Application of NAD(P)H Model Hantzsch 1,4-Dihydropyridine as a Mild Reducing Agent in Preparation of Cyclo Compounds

Xiao-Qing Zhu,*,† Hong-Yi Wang,‡
Jian-Shuang Wang,† and You-Cheng Liu*,‡,§

Department of Chemistry, National Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, Department of Chemistry and National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, and Department of Chemistry, University of Science and Technology of China, Hefei 230026, China

xqzhu@nankai.edu.cn

Received October 3, 2000

The reduced form of the nicotinamide adenine dinucleotide coenzyme [NAD(P)H] plays a vital role in many bioreductions by transferring a hydride ion or an electron to the surrounding substrates.[1] 1-Benzyl-1,4-dihydronicotinamide (BNAH), Hantzsch 1,4-dihydropyridine (HEH), 10-methyl-9,10-dihydroacridine ($ArcH_2$), and many other 1,4-dihydropyridine derivatives have been widely used as models of NAD(P)H to mimic the reductions of various unsaturated compounds such as quinones,[2] ketones,[3] aldehydes,[4] imines,[5] alkenes,[6] etc. Attention of most research has been focused only on the mechanistic details of the redox reactions. To our best knowledge, very little effort has been made toward the application of these NAD(P)H models in synthetic organic chemistry except for some chiral NAD(P)H models.[7] In fact, the use of NAD(P)H model compounds as a class of mild reducing agent in synthetic organic chemistry is also of interest. In our previous paper,[8] we reported that (*Z*)-ethyl α-cyano-*β*-bromomethylcinnamate was reduced by NAD(P)H model BNAH in acetonitrile to give a cyclopropane derivative, but the yield of the product was low (about 33%). Recently, we used NAD(P)H model, HEH, instead of BNAH to react with (*Z*)-ethyl α-cyano-*β*-bromomethylcinnamate and extended the substrate to a variety of the corresponding analogues. It is surprising to find that all the yields of the cyclized products are good or excellent. Here we report the experimental results, which provides a new and high-yielding route to synthesize various cyclopropane, indane, and exopin derivatives.

Results and Discussion

Treatment of allylic and benzylic bromides by Hantzsch 1,4-dihydropyridine (HEH) in anhydrous acetonitrile under argon atmosphere gave various types of three-, five-, and seven-membered ring compounds in good or excellent yields, respectively, which all are very important reaction intermediates in organic synthesis. Representative reactions are summarized in Table 1.

As shown in Table 1, when the substrate is an ethyl α-cyano-*β*-bromomethylcinnamate derivative (nos. 1 and 2) or a 2-bromo-1-phenylethylidenemalononitrile derivative (no. 3), the products are cyclopropane derivatives. When the cases of nos. 1 and 2 are examined, it is interesting to find that both the (*E*)-isomer (no. 1) and the (*Z*)-isomer (no. 2) of ethyl α-cyano-*β*-bromomethylcinnamate and its derivatives give (*E*)-isomers of the cyclopropane derivatives, i.e., the reaction is stereoselective. The main reason could be that the stability of the (*E*)-isomers is larger than that of the (*Z*)-isomers, due to larger steric hindrance of substituents in the (*Z*)-isomers. It is noteworthy that even though the two isomers of ethyl α-cyano-*β*-bromomethylcinnamate and its derivatives all gave the same (*E*)-isomers of the products, the reaction rates are different. Kinetic experiments show that the second-order reaction rate constant for the (*Z*)-isomer of ethyl α-cyano-*β*-bromomethylcinnamate as the substrate (1.43×10^{-1} M^{-1} s^{-1}) is larger than that for the (*E*)-isomer as the substrate (1.29×10^{-1} M^{-1} s^{-1}), which could be caused by the greater stability of the (*E*)-isomer than that of the (*Z*)-isomer.

When the substrate is *o*-bromomethylbenzylidenemalononitrile (no. 4) and its analogues (nos. 5 and 6), indane structure compounds were obtained. It is surprising to note that when the substrate is the compound of no. 7 in Table 1, a seven- rather than a five-membered ring compound was formed (see eq 3 in Scheme 1). As is well-known, seven-membered ring structures are, generally, more difficult to form than the corresponding five-membered ring, since the ring-strain of the former is

* To whom correspondence should be addressed. Fax: 86-22-23502458. Phone: 86-22-23508548.
† Nankai University.
‡ Lanzhou University.
§ University of Science and Technology of China.

