Thermal and photoinduced reduction of ethyl (*Z*)-α-cyano-β-bromomethylcinnamate by 1-benzyl-1,4-dihydronicotinamide

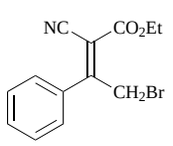
Xiao-Qing Zhu,†,[a] You-Cheng Liu,*,[a,b] Jin Li[b] and Hong-Yi Wang[a]

[a] *National Laboratory of Applied Organic Chemistry and Department of Chemistry, Lanzhou University, Lanzhou 730000, P.R. China*
[b] *Department of Chemistry, University of Science and Technology of China, Hefei, 230026, P.R. China*

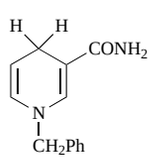
Thermal and photoinduced reduction of ethyl (*Z*)-α-cyano-β-bromomethylcinnamate (1) by coenzyme NAD(P)H model 1-benzyl-1,4-dihydronicotinamide (BNAH, 2) gives ethyl (*E*)-1-cyano-2-phenylcyclopropane-1-carboxylate (3) in the former case, and the (*E*)-4 and (*Z*)-5 isomers of ethyl α-cyano-β-methylcinnamate with the (*E*)-isomer as the major product in the latter case. The results are rationalized in terms of direct hydride transfer and electron transfer–debromination–hydrogen abstraction mechanism, respectively.

The mechanism of reduction of various substrates by coenzyme NAD(P)H models continues to be of interest.[1–3] One controversial issue concerning the mechanism is whether the formal hydride transfer from NAD(P)H model compounds to the substrate occurs in a one-step direct hydride transfer or in a multi-step sequence involving electron transfer as the initial step. Evidence has been reported to support the direct hydride transfer mechanism for many thermal reactions.[4] Evidence has also been reported to support the multi-step mechanism of many photoinduced reactions.[5] However, very little mechanistic comparison has so far been made for the thermal and photoinduced reaction of NAD(P)H models with the same substrates.

In previous articles, we reported that 2-bromo-1-phenylethylidenemalononitrile was reduced by 1-benzyl-1,4-dihydronicotinamide (BNAH) in acetonitrile at room temperature in the dark to give 2-phenyl cyclopropane-1,1-dicarbonitrile by a direct hydride transfer mechanism[6] and that 2-bromo-1-phenylethylidene malonic ester reacted with BNAH in acetonitrile under irradiation with $\lambda > 320$ nm to give three debrominated products: an α,β-unsaturated ester, a β,γ-unsaturated ester and a dimer *via* a multi-step mechanism involving electron transfer as the initial step.[7] In order to obtain further insights into the mechanistic aspects of reduction of ethylenic compounds by NAD(P)H models, we extended the study to the reaction of ethyl (*Z*)-α-cyano-β-bromomethylcinnamate (**1**) with BNAH (**2**). Since **1** contains both a nitrile



1



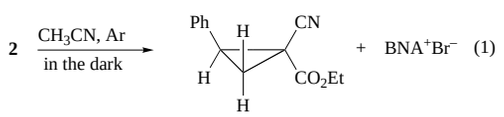
2

and an ester group, it would be of interest to compare the results with those we have reported previously.[2]

Results and discussion

Products of thermal reaction

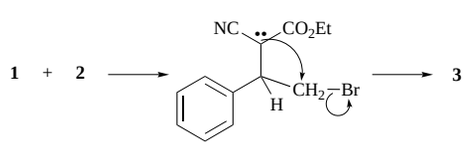
The products of thermal reaction of **1** with **2** in the dark were analyzed by NMR spectroscopy and mass spectrometry, and the results show that the cyclopropane derivative **3** was obtained [reaction (1)].



