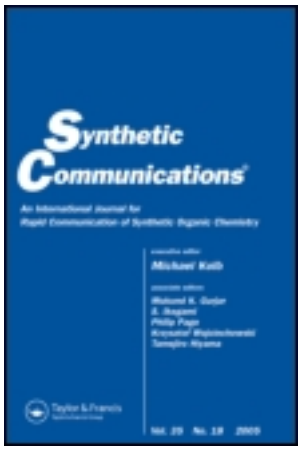
This article was downloaded by: [Johns Hopkins University]
On: 08 October 2013, At: 09:46
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

PREPARATION OF N-TERT-BUTOXYCARBONYLTHIOUREA OPENS THE WAY TO PROTECTED 2-AMINOTHIAZOLES

Bruno Schiavi [a] , Alain Ahond [b] , Christiane Poupat [a] & Pierre Potier [a]

[a] Institut de Chimie des Substances Naturelles du CNRS , Gif/Yvette Cedex, BP1, 91198, France

[b] Institut de Chimie des Substances Naturelles du CNRS , Gif/Yvette Cedex, BP1, 91198, France

Published online: 16 Aug 2006.

To cite this article: Bruno Schiavi , Alain Ahond , Christiane Poupat & Pierre Potier (2002) PREPARATION OF N-TERT-BUTOXYCARBONYLTHIOUREA OPENS THE WAY TO PROTECTED 2-AMINOTHIAZOLES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:11, 1671-1674, DOI: 10.1081/SCC-120004257

To link to this article: http://dx.doi.org/10.1081/SCC-120004257

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

©2002 Marcel Dekker, Inc. All rights reserved. This material may not be used or reproduced in any form without the express written permission of Marcel Dekker, Inc.

SYNTHETIC COMMUNICATIONS, 32(11), 1671–1674 (2002)

Downloaded by [Johns Hopkins University] at 09:46 08 October 2013

PREPARATION OF *N-TERT*-BUTOXYCARBONYLTHIOUREA OPENS THE WAY TO PROTECTED 2-AMINOTHIAZOLES

Bruno Schiavi, Alain Ahond,* Christiane Poupat, and Pierre Potier

Institut de Chimie des Substances Naturelles du CNRS, BP1, 91198 Gif/Yvette Cedex, France

ABSTRACT

The preparation of *N-tert*-butoxycarbonylthiourea from thiourea and di-*tert*-butyldicarbonate in tetrahydrofuran is described. It has been successfully used for the preparation of 2-aminothiazole intermediates.

Key Words: 2-Aminothiazole; N-*tert*-Butoxycarbonylthiourea

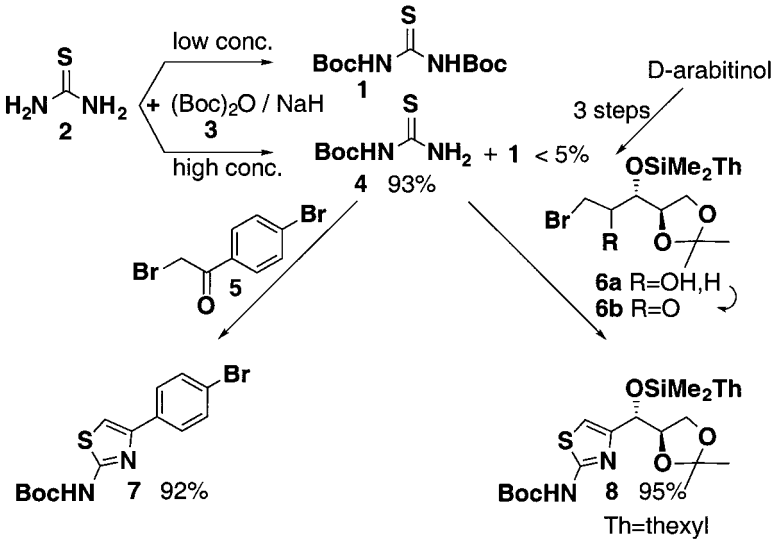
The aminothiazole group is a very well known "pharmacophore". It is, therefore, important to have in hand an easy and high yielding method to prepare it. Iwanowicz et al.[1,2] have efficiently prepared *N*,*N-bis-tert*-butoxycarbonylthiourea **1** from the sodium salt of thiourea **2** and di-*tert*-butyldicarbonate **3**. Because of low concentrations, they could avoid the formation of *S*-acylated products.

*Corresponding author. E-mail: alain.ahond@icsn.cnrs-gif.fr

Copyright © 2002 by Marcel Dekker, Inc. www.dekker.com

©2002 Marcel Dekker, Inc. All rights reserved. This material may not be used or reproduced in any form without the express written permission of Marcel Dekker, Inc.