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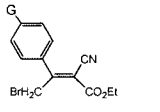
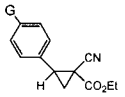
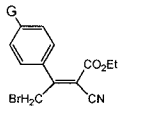
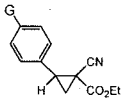
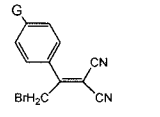
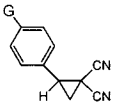
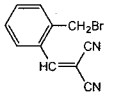
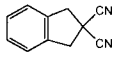
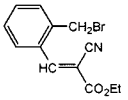
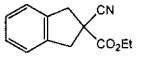
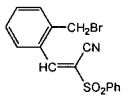
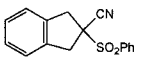
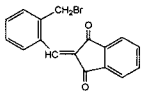
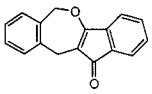
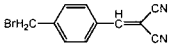
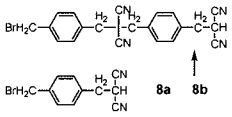
Table 1. Cyclizations of Some Allylic and Benzylic Bromides by HEH in CH_3CN under an Argon Atmosphere[a]

No.	substrate	ratio [b]	time (h)	products	yield(%)[c]	(Z/E)[d]
1	 G = CN, Cl, H, CH_3, OCH_3	2 : 1	11-15	 **1a**	>91	*E*
2	 G = CN, Cl, H, CH_3, OCH_3	2 : 1	13-17		>92	*E*
3	 G = CN, Cl, H, CH_3, OCH_3	2 : 1	7-11		>90	—
4		2 : 1	15	 **4a**	89	—
5		2 : 1	19	 **5a**	88	—
6		2 : 1	18	 **6a**	86	—
7		2 : 1	20	 **7a**	85	—
8		2 : 1	23	 **8a** **8b**	21 38	— —

[a] All reactions were carried out as described in Experimental Section. [b] Molar ratio of HEH to the substrate. [c] Yields of isolated products. [d] The *Z*/*E* ratio was determined by using ^{1}H NMR integration, and the diastereomeric configuration of (*E*) was assigned on the basis of Donald J. Cram's work.[9]

generally larger than that of the latter. However, the origin of the seven-membered ring formation can be found in the following mechanistic analysis.

It is worth noting that in the case of no. 8, when *m*- or *p*-bromomethylbenzylidenemalononitrile was used in place of *o*-bromomethylbenzylidenemalononitrile (no. 4), no cyclized compounds were obtained. For instance, *p*-bromomethylbenzylidenemalononitrile, when treated with HEH under the same experimental conditions as the corresponding ortho-substituted compound, gave two open-chain rather than cyclized compounds: *p*-bromomethylbenzylmalononitrile (**8a**) and *p*-2,2-dicyano-3-(4′-bromomethyl)phenylpropylbenzylmalononitrile (**8b**), the former of which is major product (no. 8).

Concerning the cyclization mechanisms of the substrates listed in Table 1 by HEH, it is reasonable to propose that the reactions take place via a hydride transfer mechanism, similar to the proposal in our previous papers.[8] Thus a hydride from HEH added to the benzyl position of the substrates[10] and the resulting carbanions undergo, (i) in the cases of nos. 1−3, intramolecular displacement on β-bromomethyl group to produce cyclopropane derivatives as shown in Scheme 1 (eq 1); (ii) in the cases of nos. 4−6, intramolecular nucleophilic substitution on the *o*-bromomethyl group offered indane derivatives after initial hydride transfer as shown in eq 2. But in the case of no. 8, the enol anion formed by hydride transfer has a higher charge density upon oxygen than carbon. Also, the α,β-unsaturated ketone product, **8a**, is resonance stabilized. Thus the enol anion can undergo intramolecular displacement to form seven- rather than five-membered ring structure compound as