3

In order to ascertain the location of the hydrogen transferred from BNAH to **1**, [4,4-$^2H_2$]BNAH was used as the reducing agent for the reduction of **1**, and the location of deuterium incorporated in the product determined by ^{1}H NMR spectroscopy. The results showed that the triplet at 3.20 ppm for the tertiary hydrogen disappeared and the double doublet at 2.15 ppm for the methylene hydrogen on the cyclopropane changed to a broad singlet. This indicates that the deuterium is located on the β-carbon atom to the carboxylate group.

The kinetic isotope effect was determined by using BNAH and [4,4-$^2H_2$]BNAH as the reductants to react with **1** under the same conditions, and measuring the yields of product **3** by ^{1}H NMR spectroscopy. The results gave the kinetic isotope effect (k_H/k_D) of 3.1, which clearly demonstrates a primary kinetic isotope effect. This indicates that the breakage of C–H bond at C-4 of BNAH must be involved in the rate-determining step of the reaction. In view of the fact that the ethyl (*E*)-1-cyano-2-phenylcyclopropane-1-carboxylate (**3**) was obtained as the sole product, it is reasonably certain that the reaction takes place by a direct hydride transfer mechanism as shown in Scheme 1.



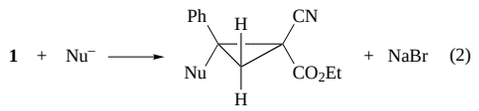
Scheme 1

According to the scheme, direct hydride transfer from BNAH to **1** takes place, the carbanion intermediate formed undergoes intramolecular nucleophilic substitution on the bromomethyl group to give the three-membered ring product. It is interesting to note that the thermodynamic stability of the (*E*)-isomer (**3**) is much greater than that of the (*Z*)-isomer;[8] the formation of the (*E*)-isomer (**3**) as the sole product is to be expected.

In order to seek support for the mechanism mentioned above, we studied the reaction of **1** with some known nucleophiles. In

† Presently at Department of Chemistry, Nankai University, Tianjin, 300071, P. R. China.

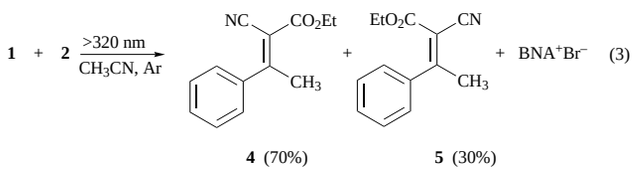
the reaction of **1** with cyanide (from NaCN) and hydride (from $NaBH_4$) ions, the substituted cyclopropane derivatives of the same favoured configurations were obtained [reaction (2)].



These results lend support to the conclusion that the direct hydride transfer is involved in the thermal reaction of BNAH with **1**.

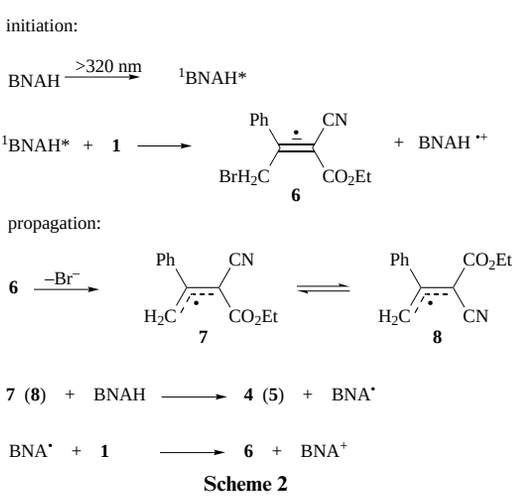
Products of photoinduced reaction

From the reaction of **1** with BNAH under irradiation with $\lambda > 320$ nm, the products obtained are as shown in reaction (3).



