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Reductive alkylation of thioureas: a highly practical synthesis of unsymmetrical *N*,*N*′-disubstituted thioureas

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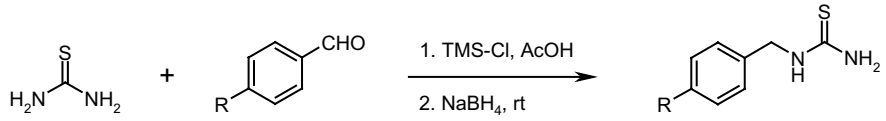
Abstract—A highly practical synthesis of unsymmetrical *N*,*N*′-disubstituted thioureas by the reductive alkylation of *N*-monosubstituted thioureas with aldehydes is described. *N*-Monosubstituted thioureas can in turn be synthesized by the reductive amination of thiourea with an appropriate aldehyde. This reductive alkylation methodology was also extended to carbamates.

Molecules containing symmetrical or unsymmetrical *N*,*N*′-disubstituted thioureas are of biological interest. Several methods are reported for the synthesis of symmetrical thioureas but additional synthetic approaches for unsymmetrical thioureas are still desirable.[1] In a development program we needed to develop an efficient and economical synthesis of *N*,*N*′-disubstituted thioureas, which prompted us to investigate a convenient method for their synthesis. In continuation of our work on the reductive amination of urea,[2] we rationalized that a straightforward approach to unsymmetrical thiourea would be the stepwise reductive amination of thioureas with aldehydes. In this paper we report our results on the development of a highly practical method for the synthesis of unsymmetrical *N*,*N*′-disubstituted thioureas by the reductive amination of *N*-monoalkylated thioureas with aldehydes in the presence of trimethylsilyl chloride as the dehydrating agent and sodium borohydride in acetic acid as the reducing agent.

To test the synthetic feasibility of our approach we first studied the reductive amination[3] of thiourea itself with 4-*tert*-butylbenzaldehyde since *N*-(4-*tert*-butyl)benzyl thiourea (**1**) was a precursor to our target molecule. Thus, treatment of thiourea with 4-*tert*-butylbenzaldehyde in acetic acid in the presence of TMS–Cl afforded the corresponding imine that was reduced with sodium borohydride[4] to afford *N*-(4-*tert*-butyl)benzyl thiourea (**1**) in 65% yield. Use of TMS–Cl was important in this reaction to obtain good yields since without it the yield of **1** reduced to almost half. Similarly, 4-methoxybenzaldehyde gave *N*-(4-methoxy)benzyl thiourea (**2**) in 50% yield. These results demonstrated that our previously reported methodology for the reductive amination of urea was also applicable to thiourea.



1: R = *t*-Bu
2: R = OCH_3

With these results in hand, we next studied the reductive amination of *N*-(4-*tert*-butyl)benzyl thiourea (**1**) with 4-methoxybenzaldehyde in the presence of TMS–Cl as the dehydrating agent and sodium borohydride as the reducing agent in acetic acid. It afforded the desired unsymmetrical *N*,*N*′-disubstituted thiourea (**3**) in 76% yield (Table 1, entry 1). To test the scope and limitations of these conditions[5] we next studied the reductive

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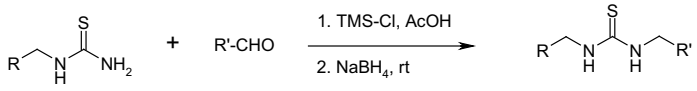
amination of several *N*-monoalkylated thioureas with various aldehydes and the results are described in Table 1.[6] In all cases the isolated yields were excellent but are unoptimized.

We have further extended the synthetic utility of this methodology to the reductive amination of carbamates[7] and the results are reported in Table 2.[6]

In summary, we have developed a highly practical synthesis of unsymmetrical *N*,*N*′-disubstituted thioureas by the reductive alkylation of *N*-monosubstituted thioureas with aldehydes. *N*-Monosubstituted thioureas can in turn be synthesized by the reductive amination of thiourea with an appropriate aldehyde. This reductive alkylation methodology was also extended to carbamates.