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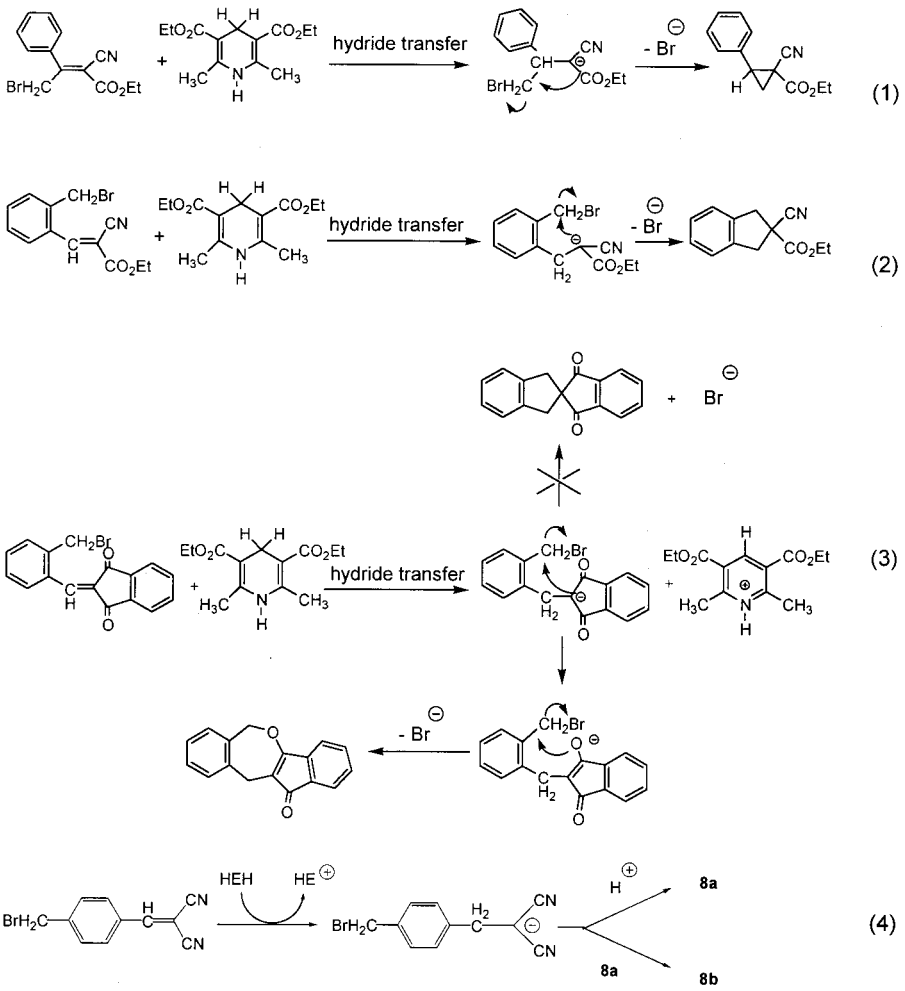
(10) The addition of *p*-dinitrobenzene, a known electron-transfer inhibitor,[11] to the reaction mixtures of the substrates and Hantzsch 1,4-dihydropyridine showed no remarkable effects on the reactions, indicating no electron transfer occurrence in the reaction processes.

Scheme 1



shown in eq 3. When the substrate is *p*- or *m*-bromomethylbenzylidenemalononitrile, the carbanion formed by hydride transfer cannot be cyclized by intramolecular displacement to form ring structure species as the final products, since the rigid benzene ring in the carbanion can prevent the carbanion from the cyclization. Thus, the final products are only two chain products (**8a** and **8b**) as shown in eq 4 (Scheme 1).

In summary, we present a convenient method for the preparation of three-, five-, and seven-membered ring compounds using NAD(P)H mimic reactions. The most advantageous features of the synthetic procedure: (i) the starting materials are readily available; (ii) the reaction yields are very high, and the reaction conditions are mild; (iii) the workup of the reaction mixtures is simple. Even so, the main purpose of this article is not only to provide a nice synthetic method, but also to demonstrate the application of NAD(P)H mimic reactions in organic synthesis, so as to attract more attention to the application of biomimetic reactions in organic synthesis.

Experimental Section

Materials and Apparatus. Hantzsch 1,4-dihydropyridine[12] and the substrates (nos. 1−3)[13] were prepared according to the literatures. *o*-Bromomethylbezylidenemalononitrile and its analogues (nos. 5 and 6) were prepared by Knoevenagel condensation of *o*- and *p*-tolualdehyde with malononitrile, α-cyanoacetate, and α-cyano sulfone followed by bromination with NBS/AIBN, respectively.[14] The other reagents were purchased from Aldrich Chemical Co. HPLC grade acetonitrile was dried and distilled from calcium hydride before use. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-400 spectrometer operating at 400.13 MHz for ^{1}H and 100 MHz for ^{13}C, using TMS as reference for spectra recorded in $CDCl_3$. Mass spectra were obtained on a VGZAB-HS mass spectrometer at an ionization potential of 70 eV.

General Procedure for the Cyclization of the Allylic and Benzylic Bromides by HEH. A mixture of the bromide (0.4 mmol) and HEH (0.8 mmol) in 40 mL of deaerated acetonitrile was set in dark at room temperature for 7−20 h. Solvent was then rotary evaporated, and the products were separated by column chromatography on silica gel with petroleum ether−ethyl acetate as eluent. The product structures were determined by NMR and mass spectrometry. The data of the representative products are shown below.

