Article

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J. Comb. Chem., **2000**, 2 (1), 75-79• DOI: 10.1021/cc990058d • Publication Date (Web): 30 November 1999

An Efficient Procedure for Traceless Solid-Phase Synthesis of N,N′-Substituted Thioureas by Thermolytic Cleavage of Resin-Bound Dithiocarbamates

Laurent Gomez,[†] Françoise Gellibert,[‡] Alain Wagner,*[,†] and Charles Mioskowski*[,†]

Laboratoire de Synthèse Bioorganique, Université Louis Pasteur de Strasbourg, Unité associée au CNRS, UMR 7514 Faculté de Pharmacie, 74 route du Rhin - BP 24 - 67401 Illkirch, France, and Laboratoire Glaxo Wellcome Centre de Recherches, Z. A. de Courtabœuf, 25 Av. du Québec, F-91951 Les Ulis CEDEX, France

Received October 4, 1999

A novel and efficient procedure which is compatible with high-throughput process for the traceless solid-phase synthesis of thioureas is described. In the presence of carbon disulfide, Merrifield resin reacts with an amine to give a resin-bound dithiocarbamate moiety. Heating this supported dithiocarbamate in the presence of a second amine at 60 °C for 12 h led to the formation of the thiourea with the release of benzylthiol bound to the resin. This process allows the preparation of N,N′-di- and trisubstituted thioureas in good yields and with satisfactory purity. Furthermore, the mild reaction conditions involved are compatible with many functional groups.

Introduction

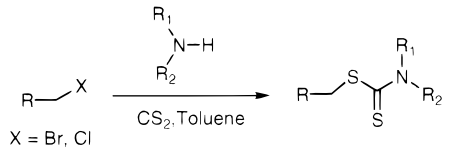
Finding new methodologies for the synthesis of a family of biologically potent compounds by assembling readily available building blocks is a key issue for combinatorial-chemistry-based drug discovery.[1]

Thioureas appear to be ideal candidates for the development of such processes, since they are the core feature in families of compounds known to display biological activities.[2,3] Their structure is formed by two amines linked by a thiocarbonyl function. However, the synthetic routes reported in the literature are not very suitable for high-throughput synthesis because the syntheses generally involve the condensation of an amine with an isothiocyanate[4] which in turn is prepared separately starting from highly toxic reagents substances such as thiophosgene[5] or its derivatives.[6]

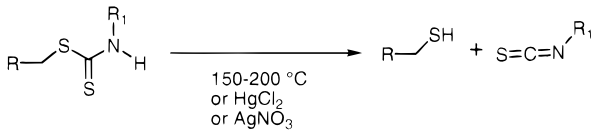
A few papers describe the synthesis of thioureas on solid support by reaction of supported amine with an isothiocyanate.[7] Unfortunately, this approach does not fully benefit from the use of the solid support technique. The diversity is indeed restricted by the limited number of commercially available isothiocyanates. Moreover, the linkage to the resin, generally an ester bond, leads after the cleavage to unwanted carboxylic or alcoholic residues.

Herein we report an efficient procedure for the traceless solid-phase synthesis of thioureas. The synthetic scheme uses two reactions described a long time ago. The first step (equation 1, Scheme 1) is the preparation of dithiocarbamates by a well-known reaction described in 1902.[8] The dithiocarbamate moiety is obtained in good yield by the condensation of an amine with carbon disulfide in the presence of an alkylating agent.

Scheme 1



Equation 1



Equation 2

The second step of the process is the thermolytic cleavage of the dithiocarbamate moiety into the corresponding isothiocyanate and alkylthiol.[9] The reaction is promoted by silver or mercury salts, both being toxic and expensive reagents. Moreover, high temperatures ranging from 150 to 200 °C are required. These drastic reaction conditions could explain why this reaction did not give rise to important synthetic developments and appeared not attractive for solid-phase synthesis.

