Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 3802–3804
Tetrahedron Letters

Thiourea catalysis of NCS in the synthesis of α-chloroketones

Yujiang Mei, Paul A. Bentley *, Juan Du

Department of Chemistry and Chemical Biology, MSC03 2060, University of New Mexico, Albuquerque, NM 87131-0001, USA

Received 25 February 2008; revised 31 March 2008; accepted 31 March 2008
Available online 4 April 2008

Abstract

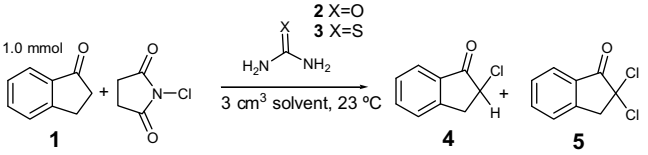
Thiourea catalyzes NCS α-chlorination of alkyl ketones to provide α-chloroketones in very high yields at exceptionally rapid reaction speeds.

α-Chlorinated carbonyl compounds are important intermediates in organic synthesis because they can be converted into a diverse array of molecules.[1,2] They also serve as metabolically more stable alternatives to hydrogen and methyl functionality in drugs without loss of therapeutic efficacy.[3] Such benefits have created considerable synthetic interest in chlorination catalysis including the innovative use of organocatalysts,[4–10] Lewis acids,[11,12] amberlyst,[13] transitional metal complexes[14,15] and inorganic reagents.[16–18] However, the need remains for a faster reaction that provides chlorides in higher yields. To address this desire we sought to exploit the capacity of thiourea to catalyze the reactions of *N*-halosuccinimides, demonstrated with chlorohydrin and β-chloroether synthesis.[19,20]

Thiourea and its derivatives activate nitro, imine and carbonyl functionality via hydrogen bonding in organocatalytic reactions,[21–39] whilst reactions that involve *N*-halosuccinimides are catalyzed by Brønsted acids.[40] We speculated that NCS[41] could be activated by thiourea hydrogen bonding to NCS oxygens.[19]

The non-catalyzed α-chlorination of ketones (e.g., **1**) is a slow reaction (Table 1, entry 1)[42] and whilst the addition of urea retarded the reaction further (Table 1, entry 2), the inclusion of thiourea gave a dramatic increase in the reaction rate (Table 1, entry 3). However, a significant amount of the dichloride (**5**) was observed. Chemoselectivity was improved with the use of less NCS and thiourea, with a reduction in the reaction time (Table 1, entries 4–9). It was hoped that the examination of alternative solvents

Table 1
Chlorination of styrene with thiourea/urea catalysts in water



Entry	Solvent	NCS (mmol)	Catalyst (mmol)	Reaction time	Conv./ yield (%)	Molar ration,[a] **4**:**5**
1	MeOH	2.5	—	72 h	100	53:1
2	MeOH	4.0	**2** (0.3)	72 h	78/—	12:1
3	MeOH	4.0	**3** (0.3)	<5 min	100/—	3:1
4	MeOH	3.0	**3** (0.3)	<5 min	100[b]	4:1
5	MeOH	2.5	**3** (0.2)	<5 min	100[b]	5:1
6	MeOH	2.5	**3** (0.05)	<5 min	100[b]	9:1
7	MeOH	2.5	**3** (0.02)	10 min	100[b]	10:1
8	MeOH	2.0	**3** (0.02)	20 min	100[b]	11:1
9	MeOH	1.2	**3** (0.02)	20 min	100/90[c]	53:1
10	DCM	4.0	**3** (0.3)	48 h	62/—	13:1
11	THF	4.0	**3** (0.3)	48 h	67/—	11:1
12	EtOAc	4.0	**3** (0.3)	8 h	100/—	4:1
13	MeCN	4.0	**3** (0.3)	4.5 h	100/—	3:1

[a] Molar ratio determined by ^{1}H NMR.
[b] The yield of mixture of **4** and **5** was 100%.
[c] 90% yield of **4**.

* Corresponding author. Tel.: +1 505 277 0369; fax: +1 505 277 2609.
E-mail address: pabco21@gmail.com (P. A. Bentley).

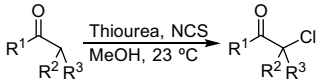
0040-4039/$ - see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2008.03.154

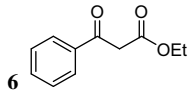
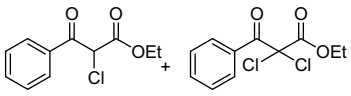
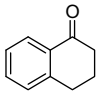
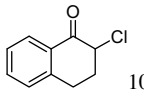
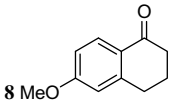
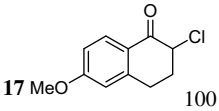
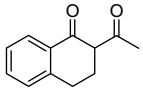
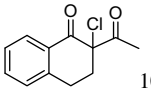
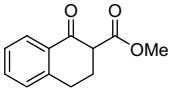
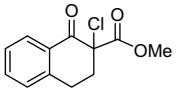
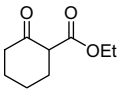
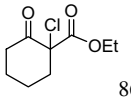
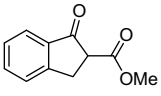
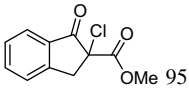
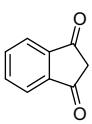
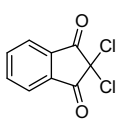
(Table 1, entries 10–13) would speed up the reaction, but protic polar methanol proved optimal. This is rationalized by further hydrogen bonding of methanol with thiourea to give even stronger hydrogen bonds.[20]

