4 and 5 by BNAH.

A mixture of **4** (or **5**) (1 mmol) and BNAH (1 mmol) in 15mL of acetonitrile was stirred at room temperature under argon in the dark and the reaction was monitored by TLC. Hydrochloric acid (1 mol/L, 5 mL) was added and the mixture was extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, after evaporation of the solvent, the residue was subjected to column chromatography on silica gel with petroleum ether-ethyl acetate (10:1 for **4** and 4:1 for **5**) as eluent. The following products were obtained: 2,2-indane-dicarbonitrile **6** (yield 90%), mp 130-131℃; δ_H 3.70 (s, 1H), 7.20 (s, 4H); m/z 168(M^+), 141, 114; (Found: C, 78.60; H, 4.80; N, 16.61. $C_{11}H_8N_2$ requires C, 78.55;

H, 4.79; N, 16.66%); *p*-bromomethylbenzylmalononitrile **7** (yield 40%), mp 82-84℃; δ_H 3.30 (d, *J* 6.0 Hz, 2H), 3.90 (t, *J* 6.0 Hz, 1H), 4.50 (s, 2H), 7.32 (m, 4H); m/z 248/250 (M^+), 169, 104; (Found: C, 53.00; H, 3.69; N, 11.19. $C_{11}H_9N_2Br$ requires C, 53.03; H, 3.64; N, 11.25%); *p*-[2,2-dicyano-3-(4'-bromomethyl)phenyl]propyl-benzylmalono-nitrile **8** (yield 50%), mp 138-140℃; δ_H 3.26 (s, 2H), 3.27 (s, 2H), 3.33 (d, *J* 6.5 Hz, 2H), 3.95 (t, *J* 6.5 Hz, 1H), 4.50 (s, 2H), 7.40-7.47(m, 8H); m/z 416/418 (M^+), 415/417, 337, 183/185, 169, 104; (Found: C, 63.10; H, 4.38; N, 13.35. $C_{22}H_{18}N_4Br$ requires C, 63.17; H, 4.31; N, 13.40%).

Reduction of 4 and 5 by $NaBH_4$.

The reduction was carried out by the same procedure as described above, except that $NaBH_4$ was used instead of BNAH and CH_3CN/CH_3OH (1:1) was used as the solvent.

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References and notes

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