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PS-SNAP, a practical polymer-supported nitrosation reagent in organic synthesis

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ABSTRACT

PS-SNAP was designed and evaluated as a practical nitrosating polymer-supported reagent for the nitrosation of *sec*-amines. Nitrosated dialkyl amines, alkyl anilines, and bis-anilines were obtained in good yields and high purities after shaking the corresponding amines in the presence of an excess of the newly described reagent followed by simple filtration and removal of solvents.

The N-nitrosation of amines is an important and well-established reaction in organic synthesis,[1,2] and the most common procedure involves the use of nitrous acid generated from sodium nitrite and mineral acids in water. However, the method is not very practical on a parallel synthesis perspective. In the frame of our work on the discovery of new biologically active compounds having both antioxidant and nitric oxide donor properties,[3] we addressed the possibility of using polymer-supported reagents to synthesize *N*-nitroso derivatives. Indeed, the development of new solid-supported reagents has increased dramatically over the past decade,[4] with the essential advantages of being able to drive reactions by mass action, and the associated ease of purification. Some heterogeneous nitrosating reagents have recently been described[5–7] and we report herein the design, synthesis, and evaluation of **PS-SNAP** as a novel polymer-supported nitrosating reagent.[8]

The classical aqueous conditions associated with the N-nitrosation of amines were clearly not compatible with the hydrophobic nature of the most commonly used resins, such as polystyrene. Our interest rapidly focused on the design of alkylnitrites or thionitrites reagents that could be utilized under neutral or basic conditions, with the additional feature of allowing the use of a wider range of non aqueous solvents. Thionitrites are much less known than the corresponding alkyl nitrites, probably because of their generally lower stability.[9,10] However, *S*-Nitroso-*N*-acetylpenicillamine (SNAP)[11] is a stable solid which has been used as a nitric oxide generator in a range of in vivo and in vitro experiments.[12,13] It was also described as a reagent for the transnitrosation of amines,[14] thiols, and phenols.[15,16] Therefore, we considered that the immobilization of SNAP on a solid support could provide us with the desired nitrosating reagent in a form that was stable and reactant enough to undergo transnitrosation of amines.

PS-SNAP was prepared in two steps from commercially available aminomethyl-polystyrene resin (Scheme 1). The resin (Novabiochem, 1.13 mmol/g loading) was treated overnight with a DMF solution of *N*-acetyl-DL-penicillamine *N*-hydroxysuccinimidate **1**[17] at room temperature to provide a colorless resin **PS-2** which gave a negative result in the Kaiser colorimetric test.[18] IR analysis of the resin confirmed the presence of the expected weak SH band at 2750 cm^{-1}. The S-nitrosation was attempted under various conditions of solvents (DCM, H_2O, MeOH, AcOH/dioxane/water, $CHCl_3$) using sodium nitrite, ethyl nitrite, *tert*-butylnitrite, or NOBF4 as nitrosonium source. Best conditions were obtained using sodium nitrite in a mixture of solvents AcOH/dioxane/water. The reaction was monitored by the appearance of a green coloration of the beads (Fig. 1) characteristic of *tert*-butylthionitrites[9,10] and the disappearance of the SH band by IR spectroscopic analysis of the beads. Elemental analysis of the **PS-SNAP** resin prepared under the optimized conditions indicated a 70% immobilization yield based on the initial loading. **PEG-SNAP** was similarly prepared from the commercially available PEG-aminomethyl resin. The butyric thionitrite analog (**PS-5**) was also prepared under similar conditions from aminomethyl-polystyrene resin and 3-mercapto-3-methyl-butyric acid.[19]

The *S*-Nitroso reagents were then evaluated in the transnitrosation of amines. Based on our experience in the synthesis of *N*-nitroso compounds, the nitrosation of biphenyl amine **6** (Fig. 2) was chosen as a model study. Indeed, its *N*-nitroso derivative **7** is a stable compound easy to characterize by NMR or HPLC.[3] The kinetics