Because we were interested in obtaining *N-tert*-butoxy-carbonyl-thiourea **4** as an intermediate to prepare protected 2-aminothiazoles, we have used the same reagents but searched for convenient conditions to reach our objective. By using higher concentrations, we obtained a mixture of *N-tert*-butoxycarbonylthiourea (90%) **4** and *N-N-bis-tert*-butoxycarbonylthiourea **1** (<5%); from this mixture, *N-tert*-butoxycarbonylthiourea was easily purified by crystallization from heptane.



N-tert-butoxycarbonylthiourea **4**, prepared by this procedure, was found to be satisfactory for the preparation of 2-aminothiazole intermediates such as **7** and **8**, on the way to the synthesis of marine metabolite analogues.[3]

EXPERIMENTAL

Melting points were determined using a Büchi BS-540 and are uncorrected; $[\alpha]_D$ was measured using a Perkin-Elmer 241 MC (589 nm, 20°C), sample in EtOH solution; UV spectra were taken with a Varian Cary 100 spectrometer, using EtOH solution. IR spectra were taken with a Perkin-Elmer BX FT-IR spectrometer, using $CHCl_3$ solution or KBr pellet. The ^1H and ^{13}C NMR spectra were recorded on Bruker AC-200, AC-250 or AC-300. Chemical ionization mass spectra were recorded on a

Downloaded by [Johns Hopkins University] at 09:46 08 October 2013

©2002 Marcel Dekker, Inc. All rights reserved. This material may not be used or reproduced in any form without the express written permission of Marcel Dekker, Inc.

Downloaded by [Johns Hopkins University] at 09:46 08 October 2013

AEI MS-9 spectrophotometer with isobutane as a vector gas, electron impact spectrum on AEI MS-50 spectrophotometer. Silica gel 60 was used for flash column chromatography and silica gel $60F_{254}$ plates (0.25 mm, Merck) were used for TLC.

Preparation of 4: To a stirred solution of thiourea **2** (2.2 g, 28.9 mmol) in THF (200 ml) under argon at 0°C was added NaH (2.7 g, as 60% dispersion in mineral oil, 2.3 eq.); after 10 min, di-*tert*-butyldicarbonate **3** (6.6 g, 1.05 eq.) in solution in THF (30 ml) was added.

The 0°C bath is removed and the reaction mixture stirred at room temperature for 1 h. Dichloromethane (200 ml) was added and the organic layer washed successively with an aqueous solution of saturated $NaHCO_3$ (100 ml) and water (100 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. Addition of heptane (500 ml) to the residue provided 4.6 g of pure crystalline **4** (90%). M.p: 145°C; ^{1}H NMR ($CDCl_3$): δ 1.61 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 182.1, 151.45, 84.0, 28.0; IR ($CHCl_3$, cm^{-1}): 1734; UV [λ_{nm} (ε)]: 263 (17000); Mass *m*/*z* (CI, 180°C): 177 $(M+H)^+$; Anal. calcd for $C_6H_{12}N_2O_2S$: C, 40.89; H, 6.86; N, 15.90. Found: C, 40.83; H, 6.88; N, 15.86.

Preparation of 2-*tert*-butoxycarbonyl-4-*p*-bromophenylthiazole 7: At room temperature, *N*-Boc thiourea **4** (100 mg, 0.56 eq.) and 2,4′-dibromoacetophenone **5** (172 mg, 0.62 eq.) are stirred in acetone (8 ml) overnight; a precipitate is formed, which is filtrated before being purified by flash-chromatography (silica gel, eluent: CH_2Cl_2/MeOH 99/1): 180 mg of pure **7** are obtained (yield: 82%); white solid; m.p. 210°C (dcp.); ^{1}H NMR (DMSO-d_6); δ 1.57 [s, 9H, $(CH_3)_3$], 7.68 and 7.75 (2d, 2H, $J = 7.3$ Hz, Ø-H), 7.71 (s, 1H, H-5), 7.88 and 7.90 (2d, 2H, $J = 7.3$ Hz, Ø-H); ^{13}C NMR (DMSO-d_6): δ 27.85–27.90 (3 $\underline{C}H_3$), 81.25–81.95 ($\underline{C}$-Me_3), 91.8–96.75 (C-Br), 108.15–108.25 (C-5), 120.7–121.6 (C-4), 127.4–129.9 (2C-Ar), 131.25–131.5 (2C-Ar), 132.4–133.55 (C-Ar), 145.05–147.95 (C-2), 159.0–159.85 (C=O): some NMR signals are split because of the presence of rotamers; IR (KBr, cm^{-1}): 1730; MS *m*/*z* (EI): 353–355 (M^+), 253–255, 174; HRMS (CI, isobutane) *m*/*z* $(MH)^+$ calcd for $C_{14}H_{16}BrN_2O_2S$: 354.0259/356.0238, found 354.0027/355.9995.