These refined conditions (Table 1, entry 9) were clearly effective with comparatively little organocatalyst (2%/mmol). They were applied to a variety of substrates (Table 2). Acyclic dicarbonyl **6** was chlorinated at the slowest reaction rate (Table 2, entry 1) and gave a small amount of the dichloride in addition to the chloride. Other cyclic ketones proved more fruitful, with tetralone **7** twice as fast as indanone **1** at chlorination and gave a higher yield (Table 2 entry 2). The methoxy derivative (**8**) was slower (Table 2, entry 3) than **7**. A range of more acidic cyclic 1,3-diketones and β-ketoesters were studied. A clear trend was discernable with 1,3-diketones reacting very rapidly (Table 2, entry 4), faster than β-ketoesters that reacted faster (Table 2, entry 5) than ketones (**7**). The most reactive substrate was diketone **13** that was transformed to the dichloride in a comparable time to that for the conversion of other substrates to chloride (Table 2, entry 8).

We have demonstrated a low organocatalyst loading approach to α-chlorination of ketones with unprecedented rapidity and yield under mild conditions by thiourea catalysis of NCS. Polar protic solvents were ideal for such transformations. A similar catalytic strategy is being applied to other halogenations with enantioselective versions of these reactions using enantiopure derivatives of thiourea.

Table 2
Thiourea catalyzed α-chlorination reactions of ketones



Entry	Ketone	Reaction time (min)	Chloride/yield (%)
1	 **6**	30	 **14** + **15** 82, 12
2	 **7**	10	 **16** 100
3	 **8** MeO	20	 **17** MeO 100
4	 **9**	<5	 **18** 100
5	 **10**	10	 **19** 100
6	 **11**	10	 **20** 86
7	 **12**	10	 **21** 95
8	 **13**	15	 **22** 51[a]

[a] In this case only 1.2 mmol of NCS was employed, but an optimal yield of the dichloride can only be obtained with +2.0 mmol of NCS. If the reaction's efficiency were the same, 2.0 mmol of NCS would give the dichloride in 85% yield.

Acknowledgements

The financial support from the Department of Chemistry and Biological Chemistry and the Research Allocation Committee, University of New Mexico is gratefully acknowledged.

Supplementary data

The supplementary data of experimental procedures with ^{1}H and ^{13}C NMR spectra for all products are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.154.

References and notes

1. De Kimpe, N.; Verhé, R. *The Chemistry of α-Haloketones, α-Haloaldehydes, and α-Haloimines*; John Wiley & Sons: New York, 1990.
2. Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; VCH: New York, 1999.
3. Thomas, G. *Medicinal Chemistry: An Introduction*; John Wiley & Sons: New York, 2000.
4. Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.
5. Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J., III; T.Lectka *J. Am. Chem. Soc.* **2001**, *123*, 1531.
6. Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108.
7. Halland, N.; Lie, M. A.; Kjærsgaard, A.; Marigo, M.; Schiøtt, B.; Jørgensen, K. A. *Chem. Eur. J.* **2005**, *11*, 7083.
8. Marigo, M.; Bachmann, S.; Halland, N.; Braunton, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5507.
9. Marigo, M.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Eur. J.* **2004**, *10*, 2133.
10. Bartoli, G.; Bosco, M.; Carlone, A.; Locatelli, M.; Melchiorre, P.; Sambri, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6219.
11. Yang, D.; Yan, Y.-L.; Lui, B. *J. Org. Chem.* **2002**, *67*, 7429.
12. Zhang, Y.; Shibatomi, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 15038.
13. Meshram, H. M.; Reddy, P. N.; Sadashiv, K.; Yadav, J. S. *Tetrahedron Lett.* **2005**, *46*, 623.
14. Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. *Org. Lett.* **2003**, *5*, 1709.
15. Hintermann, L.; Togni, A. *Helv. Chim. Acta* **2000**, *83*, 2425.
16. Cheng, S.-F.; Lin, C.-S.; Liu, L. K. *J. Chin. Chem. Soc.* **1997**, *44*, 309.
17. Meketa, M. L.; Mahajan, Y. R.; Weinreb, S. M. *Tetrahedron Lett.* **2005**, *46*, 4749.
18. Shi, X.-X.; Dai, L.-X. *J. Org. Chem.* **1993**, *58*, 4596.
19. Bentley, P. A.; Mei, Y.; Du, J. *Tetrahedron Lett.* **2008**, *49*, 1425.
20. Bentley, P. A.; Mei, Y.; Du, J. *Tetrahedron Lett.* **2008**, *49*, 2653.
21. Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407.
22. Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217.
23. Okino, T.; Hoashi, Y.; Takemoto, Y. *Tetrahedron Lett.* **2003**, *44*, 2817.
24. Sohtome, Y.; Tanatani, A.; Hashimito, Y.; Nagasawa, K. *Chem. Pharm. Bull.* **2004**, *52*, 477.
25. Manher, D. J.; Connon, S. J. *Tetrahedron Lett.* **2004**, *45*, 1301.
26. Menche, D.; Hassfeld, J.; Li, J.; Menche, G.; Ritter, A.; Rudolph, S. *Org. Lett.* **2006**, *8*, 741.
27. Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032.
28. Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.
29. Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.
30. Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102.
31. Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466.
32. Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062.
33. Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964.
34. Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9413.
35. Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418.
36. Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170.
37. Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701.
38. Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6700.
39. Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964.
40. Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1334.
41. Paquette, L. A. *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons: Chichester, 1995.
42. Vaz, A. D. N.; Schoellmann, G. *J. Org. Chem.* **1984**, *49*, 1286.