Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 8607–8610

α-Bromination of linear enals and cyclic enones

Pakorn Bovonsombat,* Rungkarn Rujiwarangkul, Thanathip Bowornkiengkai and Juthamard Leykajarakul

International College, Mahidol University, Salaya Campus, Nakorn Pathom 73170, Thailand

Received 27 July 2007; revised 1 October 2007; accepted 11 October 2007
Available online 14 October 2007

Abstract—Facile α-bromination of cyclic enones and linear enals involving *N*-bromosuccinimide and 1–2 equiv of pyridine-*N*-oxide is reported herein. α-Bromination of linear enals was found to proceed with double bond geometry retention.

In a prior report, α-iodination of cyclic and linear enones was found to be effected by pyridine and stoichiometric iodine.[1] However, with the same combination of iodine and pyridine, refluxing was necessary for the reactions of linear enones. For example, (*Z*)-4-iodo-4-hexen-3-one was obtained from *trans*-4-hexen-3-one in 62% yield in boiling acetonitrile.[1] Other α-iodinations of cyclic and linear enones include the use of iodine and excess quantities of pyridine,[2] iodine and morpholine,[3] pyridinium dichromate (PDC) with iodine[4] and IN_3, prepared in situ from ICl and NaN_3.[5] Extending the aforementioned reactions to the bromination of enones is not practical due to the handling difficulties of bromine, and its oxidative nature. Thus, milder conditions are required that will tolerate sensitive groups such as an aldehyde in α-bromination reactions. Previous examples of α-bromination involve the synthesis of α-bromo analogues of flavones using a combination of iodobenzene diacetate and tetrabutylammonium bromide.[6] Another bromination method involves the use of a rhodium(III) complex and acid halides or benzyl halides, via halogenation of diazodicarbonyl analogues.[7] The same combination was also effective for α-chloroenones.[8]

Herein, we report a methodology for the formation of cyclic α-bromo enones and linear enals, which are useful templates for synthesis.[9] Enones or enals are converted directly to their respective α-bromoenones or α-bromoenals using a combination of pyridine-*N*-oxide and *N*-bromosuccinimide (NBS) by stirring in typical organic solvents at room temperature.[10] Unlike the previously reported iodination methodology which gave excellent yields with pyridine as catalyst, α-bromination is more effective with pyridine-*N*-oxide (Table 1).[1]

Using 1 equiv of pyridine-*N*-oxide and a stoichiometric amount of NBS in acetonitrile, 2-cyclohexen-1-one (**1**) was converted to 2-bromocyclohex-2-en-1-one (**1a**) in 89% yield and 100% selectivity. Spectroscopic analysis of the isolated product matched with the reported literature values.[11–14] GC–MS analysis of the crude product mixture revealed no bromination at the C-6 position, and only one product, which had incorporated a bromine atom, was observed. A ^{1}H NMR resonance at 7.43 ppm (t, $J = 4$ Hz) was consistent with a β-vinyl hydrogen. The yield of **1a** was improved slightly to 90% using 1.5 equiv of pyridine-*N*-oxide (Table 1). In contrast to pyridine-*N*-oxide, 2.1 equiv of pyridine in acetonitrile gave a yield of **1a** of only 55% (Table 2). In acetone, the yields of **1a** were 73% and 89%, respectively, using 1 and 1.5 equiv of pyridine-*N*-oxide. The highest yield of **1a** with pyridine as catalyst (2.1 equiv) was 58% in acetone. A yield of 73% was obtained using 2.1 equiv of pyridine in THF. Remarkably, pyridine-*N*-oxide did not perform as well in THF with 1.5 equiv (61% conversion and 80% selectivity), but fared much better at 1 equiv, giving rise to a yield of 70% and 100% selectivity. With methanol as the solvent, α-bromination proceeded poorly with both pyridine and pyridine-*N*-oxide, especially with 2.0 equiv of pyridine where no product was detected by GC–MS. For both pyridine-*N*-oxide and pyridine, the reactions in methanol at 1.0 and 1.5 equiv were poor with low conversions and less than 100% selectivity.

* Corresponding author. Tel.: +66 02 441 0594; fax: +66 02 441 9745; e-mail: icpakorn@mahidol.ac.th

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.10.055

Table 1. Effects of solvent and pyridine-*N*-oxide on the bromination of **1**

Entry	Pyridine-*N*-oxide/**1** ratio	Yield of **1a**[a]			
		Methanol	Acetone	Acetonitrile	THF
1	1.0	11[b]	73	89	70
2	1.5	15[c]	89	90	49[d]
3	2.0	—	76	78	62

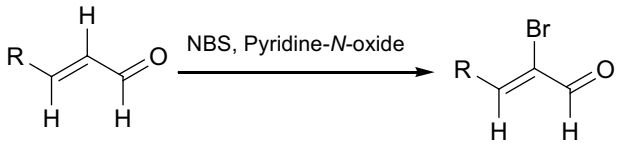
[a] Reaction conditions: Compound **1** (1 mmol), pyridine-*N*-oxide and 1 mmol of NBS in 10 mL of solvent, overnight stirring at room temperature. Yields determined by GC with 100% selectivity, unless stated otherwise.
[b] 31% conversion and 37% selectivity.
[c] 37% conversion and 40% selectivity.
[d] 61% conversion and 80% selectivity.

