Synlett T. Suzuki et al. Letter

O-Alkyl *S*-(Pyridin-2-yl)carbonothiolates: Operationally Simple and Highly Nitrogen-Selective Reagents for Alkoxy Carbonylation of Amino Groups

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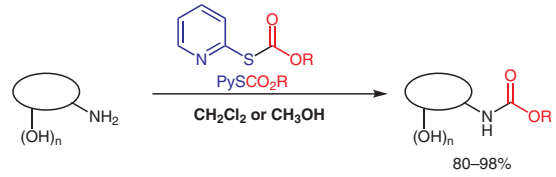


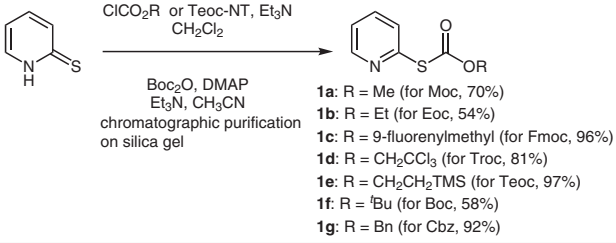
Received: 09.01.2020
Accepted after revision: 26.02.2020
Published online: 13.03.2020
DOI: 10.1055/s-0039-1690856; Art ID: st-2020-u0003-l

Abstract Amino groups are selectively protected in good yields by reaction with *O*-alkyl S-(pyridin-2-yl)carbonothiolates in an appropriate solvent at room temperature in air. Even glucosamine, which contains multiple hydroxyl groups, is selectively *N*-protected in methanol.

Key words *O*-alkyl *S*-(pyridin-2-yl)carbonothiolates, protective group, *N*-selective

Amino functionalities of biologically active natural and unnatural compounds are generally indispensable for biological activity, and synthesis of these compounds often requires adequate protection of the amino group.[1] For this reason, methods[2–5] for introducing carbamate protecting groups have been intensively investigated using different reagents,[2] catalysts,[2f,3] microwave irradiation,[4] and various reaction media.[5] However, in many cases, their usefulness is limited to the Boc[2e,5a,d] or Fmoc[4,5b,c] group. On the other hand, the (pyridin-2-yl)thio group was first introduced as a leaving group for peptide synthesis[6] and was later employed in ketone synthesis,[7] macrolactonization,[8] glycosylation,[9] disulfide formation,[10] and transition-metal-catalyzed coupling reactions.[11] *O*-*tert*-Butyl and *O*-benzyl *S*-(pyridin-2-yl)carbonothiolates (**1f** and **1g**) were reported by Kim's group as protective-group-incorporating reagents that work in DMF.[12] Quite recently we found that these compounds also act as alkoxy carbonylation reagents of Grignard reagents to give one-carbon homologated esters.[13] During preparation of the thiolates,[13] we found that the reagents were stable during chromatographic purification, suggesting that they are inert to oxygen nucleophiles such as water and alcohols, probably due to the softer electrophilic nature of their carbonyl carbons resulting from the presence of the soft sulfur atom. These results inspired us to reinvestigate alkoxycarbonyl compounds having a (pyridine-2-yl)thio leaving group as alternatives to conventional reagents such as chloroformates. We found that *O*-alkyl *S*-(pyridin-2-yl)carbonothiolates are reliable and highly nitrogen-selective alkoxy carbonylation reagents for amino groups, working even in methanol as a solvent.

We began by preparing *O*-alkyl *S*-(pyridin-2-yl)carbonothiolates **1a–g** (Scheme 1): MocSPy (**1a**),[14] EocSPy (**1b**),[14] FmocSPy (**1c**), TrocSPy (**1d**), and CbzSPy (**1g**)[12,13] by treatment of the corresponding chlorides with 2-pyridinethione in the presence of Et_3N in CH_2Cl_2. We synthesized TeocSPy (**1e**) and BocSPy (**1f**)[12,13] from 2-(trimethylsilyl)ethyl 3-nitro-1,2,4-triazole-1-carboxylate[2b] (Teoc/NT) or di-*tert*-butyl dicarbonate (Boc_2O), respectively, and 2-pyridinethione in the presence of Et_3N and a catalytic amount of DMAP in CH_3CN at room temperature. Thiolates **1a–g** were all stable and could be purified by column chromatography. They can be stored for several months in a refrigerator.



Scheme 1 Preparation of acylating reagents **1a–g**

With **1a–g** in hand, we examined their reactivity and stability by using benzylamine (**2**) as a substrate in methanol at room temperature (Table 1). In all cases, the corresponding alkoxycarbonyl-protected benzylamines **3a–g** were obtained in high yields within 3 h, without any formation of double acylated compounds. The Fmoc group was the most efficiently introduced into benzylamine (**2**), giving

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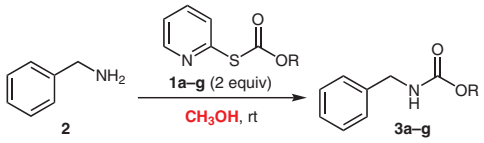
3c in 97% yield (Table 1, entry 3). It is noteworthy that even the highly electrophilic Troc group can be incorporated into **2** in nucleophilic methanol, giving **3d** in 84% yield.