Products **4** and **5** are the (*E*)- and (*Z*)-isomers and **4** is the major product. In order to detect the photoinduced isomerization of the products under the experimental conditions, we dissolved either (*E*)- or (*Z*)-isomer in CD_3CN and subjected the solution to irradiation ($\lambda > 320$ nm) at 20 °C for 1.5 h. The isomerization was followed by NMR spectroscopy at δ 2.68 (s, $-CH_3$) for (*E*)-**4** and at δ 2.54 (s, $-CH_3$) for (*Z*)-**5**. The results show that (*E*)-**4** gave no detectable (*Z*)-**5**, while (*Z*)-**5** gave trace amounts of (*E*)-**4**, indicating that the product (*Z*)-**5** was formed only from the reaction, but for (*E*)-**4**, the major portion of it was formed from the reaction and only a minor portion from (*Z*)-**5** by isomerization.

From the nature of the products, it appears likely that a free radical chain mechanism is involved. Since **1** absorbs at 289 nm and BNAH absorbs at 350 nm, only BNAH was excited to the singlet excited state[9] under the experimental conditions. The mechanism for the reaction is depicted in Scheme 2. In this



Scheme 2

scheme, initial single electron transfer takes place from BNAH in its excited state to **1**, the radical anion **6** formed rapidly dissociates to a bromide anion and a neutral radical **7**, some of the allylic radical isomerizes to radical **8**, and then the terminal γ-carbon-centered radical of **7** (or **8**) abstracts a hydrogen from BNAH to give an α,β-unsaturated ester.[7] Tanner *et al.*[10] have reported a radical chain mechanism for the reduction of α-bromoacetophonone and Fukuzumi *et al.*[11] have reported a radical chain mechanism for the reduction of benzyl bromide by BNAH.

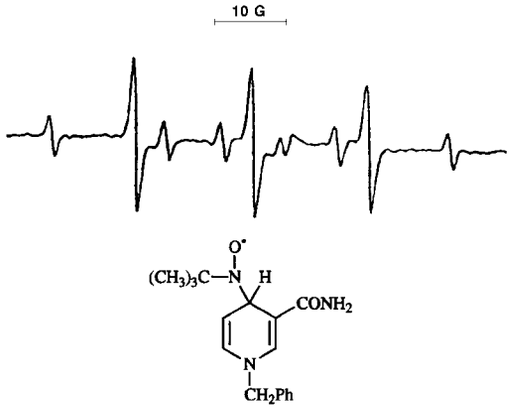


Fig. 1

Evidence for the free radical mechanism was obtained from a spin-trapping experiment. When 2-nitroso-2-methylpropane was added to the reaction, EPR spectroscopy gave a signal (Fig. 1) which is the superposition of two spectra: the one with six lines of lower intensity is assigned to the spin adduct **9**; the other with three lines of higher intensity is attributed to the di-*tert*-butyl aminoxyl radical formed as a byproduct from the spin trap by photolysis.[12]

Experimental

Instrumentation

^1H and ^{13}C NMR spectra were measured on a Bruker AM-400 MHz spectrometer operating at 400.13 MHz for ^1H and 100 MHz for ^{13}C, using TMS as reference for spectra recorded in $CDCl_3$ or in CD_3CN. All chemical shifts are denoted by δ values and J values are expressed in Hz. Mass spectra were obtained on a VGZAB-HS mass spectrometer at an ionization potential of 70 eV. EPR spectra were recorded on a Bruker ER-200D spectrometer operating at 9.8 GHz and employing 100 KHz field modulation.

Materials

BNAH[13] and [4,4-$^2H_2$]BNAH[14] were prepared according to the literature; the deuterium content of the latter was greater than 95% (^1H NMR method), MW 216 [mass spectrometry (MS)]. Ethyl (*Z*)-α-cyano-β-bromomethylcinnamate was prepared according to the literature.[15] *m/z* 293/295 (M/M+2); δ_H(400.13 MHz; $CDCl_3$) 7.51 (5H, s), 4.98 (2H, s), 4.40 (2H, q), 1.41 (3H, t); δ_C(100 MHz; $CDCl_3$) 167.60, 160.97, 136.41, 131.00, 129.65 (2C), 127.63 (2C), 115.20 (CN), 108.14, 62.81, 41.24, 13.94 (Found: C, 52.74; H, 4.16; N, 4.66. Calc. for $C_{13}H_{12}NO_2Br$: C, 53.08; H, 4.11; N, 4.76%). Other reagents were commercial products and were purified by standard procedures where necessary.

