Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 2323–2325
Tetrahedron Letters

Regioselective synthesis of *N*-acetylureas by manganese(III) acetate reaction of 1,3-disubstituted thioureas

Xue-Jun Mu,[a] Jian-Ping Zou,[a,*] Qiu-Feng Qian[a] and Wei Zhang[b,*]

[a]*Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry and Chemical Engineering, Suzhou University, 1 Shizi St. Suzhou, Jiangsu 215006, China*

[b]*Fluorous Technologies, Inc., University of Pittsburgh Applied Research Center, 970 William Pitt Way, Pittsburgh, PA 15238, USA*

Received 11 January 2006; revised 31 January 2006; accepted 2 February 2006
Available online 20 February 2006

Abstract—Reactions of asymmetrical 1,3-disubstituted thioureas with manganese(III) acetate produce regioselective *N*-acetylureas. A mechanism for this novel transformation is proposed.

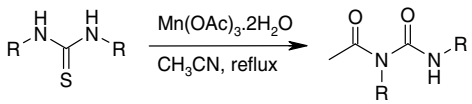
Since Bush and Finkbeiner's pioneering work reported three decades ago,[1] manganese(III)-based oxidative free radical reaction has become a powerful synthetic method.[2] One of the important applications of manganese(III) reagent is for acetylations. For example, $Mn(OAc)_3$ can be used for enantioselective acylation of α,β-unsaturated ketones[3] and acetoxylation of fullerene derivatives.[4] However, to the best of our knowledge, no such reagent has ever been used for N-acetylation reactions. We report here the first example of $Mn(OAc)_3$-promoted regioselective N-acetylation of 1,3-disubstituted thioureas in the synthesis of *N*-acetylureas.

Ureas and thioureas are useful synthons for the construction of heterocyclic compounds.[5] *N*-acylureas have important agrochemical[6] and pharmaceutical applications.[7] Dopamine D2 agonist Cabergoline, for example, has been used for the treatment of Parkinson's disease.[8] For the synthesis of *N*-acylureas,[9] direct acylation of symmetrical ureas[10] or carbodiimides[11] is an efficient approach. However, because the reactions are not regioselective, only symmetrical ureas or carbodiimides produce single products.[12] The $Mn(OAc)_3$-mediated N-acetylation reactions described in this letter can be used to produce single *N*-acetylureas from symmetrical or asymmetrical thioureas bearing aryl and alkyl groups.

We first attempted the acetylation using equimolar amount of $Mn(OAc)_3{\cdot}2H_2O$ and 1,3-di-*p*-tolylthiourea **1b** in MeCN. The 1-acetyl-1,3-di-*p*-tolylurea **2b** was generated in 10% yield. At a 2:1 molar ratio of $Mn(OAc)_3{\cdot}2H_2O$ to **1b**, the yield of **2b** was improved to 66% (Scheme 1). Reactions in different solvents (CH_2Cl_2, EtOH, MeOH, and AcOH) and at different temperatures were also attempted, but no further yield improvement was observed. The structure of compound **2b** (R = *p*-tolyl) was confirmed by X-ray crystallography analysis (Fig. 1).

Under the optimized conditions using 2 equiv of $Mn(OAc)_3{\cdot}2H_2O$ and MeCN as a solvent, reactions of symmetrical 1,3-diarylthioureas were performed and results are listed in Table 1.[13] It was found that 1,3-diarylthioureas afforded N-acetylated products in good to excellent yields (Table 1, entries 1–10). In contrast, only trace amount of product was detected from reactions of 1,3-dialkylthioureas (Table 1, entries 11–12).

Asymmetrical 1,3-disubstituted thioureas **3**[14] were used to study the regioselectivity of acetylation reactions (Table 2). We found that reactions of



1 R = Aryl **2**

Scheme 1.