Preparation of the Intermediate 8: At first, the bromoketone **6b** must be prepared, through the Swern[4] oxidation of the corresponding alcohol **6a**.[3] Oxalyle chloride (125 µl, 1.5 eq), in solution in CH_2Cl_2 (2 ml) is added dropwise, under argon atmosphere at −78°C, to DMSO (163 µl) in solution in CH_2Cl_2 (2 ml). The mixture is stirred for 10 min; then, the alcohol **6a** (378 mg, 0.95 mmol) solubilized in CH_2Cl_2 (2 ml), is added dropwise. The stirring is continued at −78°C for 15 min. After the dropwise addition of triethylamine (668 µl, 6.5 eq), the reaction is still stirred at room temperature for 45 min before being stopped with water (25 ml). The organic layer is

©2002 Marcel Dekker, Inc. All rights reserved. This material may not be used or reproduced in any form without the express written permission of Marcel Dekker, Inc.

separated, dried over anhydrous magnesium sulphate and evaporated. The crude bromoketone **6b** is purified by flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 99:1) and directly put in reaction with *N*-Boc thiourea **4** (200 mg, 1.13 eq) in acetone (15 ml). The mixture is stirred at room temperature for 12 h; then, the reaction is stopped by adding solid $NaHCO_3$: a filtration over Celite and a flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 99 : 1) provide 340 mg of the intermediate **8** (yield: 75%), as an amorphous solid; $\alpha_D + 37$ (ethanol, $c = 1.4$); ^{1}H NMR ($CDCl_3$): δ −0.08 (s, 3H, $\underline{CH}_3$-Si), 0.13 (s, 3H, $\underline{CH}_3$-Si), 0.85 (s, 3H, $\underline{CH}_3$ thexyle), 0.86 (s, 3H, $\underline{CH}_3$ thexyle), 0.89 [d, $J = 6.8$ Hz, 6H, $(\underline{CH}_3)_2$ CH], 1.33 (s, 3H, $\underline{CH}_3$C), 1.43 (s, 3H, $\underline{CH}_3$C), 1.51 [s, 9H, $(\underline{CH}_3)_3$C], 1.65 [sept., $J = 6.8$ Hz, 1H, $\underline{CH}(CH_3)_2$], 3.83 (dd, $J = 6.5$ and 7.9 Hz, 1H, H-3′), 3.99 (pseudo t, $J = 7.5$ Hz, 1H, H-3′), 4.42 (m, 1H, H-2′), 4.86 (d, $J = 4.6$ Hz, H-1′), 6.76 (s, 1H, H-5), 8.25 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 10.25–10.35 [Si-$(\underline{C}H_3)_2$], 18.7–18.8, 20.35–20.5 (4$\underline{C}H_3$ thexyle), 25.2 [Si-$\underline{C}(CH_3)_2$], 25.45–26.75 [C$(\underline{C}H_3)_2$], 28.3 [C$(\underline{C}H_3)_3$], 34.15 [$\underline{C}H(CH_3)_2$], 65.3 (C-3′), 71.3 (C-2′), 78.55 (C-1′), 82.75 [$\underline{C}(CH_3)_3$], 109.2 [$\underline{C}(CH_3)_2$], 109.4 (C-5), 152.2 (C-4), 159.2 (C-2); IR ($CHCl_3$, cm^{-1}): 1723; UV (ethanol, λ_{nm} [ε]) 259 (5700); Mass *m*/*z* (CI, $t^\circ = 180^\circ$C): 473, 417, 373; HRMS (CI, isobutane) *m*/*z* (MH^+) calcd for $C_{22}H_{41}N_2O_5SSi$: 473.2505, found 473.2517.

REFERENCES

1. Iwanowicz, E.J.; Poss, M.A.; Lin, J. Synth. Commun. **1993**, *23*, 1443.
2. Poss, M.A.; Iwanowicz, E.J.; Reid, J.A.; Gu, Z. Tetrahedron Lett. **1992**, *33*, 5933.
3. Schiavi, B. Ph.D Thesis, Paris XI Orsay University, 2000.
4. Omura, K.; Swern, D. Tetrahedron **1978**, *34*, 1651.

Received in the Netherlands April 12, 2001

Downloaded by [Johns Hopkins University] at 09:46 08 October 2013