Thermal reduction

A mixture of **1** (0.4 mmol) and BNAH (1.2 mmol) in 15 ml deaerated dry acetonitrile was thermostatted at 25 °C in the dark for 5 h. The reaction mixture was treated with some water and chloroform. The organic layer was evaporated under reduced pressure to dryness and subjected to chromatography on a silica column with light petroleum–ethyl acetate as eluent to give ethyl (*E*)-1-cyano-2-phenylcyclopropane-1-carboxylate (**3**), yield 33% (based on **1**).

Product **3**: *m/z* 215 (M^+, 17%); δ_H(400.13 MHz; $CDCl_3$) 1.39 (3H, t, *J* 7), 2.15 (2H, dd, *J* 8 and 1.86), 3.20 (1H, br t, *J* 8), 4.33 (2H, q, *J* 7), 7.36 (5H, br s); δ_C(100 MHz; $CDCl_3$) 167.3, 132.9, 116.31, 63.0, 35.32, 22.89, 22.73, 14.05 (Found: C, 72.69; H, 6.11; N, 6.59. Calc. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N,

6.51%). The yield was rather low. The reason for this was that the rate of reaction was low. The yield of BNA^+ was slightly higher than that of **3**. **1** slowly decomposed in acetonitrile to give bromine and a resinous product, which remained on the top during column chromatography and was not characterized. The bromine formed could further oxidize some BNAH to BNA^+.

Photoinduced reduction

1 (0.6 mmol) and BNAH (0.7 mmol) were dissolved in dry deaerated acetonitrile (30 ml), and the mixture was thermostatted at 20 °C and irradiated with a 500 W high pressure mercury lamp filtered through double layers of glass transmitting light of $\lambda > 320$ nm for 1.5 h. Some water and chloroform were added and the organic layer was worked up as above to yield the two isomers of ethyl α-cyano-β-methylcinnamate, total yield, 39% (based on **1**).

Product **4**: *m*/*z* 215 (M^+, 24%); δ_H(400.13 MHz; $CDCl_3$) 1.38 (3H, t, *J* 7.1), 2.68 (3H, s), 4.31 (2H, q, *J* 7.1), 7.46 (5H, s) (Found: C, 72.64; H, 6.05; N, 6.41. Calc. for $C_{13}H_{13}NO_2$: C, 72.53; H, 6.09; N, 6.50%).

Product **5**: *m*/*z* 215 (M^+, 24%); δ_H(400.13 MHz; $CDCl_3$) 1.19 (3H, t, *J* 7.1), 2.54 (3H, s), 4.14 (2H, q, *J* 7.1), 7.41 (5H, s) (Found: C, 72.14; H, 6.10; N, 6.37. Calc. for $C_{13}H_{13}NO_2$: C, 72.53; H, 6.09; N, 6.50%).

Reaction of 1 with cyanide (NaCN)

Sodium cyanide (1.1 equiv.) was added to the solution of ethyl (*Z*)-α-cyano-β-bromomethylcinnamate in acetonitrile–water (4:1 v/v). The mixture was stirred for 2 h at room temperature and then some chloroform and water were added. The organic layer was separated and subjected to chromatography on a silica column to give ethyl (*Z*)-1-cyano-2-cyano-2-phenylcyclopropane-1-carboxylate, yield 81%: *m*/*z* 240 (M^+, 15%); δ_H(400.13 MHz; $CDCl_3$) 1.42 (3H, t, *J* 7.3), 2.55 (1H, d, *J* 6.5), 2.74 (1H, d, *J* 67.5), 4.45 (2H, q, *J* 7.3), 7.5 (5H, s); δ_C(100 MHz; $CDCl_3$) 162.82, 129.16, 116.07, 113.60, 64.43, 30.66, 29.22, 24.67, 14.01 (Found: C, 69.87; H, 5.10; N, 11.42. Calc. for $C_{14}H_{12}N_2O_2$: C, 70.00; H, 5.07; N, 11.65%).