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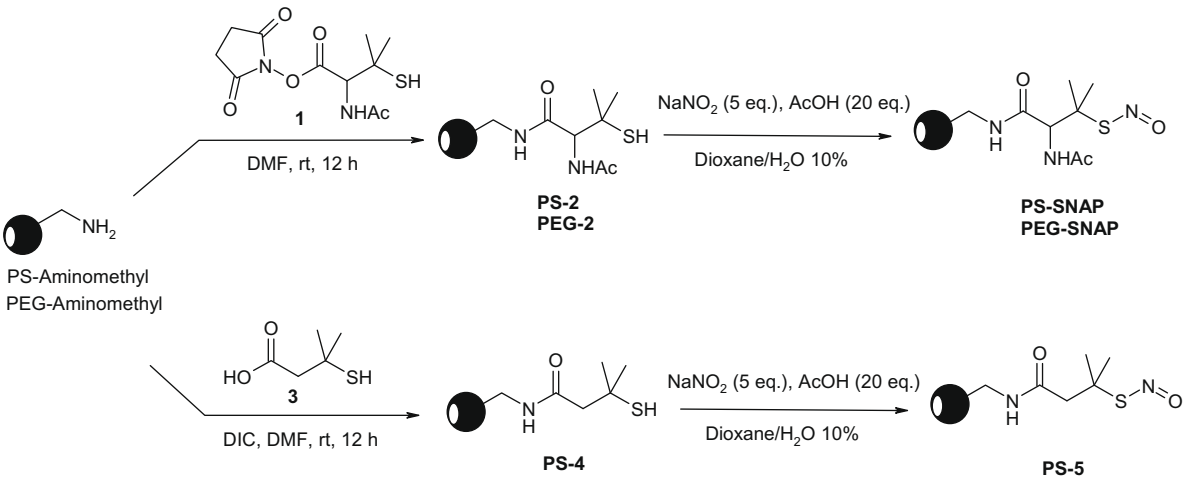


Scheme 1. Preparation of S-NO polymer-supported reagents.

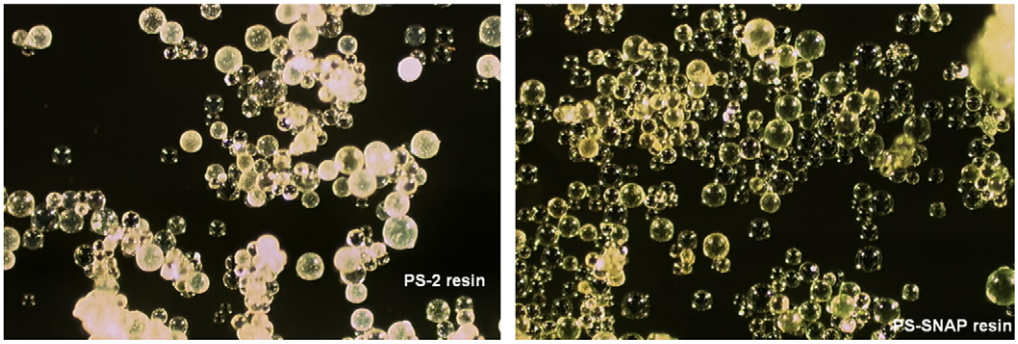
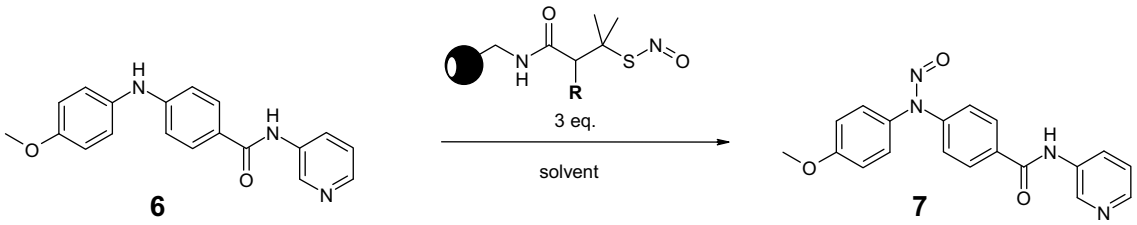


Figure 1. Microscopic view of **PS-2** (colorless) and **PS-SNAP** (green) resins (Leica/Sony 3CCD).