Table 2. Effects of solvent and pyridine on the bromination of **1**

Entry	Pyridine/**1** ratio	Yield of **1a**[a]			
		Methanol	Acetone	Acetonitrile	THF
1	1.0	18[b]	27	22	48
2	1.5	17[c]	56	49	53
3	2.1	—[d]	58	55	73

[a] Reaction conditions: Compound **1** (1 mmol), pyridine and 1 mmol of NBS in 10 mL of solvent, overnight stirring at room temperature. Yields determined by GC with 100% selectivity, unless stated otherwise.
[b] Less than 35% conversion and 53% selectivity.
[c] 27% conversion and 62% selectivity.
[d] No conversion to **1a** (2-bromocyclohex-2-en-1-one).

Under the optimised conditions for the bromination of **1** (1.5 equiv of pyridine-*N*-oxide, CH_3CN), 2-cyclopenten-1-one (**2**) was converted to 2-bromocyclopent-2-en-1-one (**2a**) with 97% conversion and 100% selectivity.[12,13]



R: C_6H_5 (**3**) or CH_3CH_2 (**4**) **3a** or **4a**

The challenge to this methodology is its application to a linear conjugated carbonyl system such as an enal, which lacks structural rigidity. Unlike previous reports on halogenation of linear enones, which required refluxing to achieve moderate conversions to the product,[1] α-bromination of linear enals using the methodology described for **1** and **2** was found to give moderate to good yields at room temperature without undesirable oxidation of the aldehyde group. Bromination of *trans*-cinnamaldehyde (**3**) with 1.5 equiv of pyridine-*N*-oxide in acetonitrile with overnight stirring at room temperature gave (*Z*)-2-bromo-3-phenyl-2-propenal (**3a**) with 100% conversion and 100% selectivity (Table 3), and which gave ^{1}H NMR data and a melting point matching those reported earlier.[13,15] α-Bromination of *trans*-2-pentenal (**4**) with the same combination of reagents and conditions gave (*Z*)-2-bromo-2-pentenal (**4a**) with 93% conversion and 100% selectivity (91% isolated yield).[16,17]

Evidence for the *Z*-isomer assignment of 2-bromo-3-phenyl-2-propenal came from its melting point and ^{1}H NMR data which matched those of the literature. Additional evidence supporting the *Z*-geometry assignment of 2-bromo-3-phenyl-2-propenal came from ^{1}H–^{1}H correlation spectroscopy (COSY), performed on the product isolated by silica gel chromatography. The argument for the assignment of the *Z*-isomer based on the COSY experiment is as follows. The optimum conformation of **3a** should be *S-trans* with the aldehyde hydrogen adopting a geometry and orientation in close proximity to the β-vinyl hydrogen. Hence, a certain amount of coupling, albeit weak, is expected between the β-vinyl and the aldehyde hydrogens, and a certain degree of cross peak intensity should be observed between these two hydrogens in the COSY plot. Indeed, the COSY spectrum of **3a** revealed cross peaks correlating the two sets of hydrogens and thereby reaffirming the previously assigned *Z*-geometry of 2-bromo-3-phenyl-2-propenal.[13,14] The product **4a** was also subjected to a COSY experiment, which also showed cross peaks between the β-vinyl hydrogen and the aldehyde hydrogen, and again confirming the structural assignment of the *Z*-isomer.

Investigations to optimise conditions for α-chlorination and α-iodination of both cyclic and acyclic enones as well as linear enal system have been undertaken. In our initial study, *N*-iodosuccinimide (NIS) and *N*-chlorosuccinimide (NCS) were employed in a similar manner to that of the synthesis of α-bromoenals to afford (*Z*)-2-iodo-3-phenyl-2-propenal and (*Z*)-2-chloro-3-phenyl-2-propenal from the starting cinnamaldehyde.