However, we found conditions that are adapted to solid-phase synthesis and overcome all the drawbacks attached to this transformation. In addition, these new conditions make the procedure highly attractive for high-throughput synthesis of N,N′-substituted thioureas.

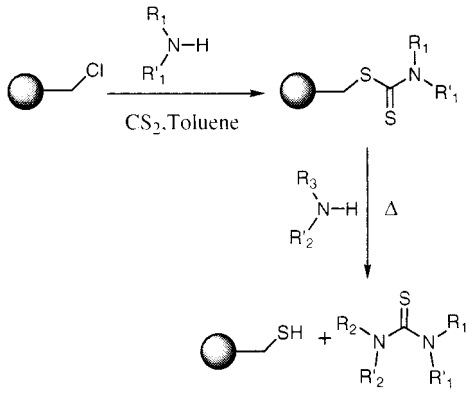
* To whom correspondence should be addressed. Dr. Charles Mioskowski: tel, (33) 3 88 67 68 63; fax, (33) 3 88 67 88 91; e-mail, mioskow@aspirine.u-strasbg.fr. Dr. Alain Wagner: tel: (33) 3 88 67 68 65; fax, (33) 3 88 67 88 91; e-mail, alwag@aspirine.u-strasbg.fr.

† Université Louis Pasteur de Strasbourg.

‡ Laboratoire Glaxo Wellcome Centre de Recherches.

10.1021/cc990058d CCC: $19.00
Published on Web 11/30/1999

Scheme 2



The use of chloromethylated resin (Merrifield) in the first step in lieu of the alkylating reagent results in the quantitative formation of the resin-bound dithiocarbamate. The excess of reagent can then be easily washed out from the resin. Heating the supported dithiocarbamate allows the thermolytic formation/release of the desired thiourea (Scheme 2). The resin-bound thiol is then easily eliminated by filtration and the thiourea purified from the excess of amine by extraction from saturated ammonium chloride with methylene chloride.

To apply this sequence to combinatorial chemistry, we investigated the influence of the substitution of the amine and of different functional groups on the outcome of the reaction. Several primary and secondary amines were tested in the first and in the following step.

Some general trends concerning the substitution of the amine can be drawn from the different experiments. When primary amines or anilines are used to form the resin-bound dithiocarbamates, the following thermolytic cleavage can be carried out at 60 °C using either primary or secondary amines as nucleophiles. However, in the presence of aniline, under the same reaction conditions, no thiourea formation was observed.

When secondary amines are involved in the first step, the resulting N,N-disubstituted dithiocarbamates are not reactive and no thiourea was formed at 60 °C in the presence of primary or secondary amine. At higher temperature (120−150 °C) with primary amines, the formation of thiourea was observed only after 3 h and merely 10% yield after 12 h, while in the presence of secondary amines no thiourea formation was observed.

These differences in reactivity can be rationalized based on mechanistic considerations if one presumes that thiourea formation proceeds through direct substitution of the amine at the dithiocarbamate sp^2 carbon atom (path A) and not through its thermal fragmentation into isothiocyanate and thiol (path B) (Scheme 3).

