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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 623–626

Amberlyst-15®-promoted efficient 2-halogenation of 1,3-keto-esters and cyclic ketones using *N*-halosuccinimides

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Received 9 September 2004; revised 15 November 2004; accepted 26 November 2004
Available online 13 December 2004

Abstract—A simple and rapid process has been developed for the α-monohalogenation of 1,3-keto-esters with *N*-halosuccinimides catalyzed by Amberlyst-15® at room temperature to produce the corresponding 2-halo 1,3-keto-esters in high yields. This protocol also extended to α-halogenation of cyclic ketones.

Preparation of 2-bromo 1,3-dicarbonyl compounds has always received attention due to their versatile uses as intermediates in organic synthesis.[1] α-Monobromination of β-keto-esters without α-substituents has been a challenging problem since the monosubstituted product is always accompanied by a small amount of disubstituted product. The most commonly used reagents include bromine,[2] copper(II) bromide[3] and *N*-bromosuccinimide.[4] In terms of accessibility and ease of handling, *N*-bromosuccinimide is a superior and inexpensive brominating reagent. The major advantage of the use of the NBS is that the byproduct succinimide can be easily recovered and reconverted to NBS to be reused in subsequent reactions. Classically, the NBS α-bromination of ketones proceeds via a radical process promoted by initiators such as azobisisobutyronitrile (AIBN) and dibenzoyl peroxide (BPO) in refluxing CCl_4.[5] Lewis acid $Mg(ClO_4)_2$ is also employed to promote 2-halogenation of 1,3-dicarbonyl compounds.[6] Recently, a mild and efficient method for the bromination of β-keto-esters using *N*-bromosuccinimide catalyzed by NH_4OAc was described.[7] Togni et al. used Ti(TADDOLato) complex to catalyze enantioselective α-halogenation of α-substituted β-keto-esters.[8] Subsequently, several methods have been developed for the 2-chlorination[9] and 2-iodination[10] of 1,3-dicarbonyl compounds using NCS or NIS, respectively. Although some of these methods were successful for the monohalogenation of β-keto-esters, a number of these methods are practically inconvenient to use or employ rather harsh reaction conditions and sometimes produce dihalogenated products. Here we report that NBS combined with the heterogeneous solid acidic catalyst Amberlyst-15® achieves fast 2-monobromination of a wide range of 1,3-keto-esters. In addition, this method can be applied to the 2-chlorination and 2-iodination of 1,3-keto-esters.[11,12]

Firstly, ethyl benzoylacetate **1a** (R^1 = Ph, R^2 = Et) was chosen as a model substrate for bromination in order to find optimal conditions. Compound **1a** was treated with 1.05 equiv NBS in the presence of Amberlyst-15® at room temperature in ethyl acetate. The reaction was complete within 15 min to give brominated product **3a** (R^1 = Ph, R^2 = Et) in 94% yield (Scheme 1). When the reaction solvent was changed to $CHCl_3$, CH_2Cl_2, or CH_3CN the reaction required a much longer time and unreacted **1a** remained, thus ethyl acetate gave the best results. Next we tested the possibility of using Amberlyst-15® to catalyze chlorination and iodination of compound **1a** using NCS or NIS. In this study, the 2-chloro- and 2-iodo-1,3-keto-esters were obtained in excellent yields. Various other 2-unsubstituted and 2-substituted 1,3-keto-esters were converted to their corresponding 2-halo products in high yields using this procedure (Table 1, entries b–f). Cyclic 1,3-keto-esters also reacted smoothly. In all cases, the reactions proceeded efficiently within 10–30 min in high yields at ambient temperature. In some cases dichlorination and diiodination was observed.