The conversion of **3** to (*Z*)-2-iodo-3-phenyl-2-propenal (**3b**) was only 8% in acetone with 2.1 equiv of pyridine and 1.1 equiv of NIS after 18 h at room temperature; the selectivity, however, was 100%. The ^{1}H NMR data of the purified product did not match the literature value

Table 3. Bromination of Linear Enals

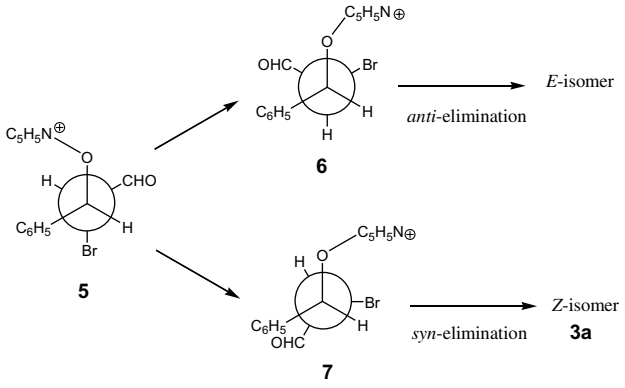
Entry	Enal	% Conversions to (*Z*)-2-bromoenals[a]	
		Acetonitrile	Acetone
1	*trans*-Cinnamaldehyde	100	82
2	*trans*-2-Pentenal	93	88

[a] 100% Selectivity, unless stated otherwise. Reaction conditions: **3** or **4** (1 mmol), 1.5 equiv pyridine-*N*-oxide and 1 mmol of NBS in 10 mL of solvent, overnight stirring at room temperature. Yields determined by GC with 100% selectivity, unless stated otherwise.

reported earlier for the *E*-isomer.[18] The spectroscopic data of the purified product, **3b**, are as follows: ^{1}H NMR (300 MHz, $CDCl_3$); δ 7.46–7.56 (m, 3H, aromatic), 7.98–8.05 (m, 2H, aromatic), 8.1 (s, 1H, βH-olefin), 8.79 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.04, 155.81, 144.81, 134.05, 131.61, 130.43, 128.61; GC/MS, *m*/*z* (rel int.) 258 (100, M^+), 131 (24, $(M-I)^+$), 130 (35, $(M-HI)^+$), 103 (77), 77 (63), 63 (10), 51 (24). Furthermore, the melting point (found: 89–90 °C) did not match that of the *E*-isomer (reported 85–86 °C).[18] In methanol, the conversion to **3b** rose to 69% but the selectivity declined to 65%, due to the formation of acetals and hemiacetals of the starting compound and the product. A COSY experiment on **3b** showed cross peaks between the aldehyde and the β-vinyl hydrogens, further reinforcing the *Z*-isomer assignment.

The product of α-chlorination of **3**, (*Z*)-2-chloro-3-phenyl-2-propenal (**3c**), was obtained with 100% selectivity and 16% conversion with a combination of 1.2 equiv of NCS and 2.1 equiv of pyridine with stirring at room temperature for 18 h in THF. As with the α-iodination of **3**, α-chlorination was less effective with pyridine-*N*-oxide. With 2 equiv of NCS, the conversion increased to 19%. Despite the low yields, **3c** could be isolated with ease by silica gel chromatography using dichloromethane/hexanes (1:1) as eluent. ^{1}H and ^{13}C NMR spectra of **3c** were found to match the previous reported values.[14,19]

The *Z*-isomeric products of **3a**, **3b**, **3c** and **4a** are thought to occur via *syn* elimination of the α-hydrogen and the pyridinium oxide group, via conformation **7** (Scheme 1). *Anti* elimination, as depicted below, of the α-hydrogen and the pyridinium-*N*-oxide (via **6**) would result in the *E*-isomer. Such *syn* elimination is not unprecedented and has been shown to occur in primary alkyltrimethylammonium salts.[20]



Scheme 1. Regioselectivity in the conversion of **5**.

Further investigation is underway to optimise the conditions for α-halogenation of enones and enals, and the results will be reported in due course.

Acknowledgements

We are grateful to the Director's Initiative Fund of Mahidol University International College. We are indebted to Dr. Sirirat Choosakoonkriang of the Department of Chemistry of Silpakorn University for spectroscopic analyses and also to Miss Josie Vayro. This Letter is dedicated to the late Professor Edward J. McNelis and Dr. Geetha J. Angara.