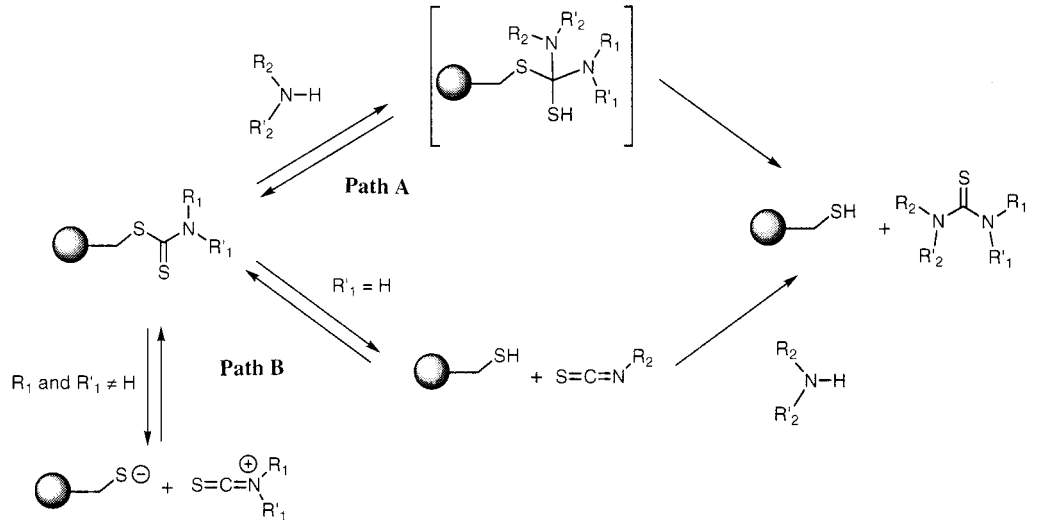
Indeed, the thiourea formation reaction appears to be influenced by steric hindrance and by the nucleophilicity of the amine used to cleave the supported dithiocarbamate. This is particularly obvious when anilin derivatives are involved in the second step. If reaction would proceed through the formation of isothiocyanate (path B), the thiourea would be obtained even in the presence of poor nucleophiles such as aniline. Moreover, another clue in favor of the mechanism is the reaction temperature (60 °C), which is much lower than that in conditions described for the fragmentation of dithiocarbamate into isothiocyanate and thiol.

The influence of the amine side chain on the outcome of the reaction was then studied. As the reaction conditions are very mild and do not involve harsh reagents, a wide variety of functional groups such as alkenes (entry 2), heterocycles (entry 3), strained carbocycles (entry 3), substituted aromatic rings (entry 6, 12), acetals (entry 7), and phosphonates (entry 10) are compatible with this procedure.

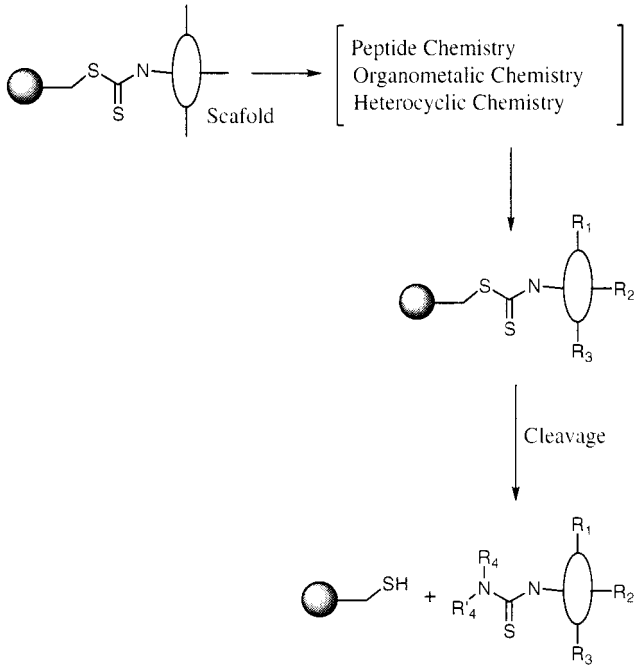
If an amino alcohol is involved in the first step, the supported dithiocarbamate intermediate cannot be isolated. It readily undergoes intramolecular nucleophilic substitution that results in the release from the solid support forming cyclic thiocarbamates in 90% yield. However, if the amino alcohol is involved in the second step, the expected thiourea is obtained in 69% yield (entry 6).

