Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 7031–7033
Tetrahedron Letters

A straightforward preparation of a polystyrene thiol resin

Jean-Michel Becht, Alain Wagner* and Charles Mioskowski*

Université Louis Pasteur de Strasbourg, UMR 7514 associée au CNRS, Laboratoire de Synthèse Bioorganique,
Faculté de Pharmacie, 74 Route du Rhin, 67401 Illkirch-Graffenstaden, France

Received 26 May 2004; revised 27 May 2004; accepted 29 July 2004

Abstract—A mild and efficient two-step synthesis of a polystyrene thiol resin is reported. Firstly, a polystyrene resin was reacted with an activated sulfoxide to afford the resin bound bis-(2-methoxy-carbonylethyl)-sulfonium trifluoromethanesulfonate. Smooth β-elimination based dealkylations afforded the polystyrene thiol resin with good and controlled loading. Its reactivity was assessed through a derivatisation step.

The establishment of solid phase synthesis processes over the last decade has resulted in tremendous work devoted to the preparation of original resins, linkers, scavengers and supported reagents.[1] Among the numerous specialised resins, the synthesis of a polystyrene thiol resin is of particular interest because of its strong radicals, metals and nucleophiles scavenger properties.[2,3]

The general procedures for the thiolation of aromatic substrates rely on a two-step process, the first to introduce an alkylsulfanyl group via either nucleophilic[4] or electrophilic[5] aromatic substitution, the second, a dealkylation reaction to generate the free thiol. These procedures are not amenable to the solid phase synthesis because the drastic reaction conditions (high temperatures and polar solvents) necessary to uncover the arylthiols cause the resin degradation.

Preparation of a polystyrene thiol resin relies on the use of a functionalised 4-bromo-polystyrene resin, which is firstly converted to the corresponding aryllithium resin and then trapped with sulfur.[6] The major drawback of this procedure is the ill-defined loading of the final polystyrene thiol resin due to the formation of di- and polysulfide bridges. To our knowledge, there is no alternative preparation of a polystyrene thiol resin with controlled loading and using a non functionalised polystyrene resin as starting material.

Recently, a two-step procedure for the introduction of a thiol group on aromatic substrates via an aromatic electrophilic substitution reaction, followed by two successive β-elimination promoted dealkylations has been reported by our group.[7]

Herein, this reaction sequence was transposed to the solid phase for an efficient two-step synthesis of a polystyrene thiol resin. For this purpose, 3-(2-methoxycarbonyl-ethanesulfinyl)-propionic acid methyl ester **1** was activated with triflic anhydride to give the highly electrophilic intermediate **1a**, which was further reacted with a polystyrene resin to afford the corresponding sulfonium trifluoromethanesulfonate resin **2**. Deprotection/dealkylation reactions in basic medium yielded the desired polystyrene thiol resin **3** (Scheme 1).

Each step of our procedure was monitored using on-bead IR spectroscopy recorded with a Perkin–Elmer 2000 FT-IR coupled to an auto-image microscope. Several amounts of **1a** were reacted with 1 g of unfunctionalised polystyrene beads (150–400 mesh). The loadings of the polystyrene sulfonium trifluoromethanesulfonate resin **2** were measured by elemental analysis of sulfur and fluorine.

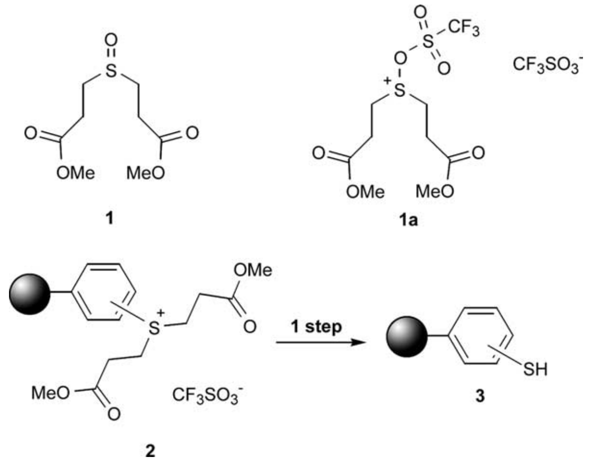
Initial experiments were performed by reacting 1 g of a polystyrene resin with 0.90 mmol of **1a** (Scheme 2 and Table 1, entry 1). The resin **2a** was best generated by adding triflic anhydride dropwise to a suspension of

---

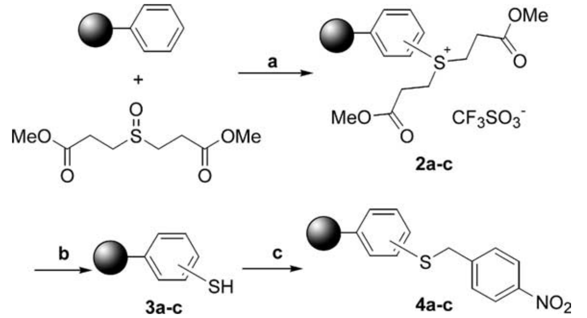
Keywords: Polystyrene thiol resin; Aromatic electrophilic substitution reaction; Activated sulfoxide.