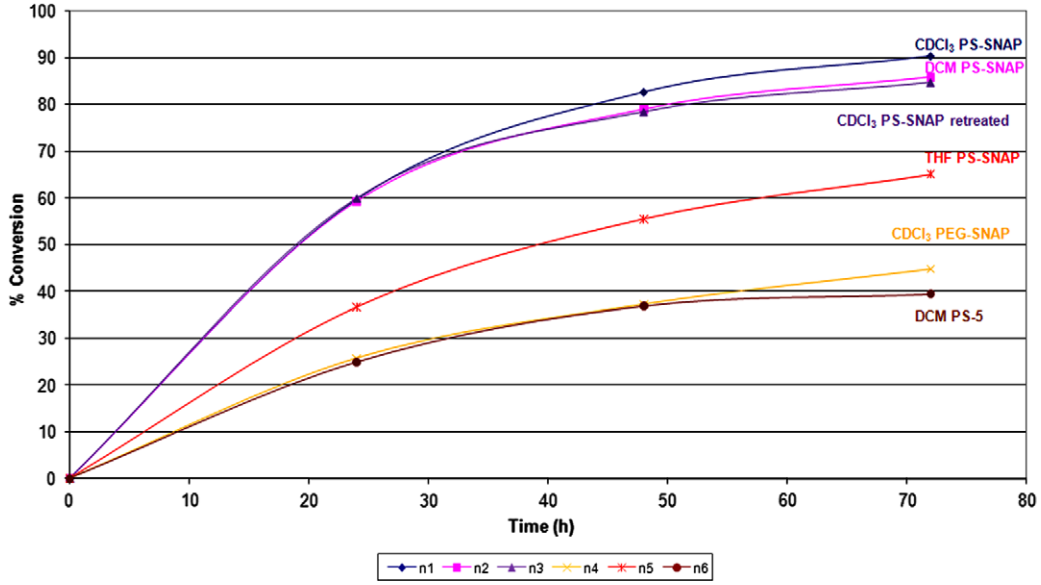
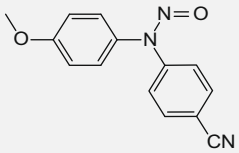
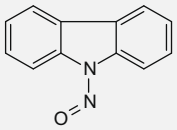
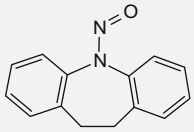
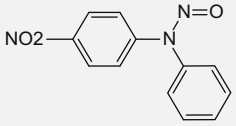
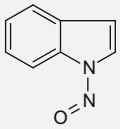
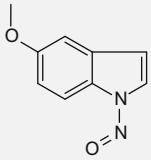
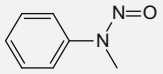
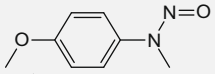
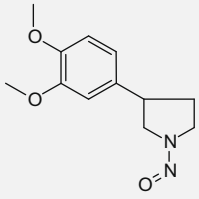
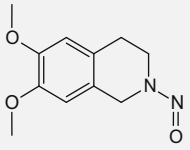
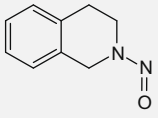


Figure 2. Kinetics of nitrosation of compound **6** with **PS-SNAP** and **PS-5**.

Table 1
R1NHR2→R1R2N–NO[17]

Entry	R1R2N–NO	MW	% Weight recovered	% Conversion		
				LC/MS	^{1}H NMR (%)	R1NHR2 (%)
1		253	95	n.d.	92	8
2		196	105	55% (DAD 200) MS ES+ 167, 197	67	33
3		224	96	92% (DAD 200) MS ES+ 225	>90	0
4		243	99	0% (ELSD)	0	100
5		146	95	0% (ELSD)	0	100
6		176	93	0% (ELSD)	0	100
7		136	97	51% (DAD 200) MS ES+ 137	69	0
8		166	98	92% (DAD 200) MS ES+ 137, 167	>90	0
9		236	90	94% (ELSD) MS ES+ 237	n.d.	n.d.
10		222	97	87% (DAD 200) MS ES+ 223	90	10
11		162	95	80% (DAD 200) MS ES+ 163	>90	0

of the formation of compound **7** using 3 equiv of polymer-supported reagent in various solvents are presented in Figure 2 (as often with polymer-supported reagents, an excess of reagent proved to be necessary to drive the reaction to completion). In $CDCl_3$, initially used to monitor the reaction by ^{1}H NMR, 92% conversion was obtained after 72 h (n1 curve). Similar results were obtained in dichloromethane (n2 curve) while the reaction was considerably slower in THF (n5 curve). Interestingly the reagent could be regenerated using sodium nitrite/acetic acid in dioxane/water and reused without loosing the reactivity or decreasing the final purity of the nitrosated amine (n3 curve). Furthermore, the reagent proved to be stable as the reaction performed with a batch of **PS-SNAP** kept for six month in the dark at 4 °C provided similar results. In comparison, the kinetics of transnitrosation obtained with

PEG-SNAP and **PS-5** under the same conditions were considerably slower (n4 and n6 curves, respectively).

The **PS-SNAP** reagent was then evaluated in the nitrosation of various *sec*-amines. The reactions were carried out by shaking the substrate in dichloromethane in the presence of 3 equiv of **PS-SNAP** for 140 h (Table 1).[20] LC/MS and ^{1}H NMR were used to determine the purity and to characterize the products.