Keywords: Ion exchange resin; *N*-Halosuccinimides; Halogenation; β-Keto-esters; Cyclic ketones.
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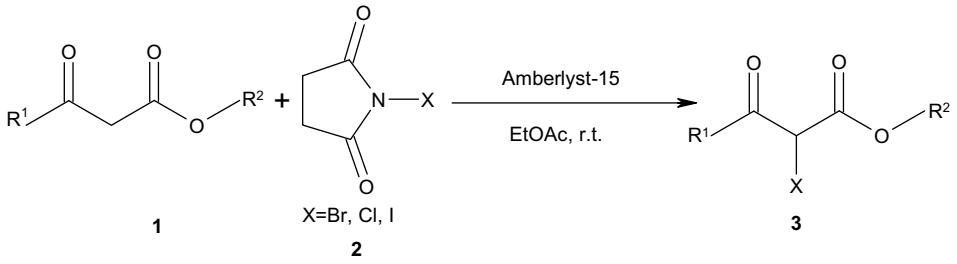
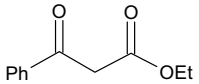
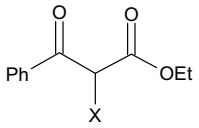
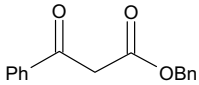
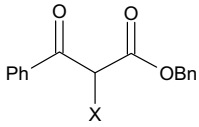
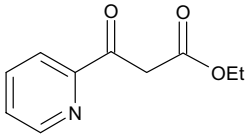
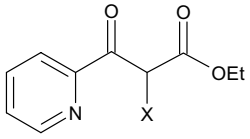
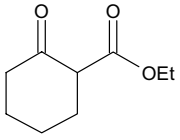
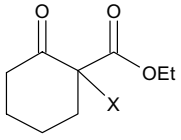
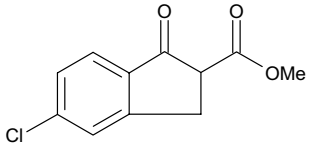
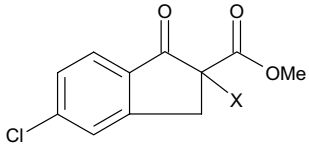
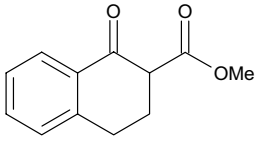
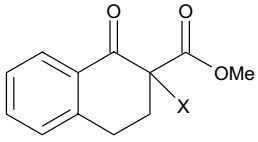
0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.11.140



Scheme 1.

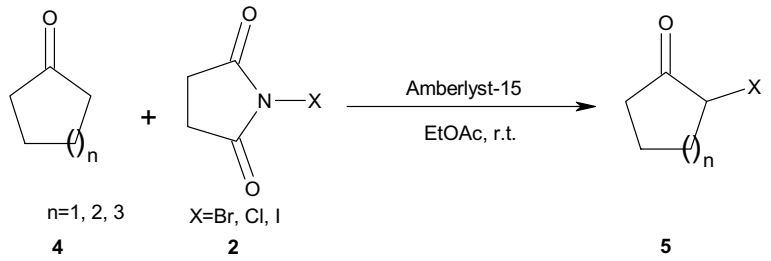
Table 1. 2-Halogenation of various 1,3-keto-esters with *N*-halosuccinimides

Entry	1,3-Keto-esters **1**	Product[a] X = **3** Br, $\mathbf{3}^{1}$ = Cl, $\mathbf{3}^{11}$ = I	X	Time (min)	Yield (%)[b]
a			Br	15	94
			Cl	10	92
			I	20	90
b			Br	10	95
			Cl	10	92
			I	15	86
c			Br	15	89
			Cl	20	85
			I	30	86
d			Br	10	90
			Cl	20	92
			I	20	88
e			Br	15	93
			Cl	15	90
			I	20	86
f			Br	30	92
			Cl	45	92
			I	30	90

[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy.
[b] Isolated and unoptimized yield.

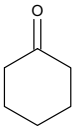
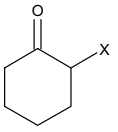
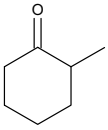
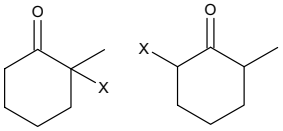
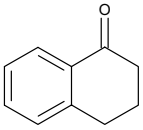
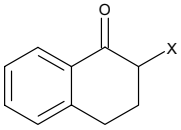
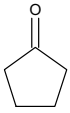
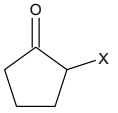
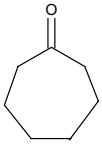
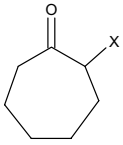
We now examined the α-halogenation of cyclic ketones under the same reaction conditions and found that the reactions proceeded rapidly at room temperature with high yields (Scheme 2). In the case of 2-methylcyclohexanone (Table 2, entry b) halogenation occurred predominantly at the more substituted position. Halogenation of acyclic ketones using NXS under these conditions failed. The scope and generality of this process is illustrated with respect to various cyclic ketones and the results are presented in Table 2.[13]

We have shown that *N*-halosuccinimides show enhanced reactivity in the presence of Amberlyst-15® thereby reducing the reaction times dramatically, and substantially improving the yields. Low conversions (35–55%) were obtained when other solid acid catalysts such as heteropoly acid $H_3PW_{12}O_{40}$, and H-ZSM were employed. The Amberlyst catalyst could be easily separated by simple filtration and the recovered acid resin could be re-used in subsequent reactions with a gradual decrease in activity. For example, cyclohexanone with *N*-bromo-



Scheme 2.