Table 1. Unsymmetrical *N*,*N*′-disubstituted thioureas



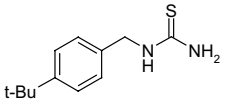
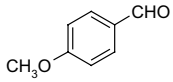
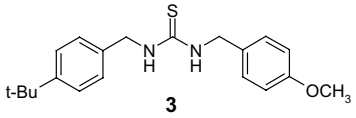
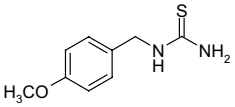
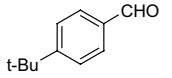
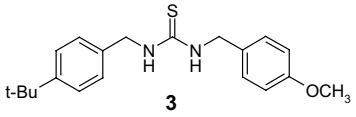
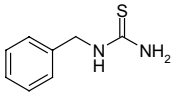
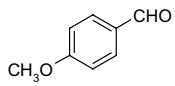
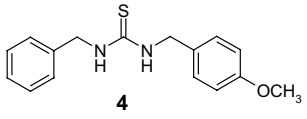
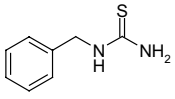
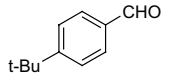
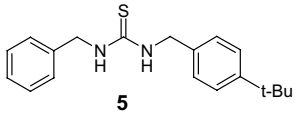
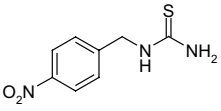
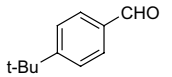
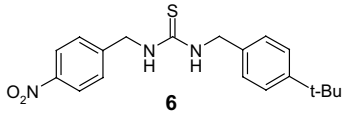
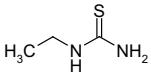
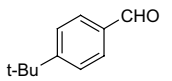
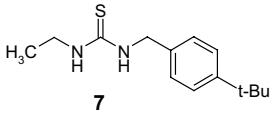
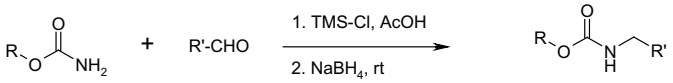
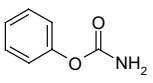
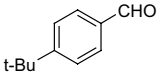
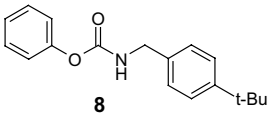
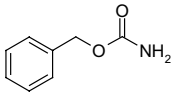
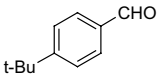
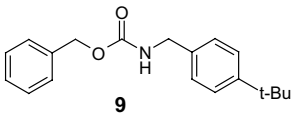
Entry	Thiourea	Aldehyde	Product	Yield (%)
1			 **3**	72
2			 **3**	66
3			 **4**	76
4			 **5**	93
5			 **6**	87
6			 **7**	82

Table 2. *N*-Alkylated carbamates



Entry	Carbamate	Aldehyde	Product	Yield (%)
1			 **8**	74
2			 **9**	79

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References and notes

1. (a) Herr, R. J.; Kuhler, L. L.; Meckler, H.; Opalka, C. J. *Synthesis* **2000**, 1569–1574; (b) Ballabeni, M.; Ballini, R.; Bigi, F.; Maggi, R.; Parrini, M.; Predieri, G.; Sartori, G. *J. Org. Chem.* **1999**, *64*, 1029–1032; (c) Ramadas, K.; Janarthanan, N.; Velmathi, S. *Synth. Commun.* **1997**, *27*, 2255–2260; (d) Boas, U.; Jakobsen, H. *J. Chem. Soc., Chem. Commun.* **1995**, 1995–1996; (e) Duceppe, J. S.; Gauthier, J. *J. Heterocycl. Chem.* **1984**, *21*, 1685–1687; (f) Ramadas, K.; Srinivasa, N.; Janarthanan, N. *Tetrahedron Lett.* **1993**, *34*, 6447–6450.
2. Xu, D.; Ciszewski, L.; Li, T.; Repič, O.; Blacklock, T. J. *Tetrahedron Lett.* **1998**, *39*, 1107–1110.
3. Typical procedure for *N*-monoalkylated thioureas: To a suspension of thiourea (15.25 g, 0.2 mol) in acetic acid (150 mL) was added an aldehyde (0.02 mol) at room temperature. The suspension was warmed to 60–65 °C to obtain a solution. The resulting solution was cooled to 45 °C, and trimethylsilyl chloride (7.61 mL, 0.06 mol) was added during 3 min. The reaction mixture was cooled to room temperature and stirred overnight. To the resulting suspension was added sodium borohydride (1.51 g, 0.04 mol) over 30 min at 23–30 °C. Completion of the reaction was monitored by HPLC. Water (70 mL) was added to the reaction mixture at room temperature and concentrated (150 mbar, 45–50 °C) to collect 150 mL of a mixture of acetic acid and water. To the suspension was added 6 N NaOH (80 mL) over 10 min at 24–30 °C to adjust the pH to 10. After stirring the mixture at room temperature for 30 min the crude product was collected by filtration, washed with water (2×50 mL). The crude product was recrystallized from a mixture of heptane and ethyl acetate.
4. Use of sodium triacetoxyborohydride in this reaction gave similar results as obtained with sodium borohydride suggesting that the actual reducing agent is sodium triacetoxyborohydride.
5. Typical procedure for unsymmetrical *N*,*N*′-disubstituted thioureas: The procedure was essentially the same as described above in Ref. 3 using *N*-alkyl thiourea (0.017 mol), and aldehyde (0.02 mol), followed by trimethylsilyl chloride (0.051 mol) and sodium borohydride (0.034 mol).
6. All the compounds gave satisfactory spectral data.
7. Typical procedure for *N*-alkylated carbamates: The procedure was essentially the same as described above in Ref. 3 using carbamate (0.01 mol) and aldehyde (0.015 mol), followed by trimethylsilyl chloride (0.03 mol) and sodium borohydride (0.03 mol).