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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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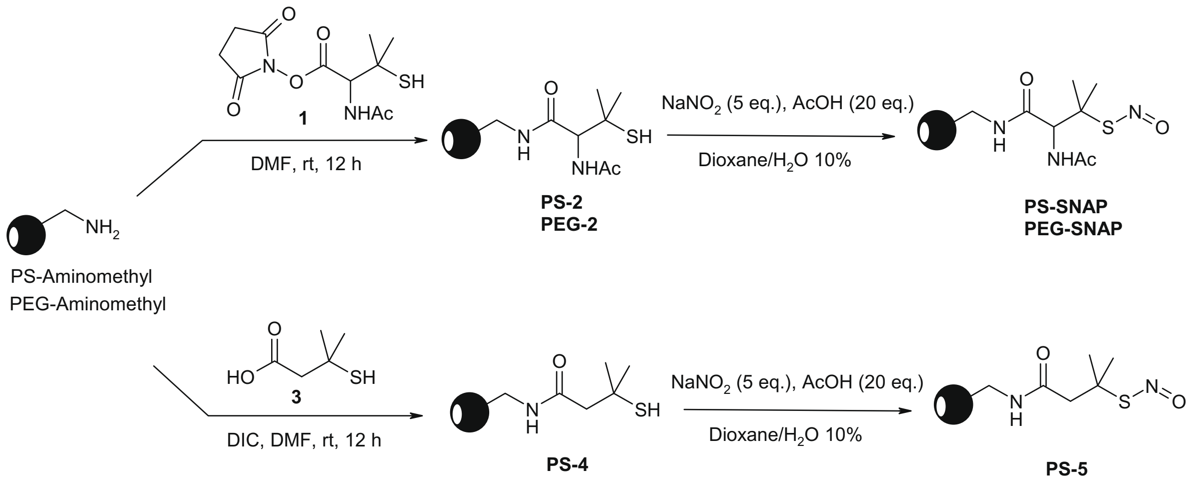


Scheme 1. Preparation of S-NO polymer-supported reagents.

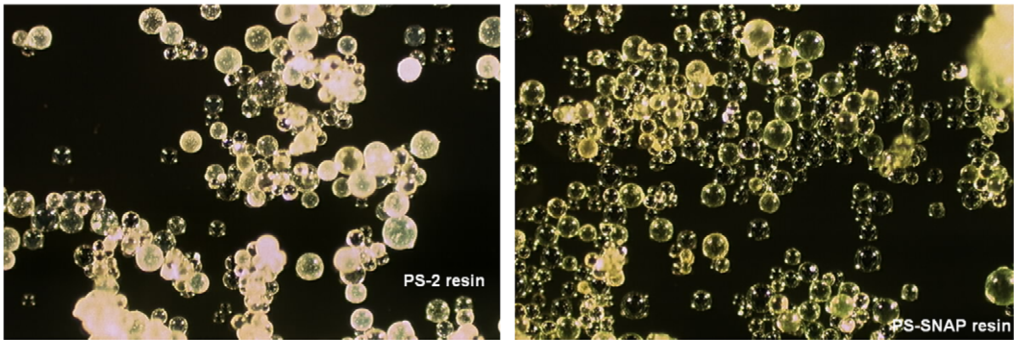
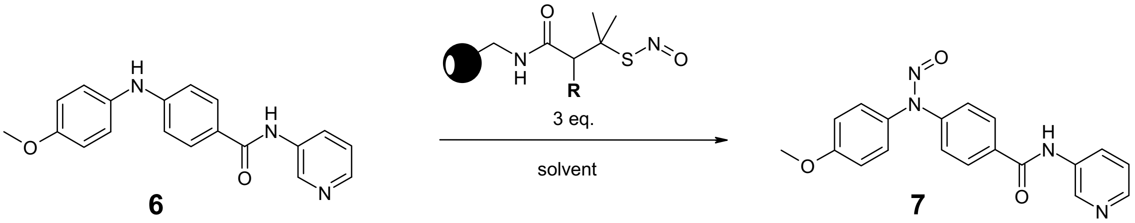


Figure 1. Microscopic view of **PS-2** (colorless) and **PS-SNAP** (green) resins (Leica/Sony 3CCD).



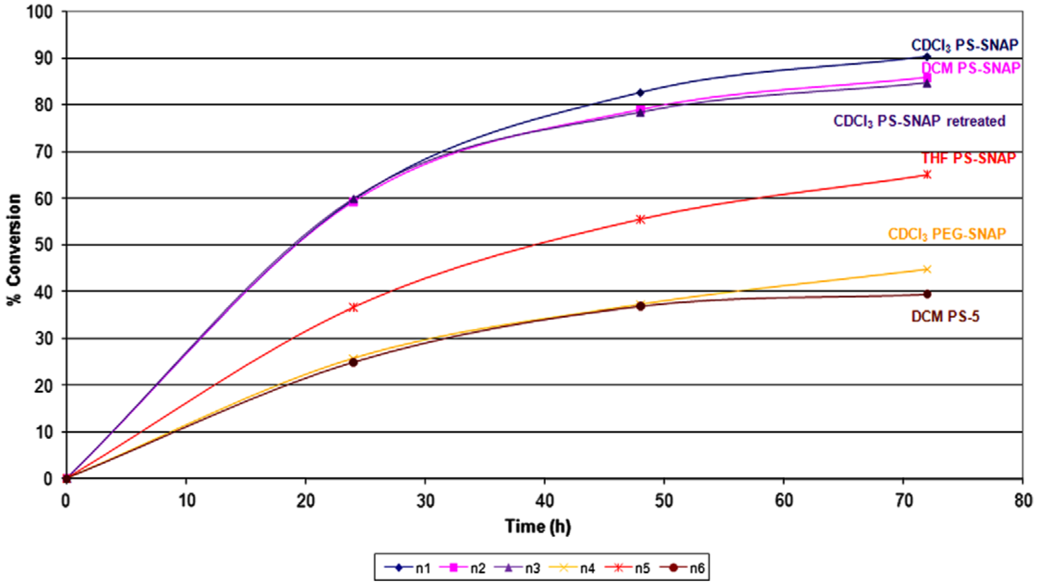


Figure 2. Kinetics of nitrosation of compound **6** with **PS-SNAP** and **PS-5**.