(*E*)-Ethyl 1-cyano-2-phenylcyclopropanecarboxylate (1a): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.39 (t, 3H, J = 7 Hz), 2.15 (dd, 2H, J = 8 and 1.86 Hz), 3.20 (br t, 1H, J = 8 Hz), 4.33 (q, 2H, J = 7 Hz), 7.36 (br s, 5H); MS: m/z = 215 ($M^{+\cdot}$, 17). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54;, H, 6.09; N, 6.51. Found: C, 72.69; H, 6.12; N, 6.60.

2-Phenylcyclopropanedicarbonitrile (3a): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (d, 2H, J = 9 Hz), 3.29 (t, 1H, J = 9 Hz), 7.38 (s, 5H); MS: m/z = 168 ($M^{+\cdot}$). Anal. Calcd for $C_{11}H_8N_2$: C, 78.57; H, 4.76; N, 16.67. Found: C, 78.53; H, 4.71; N, 16.69.

(11) Kerber, R. C.; Urry, G. W.; Kornblum, N. *J. Am. Chem. Soc.* **1964**, *86*, 3904; **1965**, *87*, 4520. (b) Korblum, N.; Michel, R. E.; Kerber, R. C. *J. Am. Chem. Soc.* **1966**, *88*, 5560, 5562.

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(13) Lehnert, W. *Tetrahedron* **1973**, *29*, 634.

(14) Kolsaker, P.; Ellingsen, P. O. *Acta Chem. Scand. B* **1979**, *33*, 138.

2,2-Indanedicarbonitrile (4a): yellow solid; mp 130−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (s, 4H), 7.2 (s, 4H). MS: m/z = 168 (100), 141 (91), 114 (7). Anal. Calcd for $C_{11}H_8N_2$: C, 78.55; H, 4.79; N, 16.66. Found: C, 78.62; H, 4.81; N, 16.63.

Ethyl 2-cyano-2-indanecarboxylate (5a): mp: 78−80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (t, 3H, J = 7.2 Hz), 3.59 (s, 4H), 4.27 (q, 2H, J = 7.2 Hz), 7.20 (s, 4H); MS: m/z: 215 (22), 188 (4), 160 (18), 142 (100), 115 (32). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.53; H, 6.09; N, 6.51. Found: C, 72.54; H, 6.15; N, 6.46.

2-Cyano-2-phenylsulfonylindane (6a): mp: 138−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (d, 2H, J = 16.6 Hz) 7.23 (s, 4H), 8.15−7.73 (m, 5H),; MS: m/z: 283 (5), 265 (76), 141 (100), 115 (36). Anal. Calcd for $C_{16}H_{13}NO_2S$: C, 67.83; H, 4.63; N, 4.95. Found: C, 67.80; H, 4.61; N, 4.97.

5H-Benz[*e*]indeno[1,2-*b*]oxepin-11-one (7a): 92% yield; yellow solid; mp 138−139 °C; IR (KBr, cm^{-1}): 1693, 1620, 1584, 1463, 1477, 1301, 1155, 935, 921, 770, 713; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.80 (s, 2H) 5.61 (s, 2H), 7.36 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3, 72.8, 107.8, 118.0, 120.9, 127.2, 128.6, 129.6, 129.9, 130.3, 131.9, 132.2, 133.9, 139.7, 141.8, 173.3, 194.2; MS: m/z = 248 (100), 191 (26), 189 (23), 133 (46), 115 (32), 105 (48), 104 (54), 77 (31), 76 (42). Anal. Calcd for $C_{17}H_{12}O_2$: C, 82.24; H, 4.88. Found: C, 82.19; H, 4.91.

2-(*p*-Bromomethylbenzyl)malononitrile (8a): mp: 82−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.30 (d, J = 6.0 Hz, 2H), 3.9 (t, J = 6.0 Hz, 1H), 4.5 (s, 2H), 7.32 (m, 4H); MS: m/z 248/250 (M^+), 169, 104. Anal. Calcd for $C_{11}H_9N_2Br$: C 53.03, H 3.64, N 11.25. Found: C 53.01, H 3.68, N 11.21.

2-(*p*-Bromomethylbenzyl)-2-[*p*-(2′,2′-dicyanoethylbenzyl)]-malononitrile (8b): mp: 138−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.26 (s, 2H), 3.27 (s, 2H), 3.33 (d, 2H, J = 6.5 Hz), 3.95 (t, 1H, J = 6.5 Hz), 4.5 (s, 2H), 7.40−7.47 (m, 8H); MS: m/z: 416/418 (M^+), 415/417, 337, 183/185, 169, 104. Anal. Calcd for $C_{22}H_{18}N_4Br$: C, 63.17; H, 4.31; N, 13.40. Found: C, 63.12; H, 4.36; N, 13.33.

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