Reaction of 1 with hydride ($NaBH_4$)

A solution of ethyl (*Z*)-α-cyano-β-bromomethylcinnamate (4 mmol) in ethanol (15 ml) was added to a suspension of sodium borohydride (10 mmol) in ethanol (10 ml), while the temperature was kept below 40 °C. The mixture was stirred for 4 h at room temperature. Excess sodium borohydride was destroyed with dilute acetic acid and the pH of the solution adjusted to 6. After addition of some water, the products were extracted with chloroform. The organic layer was dried over $MgSO_4$ and the solvent then removed. The crude products were subjected to chromatography to give ethyl (*E*)-1-cyano-2-phenylcyclopropane-1-carboxylate, yield 67%.

Spin trapping experiments

BNAH (0.4 mmol) and 2-methyl-2-nitrosopropane (0.2 mmol) were dissolved in dry acetonitrile (20 ml) and **1** (0.4 mmol) was dissolved in another 10 ml of dry acetonitrile. Both solutions were bubbled with argon for 5 min and then mixed in equal volume in a tube. The mixture was irradiated with a 500 W high pressure mercury lamp for 3 min ‡ and then kept in the dark for 1 h. The reaction mixture was introduced into the EPR tube and EPR spectra were recorded.

Conclusions

Ethyl (*Z*)-α-cyano-β-bromomethylcinnamate (**1**) reacts with BNAH (**2**) stereospecifically at room temperature in the dark to give ethyl (*E*)-1-cyano-2-phenylcyclopropane-1-carboxylate (**3**) by a direct hydride transfer mechanism. This provides a feasible route to the stereospecific synthesis of cyclopropane derivatives. The reactivity of **1** is similar to that of 2-bromo-1-phenylethylidenemalononitrile previously reported[6] and is in contrast to that of 2-bromo-1-phenylethylidenemalonic ester,[7] which did not react with **2** in the dark even at 60 °C. Furthermore, **1** reacts with **2** under irradiation with >320 nm to produce the (*E*)- and (*Z*)-isomers of ethyl α-cyano-β-methylcinnamate with the (*E*)-isomer in preponderance. The latter reaction is rationalized in terms of electron transfer, debromination of the radical anion intermediate and hydrogen abstraction chain mechanism, similar to what was reported[7] for the irradiation of 2-bromo-1-phenylethylidenemalonic ester with **2**.

‡ The short duration of irradiation is to avoid the formation of an aminoxyl radical as a decomposition product from the spin trapping reagent, see ref. 7, note 1.

Acknowledgements

This research was supported by the National Natural Science Foundation of the People's Republic of China. We are grateful to Professor L. M. Wu for discussions on the EPR spectra.

References

1 (*a*) C. Walsh, *Enzymatic Reaction Mechanism*, W. H. Freeman, San Francisco, 1979, p. 10; (*b*) I. Stryer, *Biochemistry*, W. H. Freeman, New York, 3rd edn., 1988, ch. 17; (*c*) F. H. Westheimer, in *Pyridine Nucleotide Coenzyme*, eds. D. Dolphin, R. Poulson and O. Avramovic, Wiley-Interscience, New York, 1988, Part A, p. 253.

2 (*a*) C. I. F. Watt, *Adv. Phys. Org. Chem.*, 1988, **24**, 57; (*b*) C. A. Coleman, J. G. Rose and C. J. Murray, *J. Am. Chem. Soc.*, 1992, **114**, 9755; (*c*) Y. Kim, D. G. Truhlar and M. M. Kreevoy, *J. Am. Chem. Soc.*, 1991, **113**, 7837; (*d*) N. Ono, R. Tamura and A. Kaji, *J. Am. Chem. Soc.*, 1983, **105**, 4017; (*e*) M. Goota, Y. Mikata and A. Ohno, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 2683.