* Corresponding authors. Tel./fax: +86 512 65112371 (J.-P.Z.); tel.: +1 412 826 3062; fax: +1 412 826 3053 (W.Z.); e-mail addresses: wuyanhong@pub.sz.jsinfo.net; w.zhang@fluorous.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.02.013

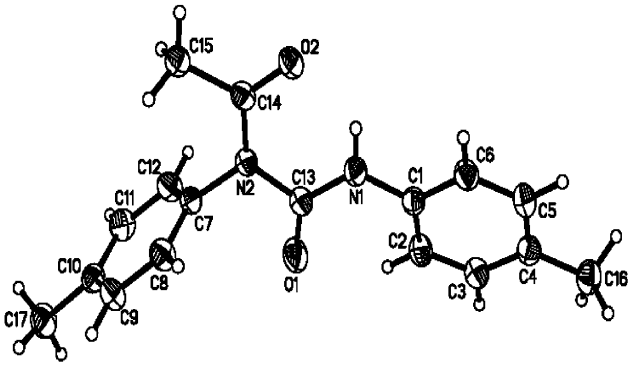
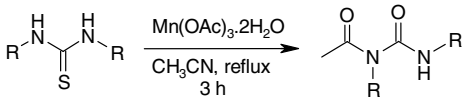


Figure 1. X-ray crystal structure of compound **2b**.

Table 1. Acetylation of disubstituted thioureas **1a–l**



1a-l **2a-l**

Entry	Product	R	Yield[a] (%)
1	**2a**	Ph	72
2	**2b**	*p*-MeC_6H_4	66
3	**2c**	*o*-MeC_6H_4	63
4	**2d**	*m*-MeC_6H_4	76
5	**2e**	*p*-$MeOC_6H_4$	63
6	**2f**	*p*-ClC_6H_4	86
7	**2g**	*o*-ClC_6H_4	76
8	**2h**	*p*-BrC_6H_4	88
9	**2i**	*m*-BrC_6H_4	69
10	**2j**	*p*-IC_6H_4	52
11	**2k**	Benzyl	Trace
12	**2l**	Cyclohexyl	Trace

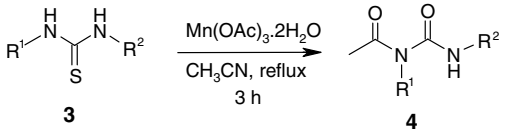
[a] After flash column chromatography.

1-aryl-3-alkylthioureas had similar or slightly lower yields than those of symmetrical 1,3-diarylthioureas, and only single regioisomer was isolated from reactions of asymmetrical 1,3-disubstituted thioureas. The structure of product **4e** was confirmed by X-ray crystallography analysis (Fig. 2).

A possible mechanism for the regioselective N-acetylation is proposed in Scheme 2. 1-Aryl-3-alkylthiourea **3** can exist as isothioureas **5** or **6**, in which **5** is more stable. Compound **5** reacts with $Mn(OAc)_3$ to produce **7**. The oxygen attack followed by the fragmentation of Mn(II) and release of H_2S[15] produces **8**. This compound undergoes O→N acyl migration[16] to give *N*-acetylurea **4**. The aryl group is needed to promote the acetylation of **7**. This mechanism explains why yields from reactions of 1,3-diarylthioureas were slightly higher than that of 1-aryl-3-alkylthioureas, and why it was difficult to acetylate 1,3-dialkylthioureas.

In summary, Mn(III)-mediated N-acetylation of 1,3-disubstituted thioureas has been developed for regioselective synthesis of *N*-acetylureas. The reaction can be performed under mild conditions and give products in good yields.

Table 2. Acetylation of asymmetrical disubstituted thioureas **3a–k**



3 **4**

R^1 = aryl; R^2 = alkyl

Entry	Product	R^1	R^2	Yield[a] (%)
1	**4a**	Ph	Cyclohexyl	68
2	**4b**	*o*-MeC_6H_4	Cyclohexyl	60
3	**4c**	*m*-MeC_6H_4	Cyclohexyl	62
4	**4d**	*p*-ClC_6H_4	Cyclohexyl	73
5	**4e**	*p*-IC_6H_4	Cyclohexyl	64
6	**4f**	Ph	Cyclopentyl	65
7	**4g**	*p*-MeC_6H_4	Cyclopentyl	59
8	**4h**	*m*-MeC_6H_4	Cyclopentyl	60
9	**4i**	*p*-ClC_6H_4	Cyclopentyl	71
10	**4j**	*p*-IC_6H_4	Cyclopentyl	64
11	**4k**	Ph	Propyl	59

[a] After flash column chromatography.