References and notes

1. Djuardi, E.; Bovonsombat, P.; McNelis, E. *Synth. Commun.* **1997**, *27*, 2497–2503.
2. Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917–918; Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 919–922.
3. Perez, A. L.; Lamoureux, G.; Herrera, A. *Synth. Commun.* **2004**, *34*, 3389–3397.
4. Bovonsombat, P.; Angara, G. J.; McNelis, E. *Tetrahedron Lett.* **1994**, *35*, 6787–6790.
5. McIntosh, J. M. *Can. J. Chem.* **1971**, *49*, 3045–3047.
6. Rho, H. S.; Ko, B.-S.; Kim, H. K.; Ju, Y.-S. *Synth. Commun.* **2002**, *32*, 1303–1310.
7. Lee, Y. R.; Sub Cho, B.; Kwon, H. J. *Tetrahedron* **2003**, *59*, 9333–9347; Lee, Y. R.; Jung, Y. U. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1309–1313; Lee, Y. R.; Kim, D. H. *Tetrahedron Lett.* **2001**, *42*, 6561–6563; Lee, Y. R.; Suk, J. Y. *Chem. Commun.* **1998**, 2621–2622.
8. Kim, K. M.; Chung, K. H.; Kim, J. N.; Ryu, E. R. *Synthesis* **1993**, 283–284.
9. Rossi, R.; Bellina, F.; Ciucci, D. *J. Organomet. Chem.* **1997**, *542*, 113–120; Bhanu Prasad, A. S.; Knochel, P. *Tetrahedron* **1997**, *53*, 16711–16720; Demay, S.; Harms, K.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 4981–4984; Soorukram, D.; Knochel, P. *Org. Lett.* **2004**, *6*, 2409–2411; Bamba, M.; Nishikawa, T.; Isobe, M. *Tetrahedron* **1998**, *54*, 6639–6650; Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264–10269; Souza, F. E. S.; Sutherland, H. S.; Carlini, R.; Rodrigo, R. *J. Org. Chem.* **2002**, *67*, 6568–6570; Ohshima, T.; Xu, Y.;

Takita, R.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 9569–9588; Lioa, B.; Negishi, E.-i. *Heterocycles* **2000**, *52*, 1241–1249.

10. For the use of *N*-halosuccinimides for α-halogenation of 5-amino-*endo*-tricyclo[5.2.1.02,6]deca-4,8-dien-3-one, see: Ramesh, N. G.; Heijne, E. H.; Klunder, A. J. H.; Zwannenburg, B. *Tetrahedron Lett.* **1998**, *39*, 3295–3298; Ramesh, N. G.; Heijne, E. H.; Klunder, A. J. H.; Zwannenburg, B. *Tetrahedron* **2002**, *58*, 1361–1368.
11. Dunn, G. L.; DiPasquo, V. J.; Hoover, J. R. E. *J. Org. Chem.* **1968**, *33*, 1454–1459.
12. Guaciaro, M. A.; Wovkulich, P. M.; Smith, A. B., III. *Tetrahedron Lett.* **1978**, *19*, 4661–4664; Smith, A. B., III; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855–1869.
13. Kowalski, C. J.; Weber, A. E.; Fields, K. W. *J. Org. Chem.* **1982**, *47*, 5088–5093.
14. Kim, K.-M.; Park, I.-H. *Synthesis* **2004**, 2641–2644.
15. *Compound* **3a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.55 (m, 3H, aromatic), 7.91 (s, 1H, βH-olefin), 7.97–8.05 (d, $J = 7$ Hz, 2H, aromatic), 9.35 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.3, 149.3, 133.2, 131.8, 131.2, 129.0, 124.5; GC/MS, *m*/*z* (rel int.) 212/210 (60, M^+), 211/209 (85, $(M\text{-}1)^+$), 131 (30, $(M-Br)^+$), 103 (100), 77 (67), 63 (14), 51 (37); melting point, found: 69–70 °C, reported: 70–71 °C.
16. Lutjens, H.; Knochel, P. *Tetrahedron: Asymmetry* **1994**, *5*, 1161–1162.
17. *Compound* **4a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.22 (s, 1H, CHO), 7.14–7.18 (t, $J = 7$ Hz, 1H), 2.62–2.52 (m, 2H), 1.17–1.22 (t, $J = 7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.2 (CHO), 156.9 (C3), 148.7 (C2), 25.5 (CH_2), 11.9 (CH_3); GC/MS, *m*/*z* (rel int.) 164/162 (75, M^+), 147/149 (3, $(M-CH_3)^+$), 133/135 (14, $(M-CHO)^+$), 119/121 (12), 83 (100, $(M-Br)^+$), 55 (96), 39 (79), 29 (40).
18. Suzuki, H.; Aihara, M.; Yamamoto, H.; Takamoto, Y.; Ogawa, T. *Synthesis* **1988**, 236–238.
19. Kamigata, N.; Satoh, T.; Yoshida, M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 449–454; Satoh, T.; Kitoh, Y.; Onada, K.-i.; Takano, K.; Yamakawa, K. *Tetrahedron* **1994**, *50*, 4957–4972.
20. Tao, Y.-T.; Saunders, W. H. *J. Am. Chem. Soc.* **1983**, *105*, 3183–3188; Dohner, B. R.; Saunders, W. H. *J. Am. Chem. Soc.* **1986**, *108*, 245–247.