* Corresponding authors. Tel.: +33 3 90 24 42 95; fax: +33 3 90 24 43 06; e-mail addresses: wagner@bioorga.u-strasbg.fr; mioskowski@bioorga.u-strasbg.fr

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.07.147



Scheme 1. Reagent and intermediates involved in the preparation of a polystyrene thiol resin.



Scheme 2. Reagents and conditions: (a) (i) Tf_2O, −40 °C, 20 min, (ii) 0 °C to rt, 12 h; (b) (i) 1 M *t*-BuOK, THF, −50 °C, 1 h, (ii) rt, 24 h; (c) 4-nitro-benzylbromide, NaOH, dioxane/H_2O 3:1, 60 °C, 24 h.

Table 1. Reaction of several amounts of **1a** with the polystyrene resin

Entry	mmol **1a**[a]	Loading[b]	Resin
1	0.90	0.33	**2a**
2	2.60	1.05	**2b**
3	3.50	1.46	**2c**

[a] Reaction with 1 g of a polystyrene resin and 1.2 equiv of triflic anhydride.

[b] Measured by elemental analysis of sulfur and fluorine.

the polystyrene resin and **1** in dry DCM (12 mL) at −40 °C under an atmosphere of argon. The slurry was gently stirred at −40 °C for 20 min, then warmed to 0 °C and eventually to rt for 12 h (Scheme 2). The resulting resin was then filtered and washed three times, subsequently, with DCM, MeOH and Et_2O. The resin **2a** was finally dried under vacuum overnight. The formation of **2a** was assessed by FT-IR spectroscopy that showed two intensive carbonyl bands at 1739 and 1731 cm^{-1}. Sulfur and fluorine elemental analysis, showed a consistent loading of 0.33 $mmol\cdot g^{-1}$.

In order to achieve higher loadings, larger amounts of **1a** were reacted with the polystyrene resin (Table 1) using the same amount of DCM. Reacting 1 g of the polystyrene resin with 2.60 mmol of **1a** gave the resin **2b** with an increased 1.05 $mmol\cdot g^{-1}$ loading (entry 2). Eventually, a loading of 1.46 $mmol\cdot g^{-1}$ was obtained by using 3.50 mmol of **1a** (entry 3). Noteworthy, by varying the polystyrene resin and **1a** ratio, the loading of **2** could be adjusted from low to high.

The deprotection/dealkylation of the resin **2b** to the corresponding arylthiol resin **3b** was performed by adding dropwise at −50 °C a 1 M solution of *t*-BuOK in THF to a suspension of **2b** in dry THF under an atmosphere of argon. The slurry was gently stirred at −50 °C for 1 h, then slowly warmed to rt for 24 h (Scheme 2). Noteworthy, as proved by FT-IR spectroscopy, shorter reaction times gave an incomplete reaction. The resulting resin **3b** was then filtered, washed twice subsequently with THF, 1 M HCl and H_2O. The resin was then washed with a 0.8 M solution of PBu_3 in a 1:1 mixture of THF/H_2O (to reduce possible disulfide bridges), then three times with THF, MeOH, DCM and Et_2O. The resin **3b** was eventually dried under vacuum overnight. The formation of **3b** was assessed by FT-IR spectroscopy that showed the disappearance of the two carbonyl bands at 1739 and 1731 cm^{-1}. Sulfur elemental analysis showed that the loading of **3b** was 1.25 $mmol\cdot g^{-1}$ (theoretical loading starting from **2b**: 1.57 $mmol\cdot g^{-1}$).

Next, the presence of free arylthiol functions in the polystyrene thiol resin was probed by reacting **3b** with an excess (30 equiv) of 4-nitro-benzylbromide and NaOH in a 3:1 mixture of dioxane/H_2O at 60 °C for 24 h (Scheme 2). The resulting resin **4b** was then filtered and washed three times, subsequently with THF, DCM and Et_2O. The resin was finally dried under vacuum overnight. The formation of the desired resin **4b** was confirmed by FT-IR spectroscopy that showed the presence of a nitro band at 1522 cm^{-1}. Sulfur elemental analysis showed a loading of 1.10 $mmol\cdot g^{-1}$ (theoretical loading starting from **3b**: 1.07 $mmol\cdot g^{-1}$). Nitrogen elemental analysis gave a loading of 1.29 $mmol\cdot g^{-1}$ probably resulting from the presence of sulfonium moieties in the resin due to overalkylation. This derivatisation step proved the functional efficacy of **3b** and confirmed the presence of nucleophilic arylthiol functions.