The indicated yields are based on the amount of product recovered by methylene chloride extraction from saturated aqueous ammonium chloride solution. Thioureas were characterized by ^{1}H NMR and mass spectra analysis. The purity was checked by NMR and HPLC and found to be around 90% in most of the cases. The lower yield observed for the pyridine-substituted thiourea (entry 3) is due to poor extrac-

Scheme 3



Scheme 4



tion. The purity of this compound was also found to be lower (60% according to NMR), due to contamination by (methylamino)pyridine. If the crude cleavage mixture is purified by preparative TLC, the yield rises to 85% and the thiourea is obtained with high purity. However for high-throughput synthesis compatibility, purification by extraction is preferred.

It has to be noticed that supported dihiocarbamates are susceptible to further functionalizations prior to the thermolytic cleavage. For example, dithiocarbamates (entry 8) could be further elaborated by peptide type chemistry and bromobenzene dithiocarbamate (entry 12) via palladium coupling chemistry. Thus, an extension of this work would be to use dithiocarbamate as a linker for traceless synthesis of other families of compounds (Scheme 4).

In summary, we describe here an efficient and traceless solid-phase synthesis of di- and trisubstituted thioureas. This process involves two successive reactions of amino compounds. The mild reaction conditions involved are compatible with many functional groups and with the automation of the process. Hence, preparation of a huge number of structurally diverse thioureas can be achieved. An extension of this work will involve the use of dithiocarbamates as thermocleavable linkers for traceless solid-phase synthesis.

Experimental Section

General. All chemicals were obtained from commercial suppliers. The Merrifield resin was purchased from Nova Biochem. Filtration devices equipped with 5 μm pore size PTFE membrane were purchased from Whatman. Solvents for reaction were distilled prior to use. Analytical grade solvents were used for both reactions and resin washing. On-bead IR analysis was carried out using a Perkin-Elmer 2000 FT spectrometer coupled to an autoimage microscope. NMR analyses were performed on Bruker 300- or 200-Avance DPX spectrometer.

HPLC/mass spectroscopy analyses were performed using a Micromass platform LC coupled to a 1100 HP HPLC equipped with a Kromasil C8 (3.5 μm, 100 A, 100 $\times$ 3) column. The solvent gradient was acetonitrile−water + 0.1% acetate buffer from 40/60 to 80/20 in 8 min.

General Procedure for the Preparation of the Supported Dithiocarbamate. To a slurry of Merrifield resin (0.5 g, 0.62 mmol, loading 1.24 mmol/g) in THF (5 mL) were added successively carbon disulfide (0.12 mL, 2 mmol), *N*-ethyldiisopropylamine (0.21 mL, 1.24 mmol), and the amine (1.86 mmol) at room temperature. The mixture was then gently shaken for 12 h at room temperature. The excess of reagents were eliminated by washing the resin four times successively with THF (15 mL), CH_2Cl_2 (15 mL), and MeOH (15 mL). After the resin was dried under vacuum, IR analysis showed the characteristic bands of the supported dithiocarbamate at 3353 (NH), 3255 (NH), 1377, 1328, 1059 cm^{-1}.

The coupling efficiency is evaluated by elemental analysis and is found to be more than 90%.

General Procedure for the Formation of Thioureas. An excess of amine (3.7 mmol) was added to a suspension of the polymer-bound dithiocarbamate (0.5 g) in toluene (5 mL) at room temperature. The mixture was heated at 60 °C for 12 h to promote thiourea formation. The resin was then filtered off and washed four times successively with CH_2Cl_2 (15 mL) and MeOH (15 mL). The filtrate was concentrated under vacuum to afford a mixture containing the thiourea and excess of amine. The excess of amine was then removed by dissolving the crude in CH_2Cl_2 (5 mL) and washing it with an aqueous solution of ammonium chloride (5 mL). After concentration of the organic phase, the thioureas were analyzed by ^{1}H NMR and HPLC/mass spectroscopy. See Table 1 for yields.