Table 2. α-Halogenation of various cyclic ketones using *N*-halosuccinimides

Entry	Cyclic ketones	Product[a] X = **5** Br, **5**[1] = Cl, **5**[11] = I	X	Time (min)	Yield (%)[b]
a			Br	25	90
			Cl	30	87
			I	40	84
b			Br	20	88
			Cl	30	90
			I	60	82
c			Br	30	90
			Cl	25	84
			I	40	79
d			Br	30	86
			Cl	30	81
			I	60	78
e			Br	20	92
			Cl	25	90
			I	30	86

[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy.
[b] Isolated and unoptimized yield.

succinimide given 2-bromocyclohexanone in 90%, 86%, 80%, and 75% yields over four cycles.

In conclusion, we have developed a novel and efficient approach for the mild 2-halogenation of 1,3-keto-esters and α-halogenation of cyclic ketones with *N*-halosuccinimides using Amberlyst-15® as a heterogeneous solid acid catalyst. Because of its simplicity, high selectivity, short reaction times, high yields, the use of an inexpensive and recyclable acid resin, this method is simple, convenient and economically viable.

References and notes

1. (a) Misra, A. P.; Raj, K.; Bhaduri, A. P. *Synth. Commun.* **1999**, *29*, 3227–3236; (b) Coats, S. J.; Wasserman, H. H. *Tetrahedron Lett.* **1995**, *36*, 7735–7738; (c) Endo, M.; Droghini, R. *Can. J. Chem.* **1988**, *66*, 1400–1404; (d) Hlavka, J.; Bitha, P.; Lin, Y.; Strohmeyer, T. *J. Heterocycl. Chem.* **1985**, *22*, 1317–1322; (e) Yoshida, J.; Yano, S.; Ozawa, T.; Kawabata, N. *Tetrahedron Lett.* **1984**, *25*, 2817–2820; (f) Kaye, P. T.; Meakins, G. D.; Smith, A. K.; Tirel, M. D. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1677–1680.
2. (a) Bigelow, L. A.; Hanslick, R. S. *Org. Synth. Collect.*; Wiley: New York, 1943; Vol. 2, p 244; (b) Hakam, K.; Thielmann, M.; Thielmann, T.; Winterfeldt, E. *Tetrahedron* **1987**, *43*, 2035–2044; (c) Ogilvie, W.; Rank, W. *Can. J. Chem.* **1987**, *65*, 166–169; (d) Dowd, P.; Kaufman, C.; Kaufman, P. *J. Org. Chem.* **1985**, *50*, 882–885.
3. (a) Coats, S. J.; Wasserman, H. H. *Tetrahedron Lett.* **1995**, *36*, 7735–7738; (b) Rao, A. V. R.; Singh, A. K.; Reddy, K. M.; Ravikumar, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3171–3175; (c) Shi, X.; Dai, L. *J. Org. Chem.* **1993**, *58*, 4596–4598.