Several bis-anilines could be nitrosated in moderate to good yields including both the carbazole and iminodibenzyl moieties (entries 1–3). Discoloration of the beads from green to pale yellow was self-indicative of the substrate reactivity. The presence of a strong electron withdrawing group in the para position, such as the nitro group, prevented any reaction and the starting material was fully recovered (entry 4). Similarly, both the transnitrosation of indole and 4-methoxyindole did not provide the desired *N*-nitroso derivatives (entries 5 and 6), probably because of the poor nucleophilicity of the indolic nitrogen (no discoloration of the **PS-SNAP** beads in these experiments). Overall, the transfer reaction was successful with many nucleophiles and several nitrosated alkyl anilines or dialkyl amines were obtained in very good yields (entries 7–11). The reaction was considerably faster with these substrates (100% completion after 20–30 h) and no degradation was observed on pursuing the reaction longer. It is worth noting that although this method is considerably slower compared to a typical sodium nitrite N-nitrosation, its ease of use makes it particularly attractive for automation.

To conclude, **PS-SNAP** is a stable, thionitrite-derived reagent, easy and safe to handle. Caution should be given nevertheless in handling reagents leading to potentially carcinogenic *N*-nitrosoamines. Bis-anilines, alkyl anilines, and dialkyl amines were cleanly nitrosated and the method is perfectly designed for an automated parallel synthesis strategy. Application of the **PS-SNAP** reagent to the synthesis of libraries of nitrosated amines as well as further applications of the reagent in organic synthesis are in progress and will be reported in due course.

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References and notes

1. Keefer, L. K.; Williams, D. L. H. *Methods in Nitric Oxide Research*; John Wiley & Sons, Ltd: New York, 1996. pp 509–519.
2. Vogels *Text Book of Practical Organic Chemistry*, 4th ed.; Longman: London and New York, 1986.
3. (a) Lardy, C.; Guedat, P.; Caputo, L. FR. Demande 2005, FR 2862966.; (b) Lardy, C.; Festal, D.; Caputo, L.; Guerrier, D. FR. Demande 2003, FR 2836917.
4. (a) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815–4195; (b) Kirschning, A.; Monenschain, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650–679; (c) Bhalay, G.; Dunstan, A.; Glen, A. *Synlett* **2000**, 1846–1859.
5. Zarchi, M. A.; Noei, J. *J. Appl. Polym. Sci.* **2007**, *104*, 1064–1067.
6. Montazerozohori, M.; Karami, B. *Helv. Chim. Acta* **2006**, *89*, 2922–2926.
7. (a) Niknam, K.; Ali Zolfigol, M. *Synth. Commun.* **2006**, *36*, 2311–2319; (b) Iranpoor, N.; Firouzabadi, H.; Pourali, A. *Synth. Commun.* **2005**, *35*, 1517–1526.
8. Roche, D.; Lardy, C.; FR. Demande 2004, FR 2845090.
9. Oae, S.; Kukushima, D.; Kim, Y. H. *J. Chem. Soc., Chem. Commun.* **1977**, 407–408.
10. Roy, B.; du Moulinet d'Hardemare, A.; Fontecave, M. *J. Org. Chem.* **1994**, *59*, 7019–7026.
11. Field, L.; Dilts, R. V.; Ravichandran, R.; Galen Lenhert, P.; Carnahan, G. E. *J. Chem. Soc., Chem. Commun.* **1978**, 249–250.
12. Kowaluk, E. P.; Fung, H. L. J. *J. Pharmacol. Exp. Ther.* **1990**, *155*, 1256.
13. Hogg, N.; Struck, A.; Goss, S. P. A.; Santanam, N.; Joseph, J.; Parthasarathy, S.; Kalyanaraman, B. *J. Lipid Res.* **1995**, *36*, 1756–1762.
14. Munro, A. P.; Williams, D. L. H. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1989–1993.
15. Barnett, D. J.; Rios, A.; Williams, D. L. H. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1279–1282.
16. Shirlene, M. N. Y. F.; Williams, D. L. H. *J. Chem. Soc., Perkin Trans. 2* **1991**, 685–688.
17. Compound **1** was prepared in quantitative yield from the reaction of (±)-*N*-acetylpenicillamine (24 g, 125 mmol) with *N*-hydroxysuccinimide (14.4 g, 125 mmol) in the presence dicyclohexylcarbodiimide (25.8 g, 125 mmol) in THF (500 mL) at rt for 12 h.
18. Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I. *Anal. Biochem.* **1970**, *34*, 595–598.
19. 3-Mercapto-3-methyl-butyric acid was prepared according to: Sweetman, B. J. *J. Med. Chem.* **1971**, *14*, 868–872.
20. *Typical procedure*: **PS-SNAP** (100 mg, 3 equiv) was added to a solution of **6** (10 mg, 0.03 mmol) in dichloromethane (3 ml) and the mixture was stirred with an orbital shaker for 140 h. After filtration, the resin was washed with dichloromethane and the filtrate was concentrated to afford **7** (10 mg, 91% yield) as a pale yellow solid.