Analytical Data. 1,3-Dibutyl-thiourea (1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, J = 7.5 Hz, 6 H), 1.41 (qt, J = 7.5, 7.2 Hz, 4 H), 1.59 (qt, J = 7.2, 7.0 Hz, 4 H), 3.42 (m, 4 H), 5.75 (br s, 2 H); MS (IC/NH_4^+) 189 (M + H^+).

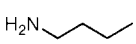
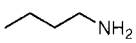
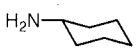
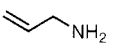
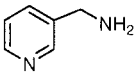
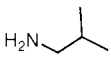
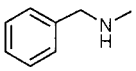
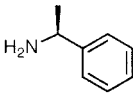
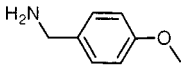
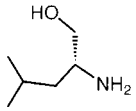
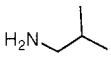
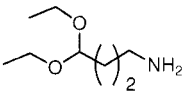
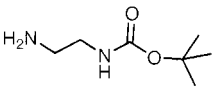
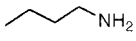
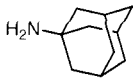
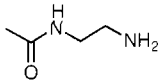
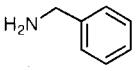
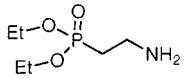
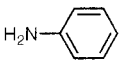
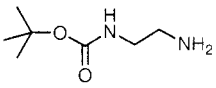
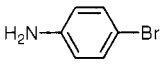
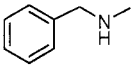
1-Allyl-3-cyclohexyl-thiourea (2): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15−2.00 (m, 10 H), 3.91 (m, 1 H), 4.03 (m, 2 H), 5.15−5.27 (m, 2 H), 5.74−5.89 (m, 1 H), 5.91 (br s, 1 H), 6.23 (br s, 1 H); MS (IC/NH_4^+) 199 (M + H^+).

1-Cyclopropyl-3-pyridin-3-yl-methyl-thiourea (3). Contaminated by 30% of protonated (methylamino)pyridine: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.68−0.79 (m, 2 H), 0.80−0.82 (m, 2 H), 2.00 (br s, 1 H), 2.48 (m, 1 H), 4.94 (d, J = 6.0 Hz, 2 H), 6.66 (br s, 1H), 7.26−7.30 (m, 1H), 7.67−7.77 (m, 1 H), 8.47−8.89 (m, 2H); MS (IC/NH_4^+) 208 (M + H^+). Protonated (methylamino)pyridine: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.84 (s, 2 H), 6.66 (br s, 1H), 7.30−7.35 (m, 1H), 7.67−7.74 (m, 1 H), 8.47−8.89 (m, 2H).

1-Benzyl-3-isobutyl-1-methyl-thiourea (4): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (d, J = 6.8 Hz, 6 H), 1.91 (tseptet, J = 5.3, 6.8 Hz, 1 H), 3.20 (s, 3 H), 3.48 (dd, J = 5.3 Hz, 5.0 Hz, 2 H), 5.02 (s, 2 H), 5.52 (br s, 1 H), 7.25−7.43 (m, 5 H); MS (IC/NH_4^+) 237 (M + H^+).

3-Pentamethylen-1-(1-(*S*)-phenyl-ethyl)-thiourea (5): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.49 (d, J = 6.8 Hz, 3 H), 1.54

Table 1[a]

Entry			Yield (%)
1			70
2			50
3			33
4			47
5			80
6			69
7			48
8			60
9			81
10			97
11			71
12			77

[a] Each compound was characterized by ^{1}H NMR and by mass spectroscopy analysis. The yields are based on the amount of recovered thiourea, considering an initial loading of the Merrifield resin of 1.24 mequiv/g. The purity, according to HPLC analysis of the crude mixture, was always found to be higher than 90%.

(m, 6 H), 3.67−3.69 (m, 4 H), 5.64 (br s, 1 H), 5.76 (qd, J = 6.8 Hz, 9.3 Hz, 1 H), 7.15−7.29 (m, 5H); MS (IC/NH_4^+) 250 ($M + H^+$).