3 (*a*) G.-X. He, A. Blasko and T. C. Briuce, *Bioorg. Chem.*, 1993, **21**, 423; (*b*) L. P. Olson and T. C. Bruice, *Biochemistry*, 1995, **34**, 7335; (*c*) O. Almarsson, E. Gopinath and T. C. Bruice, *J. Am. Chem. Soc.*, 1993, **115**, 7093.

4 (*a*) M. F. Powell and T. C. Bruice, *J. Am. Chem. Soc.*, 1982, **104**, 5834; 1983, **105**, 1014; (*b*) J. W. Verhoeven, W. van Gerresheim, F. M. Martiens and S. M. van der Kerk, *Tetrahedron*, 1986, **42**, 975; (*c*) L. L. Miller and J. R. Valentine, *J. Am. Chem. Soc.*, 1988, **110**, 3982; (*d*) B. W. Carlson and L. L. Miller, *J. Am. Chem. Soc.*, 1985, **107**, 479; (*e*) D. Ostovic, R. M. G. Roberts and M. M. Kreevoy, *J. Am. Chem. Soc.*, 1983, **105**, 7629; (*f*) D. Ostovic, J. S. Lee, R. M. G. Roberts and M. M. Kreevoy, *J. Org. Chem.*, 1985, **50**, 4206; (*g*) L. W. Bunting and S. Sindhuatmadja, *J. Org. Chem.*, 1981, **46**, 4211.

5 (*a*) S. Fukuzumi and T. Tanaka, in *Photoinduced Electron Transfer*, eds. M. Fox and M. Chanon, Elsevier, Amsterdam, 1988, ch. 4–10; (*b*) S. Fukuzumi, S. Mochizuki and T. Tanaka, *J. Phys. Chem.*, 1990, **94**, 722; (*c*) H.-J. Xu, G. Deng and Q. Yu, *J. Chem. Soc., Chem. Commun.*, 1987, 916.

6 Y. C. Liu, B. Li and Q. X. Guo, *Tetrahedron Lett.*, 1994, **35**, 8429; *Tetrahedron*, 1995, 9671.

7 B. Li, Y. C. Liu and Q. X. Guo, *J. Photochem. Photobiol. A: Chemistry*, 1997, **103**, 101.

8 E. W. Yankee, B. Spencer, N. E. Howe and D. J. Cram, *J. Am. Chem. Soc.*, 1973, **95**, 4220.

9 S. Kukuzumi, K. Hironaka and T. Tanaka, *Chem. Lett.*, 1982, 1583; *J. Am. Chem. Soc.*, 1983, **105**, 4722.

10 (*a*) D. D. Tanner, K. Singh, A. Kharrat and A. R. Stein, *J. Org. Chem.*, 1987, **52**, 2142; (*b*) D. D. Tanner and A. R. Stein, *J. Org. Chem.*, 1988, **53**, 1642.

11 S. Fukuzumi, S. Mochizuki and T. Tanaka, *Chem. Lett.*, 1988, 1983; *J. Chem. Soc., Perkin Trans. 2*, 1989, 1583.

12 M. J. Perkins, *Radical Chemistry*, Ellis Horwood, New York, London, 1994, p. 65.

13 A. C. Anderson and G. Berkelnammer, *J. Am. Chem. Soc.*, 1958, **80**, 992.

14 W. S. Caughey and K. A. Schellenberg, *J. Org. Chem.*, 1966, **31**, 1978.

15 W. Lehnert, *Tetrahedron*, 1973, **29**, 635.

Paper 7/03967K
Received 6*th June* 1997
Accepted 14*th July* 1997