The scavenger property of our thiol resin was assessed by reaction of **3b** with a default of bromodecane. For this purpose, the polystyrene thiol resin **3b** (2 g) was reacted with bromodecane (1.0 mmol) in a mixture of dioxane and 0.5 M NaOH. After 24 h stirring at rt, the reaction mixture was filtered and the solvent was concentrated under vacuum. ^1H NMR and GC analysis of the filtrate showed that there was no bromodecane left. This reaction confirmed the high scavenger capacity of our polystyrene thiol resin.

In conclusion, a versatile two-step synthesis of a polystyrene thiol resin has been developed. Reaction of the polystyrene resin and sulfoxide **1** in the presence of triflic anhydride, followed by two one-pot β-elimination reactions yielded the polystyrene thiol resin. Noteworthy, our synthesis has been realised successfully on a 10 g scale.[8,9] Applications of our polystyrene thiol resin for the preparation of supported reagents, catalysts and scavengers are currently in progress.

Acknowledgements

We thank the Ministère de l'Education Nationale, de la Recherche et de la Technologie for financial support of this work through a MENRT grant to J.-M.B.

References and notes

1. (a) Wallace, R. W. *Drug Disc. Today* **1997**, *2*, 355; (b) Burbaum, J. J.; Sigal, N. H. *Curr. Opin. Chem. Biol.* **1997**, *1*, 72; (c) James, I. W. *Tetrahedron* **1999**, *55*, 4855.
2. (a) Karyakin, A. A.; Presnova, G. V.; Rubtsova, M. Y.; Egorov, A. M. *Anal. Chem.* **2000**, *72*, 3805; (b) Lindstad, R. I.; McKinley-McKee, J. S. *Eur. J. Biochem.* **1996**, *241*, 142; (c) Devasagayam, T. P.; Sundquist, A. R.; Di Mascio, P.; Kaiser, S.; Sies, H. *J. Photochem. Photobiol.* **1991**, 105; (d) Motohashi, N.; Mori, I. *J. Inorg. Biochem.* **1986**, *26*, 205.
3. (a) Katoh, M.; Sodeoka, M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 881; (b) Sheppeck, J. E.; Kar, H.; Hong, H. *Tetrahedron Lett.* **2000**, *41*, 5329.
4. Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D. *Synthesis* **1983**, 751.
5. (a) Hocker, J.; Ley, K.; Merten, R. *Synthesis* **1975**, 334; (b) Nenajdenko, V. G.; Vertelezkij, P. V.; Balenkova, E. S. *Sulfur Lett.* **1996**, *20*, 75.
6. Farrall, M. J.; Fréchet, M. J. *J. Org. Chem.* **1976**, *41*, 3877.
7. Becht, J.-M.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **2003**, *68*, 5758.
8. All the reactions were performed using the Fluka polystyrene resin, copolymere of styrene (98.5%) and divinylbenzene (1.5%), reference 27833, cas: [9003-70-7].
   Preparation of a polystyrene sulfonium resin **2**: Triflic anhydride (5.27 mL, 31.2 mmol) is added dropwise at −40 °C to a suspension of a polystyrene resin (10 g) and **1** (5.78 g, 26.0 mmol) in dry DCM (120 mL) under an atmosphere of argon. The reaction mixture is gently stirred at −40 °C for 20 min, warmed to 0 °C and to rt for 12 h. The orange resin is filtered under vacuum and washed three times subsequently with DCM (3 × 150 mL), MeOH (3 × 150 mL) and Et_2O (3 × 150 mL). The polystyrene sulfonium resin **2** is finally dried under vacuum overnight (15.4 g, loading: 1.09 $mmol\cdot g^{-1}$).
9. Preparation of a polystyrene thiol resin **3**: A 1 M solution of *t*-BuOK in THF (75.0 mL, 75.0 mmol) is added dropwise at −50 °C to a suspension of **2** (10 g) in dry THF (90 mL) under an atmosphere of argon. The reaction mixture is gently stirred at −50 °C for 1 h, then warmed to rt for 24 h. The orange resin is filtered under vacuum and washed twice subsequently with THF (2 × 200 mL), 1 M HCl (2 × 200 mL) and H_2O (2 × 200 mL). The resin is then washed with a 0.8 M solution of PBu_3 in a 1:1 mixture of THF/H_2O (200 mL), then three times subsequently with THF (3 × 200 mL), MeOH (3 × 200 mL), DCM (3 × 200 mL) and Et_2O (3 × 200 mL). The polystyrene thiol resin **3** is finally dried under vacuum overnight (7.16 g, loading: 1.34 $mmol\cdot g^{-1}$).