1-(1-(*R*)-Hydroxy-methyl-3-methyl-butyl)-3-(4-methoxy-benzyl)-thiourea (6): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6.40 Hz, 6 H), 1.20−1.49 (m, 4 H), 3.43 (AB system, J = 4.1, 6.8 Hz, 1 H), 3.65 (AB system, J = 4.1, 6.8 Hz, 1 H), 3.75 (s, 3 H), 4.52 (s, 2 H), 6.21 (br s, 1 H), 6.83 (d, J = 8.6 Hz, 2 H), 6.99 (br s, 1 H), 7.25 (d, J = 8.6 Hz, 2 H); MS (IC/NH_4^+) 297 ($M + H^+$).

1-(3,3-Diethoxy-propyl)-3-isobutyl-thiourea (7): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.81 (d, J = 6.3 Hz, 6 H), 1.07 (t, J = 6.8 Hz, 6 H), 1.55 (m, 2 H), 1.76 (tseptet, J = 6.3 et 6.9 Hz, 1 H), 3.12 (m, 2H), 3.37 (m, 4 H), 3.48 (q, J = 6.8 Hz, 4 H), 4.37 (m, 1 H), 6.55 (br s, 2 H); MS (IC/NH_4^+) 277 ($M + H^+$).

[2-(3-Butyl-thioureido)-ethyl]-carbamic acid *tert*-butyl ester (8): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 3 H), 1.41 (s, 9 H), 1.30−1.45 (m, 2 H), 1.55 (tt, J = 7.5 Hz, 7.1 Hz, 2 H), 3.30 (m, 4 H), 3.58 (m, 2 H), 5.24 (br s, 1 H), 6.45 (br s, 1 H), 7.04 (br s, 1 H); MS (IC/NH_4^+) 276 ($M + H^+$).

***N*-[3-(Adamant-1-yl)-thioureido-ethyl]-acetamide (9):** ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.70 (m, 6 H), 1.99 (s, 3 H), 1.97−2.16 (m, 9 H), 3.47 (m, 2 H), 3.75 (m, 2 H), 6.09 (br s, 1 H), 6.72 (br s, 2 H); MS (IC/NH_4^+) 296 ($M + H^+$).

[2-(3-Benzyl-thioureido)-ethyl]-phosphonic acid diethyl ester (10): presence of rotamers; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.20 (t, J = 6.8 Hz, 6 H), 2.10 (td, J = 6.3 Hz, 16.58 Hz, 2 H), 3.85 (t, J = 6.3 Hz, 2 H), 3.99 (qd, J = 6.8 Hz, 16.6 Hz, 4 H), 4.83 (d, J = 4.5 Hz, 2 H), 7.24−7.30 (m, 5 Hz); MS (IC/NH_4^+) 331 ($M + H^+$).

[2-(3-Anilin-thioureido)-ethyl]-carbamic acid *tert*-butyl ester (11): doubling due to thiourea rotamers; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.36 (s, 5 H), 1.43 (s, 4 H), 3.33 and 3.45 (t, J = 6.9 Hz, 2 H), 3.88 and 4.14 (t, J = 6.9 Hz, 2 H), 4.90 (br s, 1 H), 6.90 (br s, 1 H), 7.17−7.57 (m, 5 H), 7.80 (br s, 1 H); MS (IC/NH_4^+) 296 ($M + H^+$).

1-Benzyl-3-(4-bromo-phenyl)-1-methyl-thiourea (12): ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.31 (s, 3 H), 5.01 (s, 2 H), 7.06 (br s, 1 H), 7.17 (d, J = 5.8 Hz, 2 H), 7.32−7.40 (m, 5 H), 7.44 (d, J = 5.8 Hz, 2 H); MS (IC/NH_4^+) 335 ($M + H^+$).

Supporting Information Available. ^{1}H NMR and mass spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC990058D