4. (a) NBS or Br_2/NaH: Boyd, R. E.; Rasmussen, C. R.; Press, J. B. *Synth. Commun.* **1995**, *25*, 1045–1051; (b) NBS/NEt_3: Karimi, S.; Grohmann, K. G. *J. Org. Chem.* **1995**, *60*, 554–559; (c) NBS/NaH: Curran, D. P.; Bosch, E.; Kaplan, J.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 1826–1831; (d) NBS/KH: Curran, D. P.; Chang, C. T. *J. Org. Chem.* **1989**, *54*, 3140–3157.
5. Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1946**, *29*, 573–581.
6. Yang, D.; Yan, Yi.-L.; Lui, B. *J. Org. Chem.* **2002**, *67*, 7429–7431.
7. Tanemura, K.; Suzuki, T.; Nishida, Y.; Satsumabayashi, K.; Horaguchi, T. *Chem. Commun.* **2004**, 470–471.
8. (a) Hintermann, L.; Togni, A. *Helv. Chem. Acta* **2000**, *83*, 2425–2435; (b) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359–4362; (c) Piana, S.; Devillers, I.; Togni, A.; Rothlisberger, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 979–982.
9. Chlorination with NCS: (a) Davis, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron* **2000**, *56*, 3941–3949; (b) Tanaka, K.; Chen, X.; Yoneda, F. *Tetrahedron* **1988**, *44*, 3241–3249.
10. Iodination with NIS: (a) Cossy, J.; Thellend, A. *Tetrahedron Lett.* **1990**, *31*, 1427–1428; (b) Curran, D. P.; Morgan, T. M.; Schwartz, C. E.; Snider, B. B.; Dombroski, M. A. *J. Am. Chem. Soc.* **1991**, *113*, 6607–6617.
11. For examples of 2-chloro 1,3-dicarbonyl compounds in organic transformations, see: (a) Hayashi, Y.; Orikasa, S.; Tanaka, K.; Kanoh, K.; Kiso, Y. *J. Org. Chem.* **2000**, *65*, 8402–8405; (b) Guerin, D.; Carlier, R.; Lorcy, D. *J. Org. Chem.* **2000**, *65*, 6069–6072; (c) Vasudevan, A.; Mavandadi, F.; Chen, L.; Gangjee, A. *J. Org. Chem.* **1999**, *64*, 634–638; (d) Hayes, T.; Villani, R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1988**, *110*, 5533–5543; (e) Blount, J. F.; Coffen, D. L.; Katonak, D. A. *J. Org. Chem.* **1978**, *43*, 3821–3824.
12. For examples of 2-iodo 1,3-dicarbonyl compounds in organic transformations, see: (a) Kang, J.; Lee, J. H.; Noh, S. B.; Oh, C. S.; Kim, H. Y.; Chung, B. Y. *Synlett* **1990**, 153–154; (b) Curran, D. P.; Chen, M. S.; Spletzer, E.; Seong, C. M.; Chang, C. T. *J. Am. Chem. Soc.* **1989**, *111*, 8872–8878.
13. General procedure: A mixture of 1,3-keto-ester or cyclic ketone (1 mmol), *N*-halosuccinimide (1.05 mmol), and Amberlyst-15® (0.75 g) in ethyl acetate (10 mL) was stirred at room temperature for the appropriate time (see Tables 1 and 2). After completion of the reaction, as indicated by TLC, the reaction mixture was filtered and washed with ethyl acetate (2×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 concentrated in vacuo and the resulting product was directly charged on a small silica gel (Merck, 60–120 mesh) column and eluted with a mixture of ethyl acetate: *n*-hexane (1:9) to afford the corresponding pure product. Compound **3b**: IR (KBr): υ2966, 1743, 1682, 1450, 1258, 964, 737, 688, 615 cm^{-1}. ^1H NMR (300 Hz, $CDCl_3$): δ 5.23 (s, 2H), 5.60 (s, 1H), 7.24–7.31 (m, 5H), 7.44 (t, 2H, $J = 7.5$ Hz), 7.58 (t, 1H, $J = 7.5$ Hz), 7.94 (d, 2H, $J = 7.5$ Hz). EIMS Mass: *m*/*z*: 335 (^{81}Br, M^+, 17), 333 (^{79}Br, M^+, 17), 120 (9), 105 (100), 91 (9), 77 (26), 57 (25). Compound **3**^{1}**d**: IR (KBr): υ 2946, 2871, 1732, 1451, 1241, 751, 562 cm^{-1}. ^1H NMR (300 Hz, $CDCl_3$): δ 1.27 (t, 3H, $J = 7.4$ Hz), 1.66–1.75 (m, 1H), 1.82–1.96 (m, 3H), 2.03–2.11 (m, 1H), 2.30–2.39 (m, 1H), 2.67–2.74 (m, 1H), 2.75–2.83 (m, 1H), 4.23 (q, 2H, $J = 7.4$ Hz). EIMS Mass: *m*/*z*: 206 (^{37}Cl, M^+, 7), 204 (^{35}Cl, M^+, 19), 169 (12), 139 (100), 43 (60). Compound **3**^{1}**f**: IR (KBr): υ 2954, 2849, 1760, 1693, 1601, 1438, 1252, 738, 582 cm^{-1}. ^1H NMR (300 Hz, $CDCl_3$): δ 2.44–2.55 (m, 1H), 2.92–3.04 (m, 2H), 3.22–3.35 (m, 1H), 3.84 (s, 3H), 7.24 (d, 1H, $J = 7.5$ Hz), 7.34 (t, 1H, $J = 7.5$ Hz), 7.51 (t, 1H, $J = 7.5$ Hz), 8.05 (d, 1H, $J = 7.5$ Hz); EIMS Mass: *m*/*z*: 240 (^{37}Cl, M^+, 2), 238 (^{35}Cl, M^+, 4), 203 (29), 171 (21), 118 (100), 90 (47), 63 (8). Compound **5c**: IR (KBr): υ 2925, 1683, 1599, 1454, 1217, 888, 772, 594 cm^{-1}. ^1H NMR (300 Hz, $CDCl_3$): δ 2.41–2.57 (m, 2H), 2.89 (dt, 1H, $J = 3.7$, 17 Hz), 3.29–3.38 (m, 1H), 4.67 (t, 1H, $J = 3.7$ Hz), 7.25 (d, 1H, $J = 8.1$ Hz), 7.33 (t, 1H, $J = 7.4$ Hz), 7.49 (t, 1H, $J = 8.1$ Hz), 8.06 (d, 1H, $J = 8.1$ Hz). EIMS Mass: *m*/*z*: 226 (^{81}Br, M^+, 16), 224 (^{79}Br, M^+, 16), 144 (23), 118 (100), 90 (40), 63 (13).