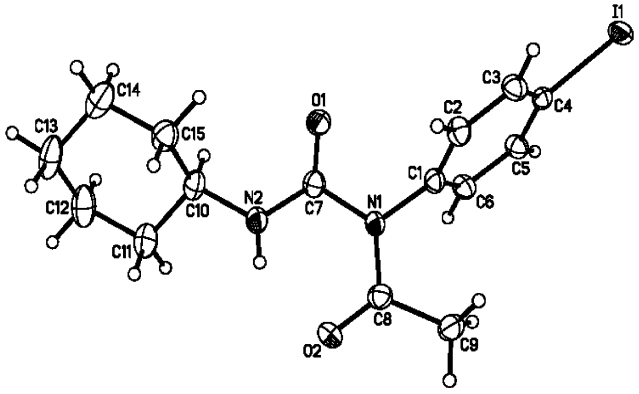
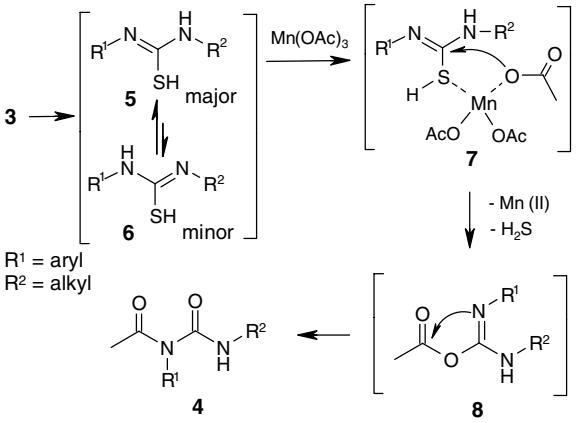


Figure 2. X-ray crystal structure of compound **4e**.



Scheme 2. Proposed mechanism for N-acetylation.

Acknowledgements

We thank the Key Laboratory of Organic Synthesis of Jiangsu Province and Suzhou Scientific Committee, for financial supports (JSK016 and SG 0219).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.02.013.

References and notes

1. Bush, J. B., Jr.; Finkbeiner, H. *J. Am. Chem. Soc.* **1968**, *90*, 5903; See also Williams, G. J.; Hunter, N. R. *Can. J. Chem.* **1976**, *54*, 3830.
2. Reviews on manganese(III)-based oxidative free radical reaction: (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339; (b) Melikyan, G. G. *Synthesis* **1993**, 833; For recent examples of manganese(III)-based radical reactions, see: (c) Demir, A. S.; Reis, O.; Emrullahoglu, M. *J. Org. Chem.* **2003**, *68*, 578; (d) Zhang, Z.; Wang, G.-W.; Miao, C.-B.; Dong, Y.-W.; Shen, Y.-B. *Chem. Commun.* **2004**, 1832; (e) Snider, B. B.; Duvall, J. R. *Org. Lett.* **2004**, *6*, 1265–1268; (f) Swain, N. A.; Brown, R. C. D.; Bruton, G. *J. Org. Chem.* **2004**, *69*, 122; (g) Huang, J. W.; Shi, M. *J. Org. Chem.* **2005**, *70*, 3859.
3. $Mn(OAc)_3$-mediated acetoxylation of α,β-unsaturated ketones: (a) Demir, A. S.; Camkerten, N.; Gercek, Z.; Duygu, N.; Reis, O.; Arikan, E. *Tetrahedron* **1999**, *55*, 2441; (b) Demir, A. S.; Hamamci, H.; Doganel, F.; Camkerten, N.; Aksoy-Cam, H. *Turkish J. Chem.* **2000**, *24*, 141; (c) Demir, A. S.; Hamamcl, H.; Sesenoglu, O.; Aydogan, F.; Capanoglu, D.; Neslihanoglu, R. *Tetrahedron: Asymmetry* **2001**, *12*, 1953; (d) Demir, A. S.; Sesenoglu, O. *Org. Lett.* **2002**, *4*, 2021; (e) Tanyel, C.; Iyigun, C. *Tetrahedron* **2003**, *59*, 7135; (f) Demir, A. S.; Reis, O.; Igdir, A. C. *Tetrahedron* **2004**, *60*, 3427.
4. Chen, Z. X.; Wang, G. W. *J. Org. Chem.* **2005**, *70*, 2380.
5. Zeng, R. S.; Zou, J. P.; Zhi, S. J.; Chen, J.; Shen, Q. *Org. Lett.* **2003**, *5*, 1657.
6. (a) Wellinga, K.; Mulder, R.; van Daalen, J. J. *J. Agric. Food Chem.* **1973**, *21*, 348; (b) Nakagawa, Y.; Kitahara, K.; Nishioka, T.; Iwamura, H.; Fujita, T. *Pestic. Biochem. Physiol.* **1984**, *21*, 309.
7. Goodman, L. S.; Gilman, A. *The Pharmacological Basis of Therapeutics*, 6th ed.; MacMillan: New York, 1980.
8. Brambilla, E.; Di Salle, E.; Briatico, G.; Mantegani, S.; Temperilli, A. *Eur. J. Med. Chem.* **1989**, *24*, 421.
9. Ravn, J.; Ankersen, M.; Begtrup, M.; Lau, J. F. *Tetrahedron. Lett.* **2003**, *44*, 6931, and references cited therein.
10. (a) Weisz, I. Hung. Patent 49848; *Chem. Abstr.* **1990**, *113*, 171518; (b) Dmitrichenko, M. Y.; Rozinov, V. G.; Donskikh, V. I.; Ratovskii, G. V.; Sergienko, L. M.; Dolgushin, G. V.; Valeev, R. B. *Zh. Obshch. Khim.* **1988**, *58*, 2252–2261; (c) Yamada, K.; Kishikawa, K.; Kohmoto, S. *Chem. Lett.* **1988**, 351; (d) Panzeri, A.; Ceriani, L.; Griggi, P.; Nesi, M. Eur. Patent 523668; *Chem. Abstr.* **1993**, *118*, 234337; (e) Panzeri, A.; Nesi, M.; DiSalle, E. WO Patent 9220700; *Chem. Abstr.* **1993**, *118*, 124875; (f) Maki, T.; Ishihara, K.; Yamamoto, H. *Synlett* **2004**, 1355.
11. (a) Corriu, R. J. P.; Gerard, F. L.; Perot-Petta, M. *Synthesis* **1991**, 954; (b) Anglada, J. M.; Campos, T.; Camps, F.; Moreto, J. M.; Pages, L. *J. Heterocycl. Chem.* **1996**, *33*, 1259; (c) Zimmermann, D. M.; Olofson, R. A. *Tetrahedron Lett.* **1970**, *11*, 3453.
12. Scott, W. A.; Kevin, E. H.; Andrew, M. A.; Peter, G. M. W. *J. Org. Chem.* **2002**, *67*, 7147.
13. General procedures for preparation of 1-acetyl-1,3-di-*p*-tolylurea **2b**: To a solution of 1,3-di-*p*-tolylthiourea **1b** (0.26 g, 1 mmol) dissolved in 15 mL of acetonitrile was added $Mn(OAc)_3{\cdot}2H_2O$ (0.54 g, 2 mmol) in two portions. The solution was refluxed for 3 h until the color of solution changed from brown to pale yellow. After the removal of acetonitrile under vacuum, the residue was dissolved in acetone, filtered, concentrated and purified by flash column chromatography on silica gel and eluted with 4:1 petroleum ether/acetone to give 1-acetyl-1,3-di-*p*-tolylurea **2b** in 66% yield; mp 138–140 °C; IR (KBr, cm^{-1}) υ 3211, 1713, 1663; ^1H NMR ($CDCl_3$): δ 11.35 (s, 1H, NH), 7.45–7.09 (m, 8H, $2C_6H_4$), 2.40 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 1.99 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 175.5, 152.4, 139.5, 136.7, 135.6, 134.0, 130.8, 129.9, 129.1, 120.5, 27.0, 21.6, 21.3; HRMS (M^+) *m*/*z* calcd for $C_{17}H_{18}N_2O_2$ 282.1368, found 282.1364.
14. Ramadas, K.; Srinivasan, N.; Janarthanan, N. *Tetrahedron Lett.* **1993**, *34*, 6447.
15. H_2S was checked by $Pb(OAc)_2$ test paper.
16. Volonterio, A.; Arellano, C. R.; Zanda, M. *J. Org. Chem.* **2005**, *70*, 2161.