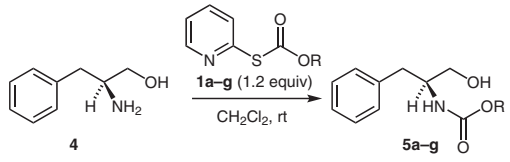
Table 1 Reaction of Benzylamine (**2**) with Acylating Reagents **1a–g** in CH_3OH



Entry	R (protective group)	Time (h)	Product **3**	Yield (%)
1	Me (Moc)	3	**3a**	86
2	Et (Eoc)	3	**3b**	93
3	9-fluorenylmethyl (Fmoc)	1	**3c**	97
4	CH_2CCl_3 (Troc)	0.5	**3d**	84
5	CH_2CH_2TMS (Teoc)	1.5	**3e**	93
6	*tert*-Bu (Boc)	2.5	**3f**	81
7	Bn (Cbz)	1	**3g**	83

To examine the chemoselectivity, the reactions of three types of amino alcohols, phenylalaninol (**4**), valinol (**6**), and prolinol (**8**), were conducted in CH_2Cl_2 at room temperature (Tables 2–4). In the case of phenylalaninol (**4**), all reactions were completed within one day to afford the *N*-protected compounds **5a–g** in 80–94% yields without the formation of any *O*-protected compound (Table 2). The incorporation of the Troc and Cbz groups was especially efficient, affording **5d** and **5g** in 89% and 94% yields, respectively.

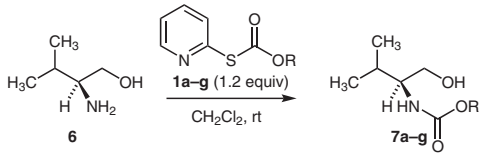
Table 2 Reaction of Phenylalaninol (**4**) with Acylating Reagents **1a–g** in CH_2Cl_2



Entry	R (protective group)	Time (h)	Product **5**	Yield (%)
1	Me (Moc)	24	**5a**	83
2	Et (Eoc)	24	**5b**	85
3	9-fluorenylmethyl (Fmoc)	15	**5c**	80
4	CH_2CCl_3 (Troc)	3	**5d**	89
5	CH_2CH_2TMS (Teoc)	22	**5e**	87
6	*tert*-Bu (Boc)	24	**5f**	80
7	Bn (Cbz)	10	**5g**	94

Next, we examined a sterically demanding β-branched amino alcohol, valinol (**6**, Table 3). All the reactions proceeded without difficulty to afford the *N*-protected compounds **7a–g** in high yields. Interestingly, the reaction periods required for protection of valinol (**6**) were even shorter than those for the protection of phenylalaninol (**4**). Again, reagents **1d** and **1g** exhibited high reactivity, providing Troc- and Cbz-protected compounds **7d** and **7g** in 94% and 96% yields, respectively (Table 3, entries 4 and 7).

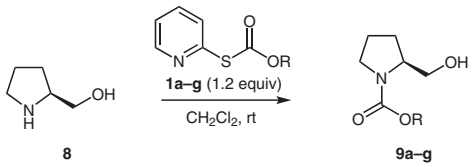
Table 3 Reaction of Valinol (**6**) with Acylating Reagents **1a–g** in CH_2Cl_2



Entry	R (protective group)	Time (h)	Product **7**	Yield (%)
1	Me (Moc)	17	**7a**	82
2	Et (Eoc)	10	**7b**	93
3	9-fluorenylmethyl (Fmoc)	8.5	**7c**	80
4	CH_2CCl_3 (Troc)	1.5	**7d**	94
5	CH_2CH_2TMS (Teoc)	16	**7e**	88
6	*tert*-Bu (Boc)	14	**7f**	90
7	Bn (Cbz)	6	**7g**	96

Finally, the secondary amino alcohol prorinol (**8**) was examined (Table 4). The reaction rates with **8** were higher than those with **4** or **6**, and high yields of *N*-protected compounds **9a–g** were obtained. Once again, incorporation of the Troc group was the fastest reaction, affording **9d** in 97% yield (Table 4, entry 4).

Table 4 Reaction of Prolinol (**8**) with Acylating Reagents **1a–g** in CH_2Cl_2

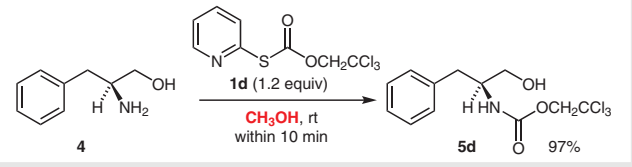


Entry	R (protective group)	Time (h)	Product **9**	Yield (%)
1	Me (Moc)	4	**9a**	83
2	Et (Eoc)	2.5	**9b**	94
3	9-fluorenylmethyl (Fmoc)	1	**9c**	94
4	CH_2CCl_3 (Troc)	0.5	**9d**	97
5	CH_2CH_2TMS (Teoc)	1.5	**9e**	98
6	*tert*-Bu (Boc)	3.5	**9f**	88
7	Bn (Cbz)	1.5	**9g**	93

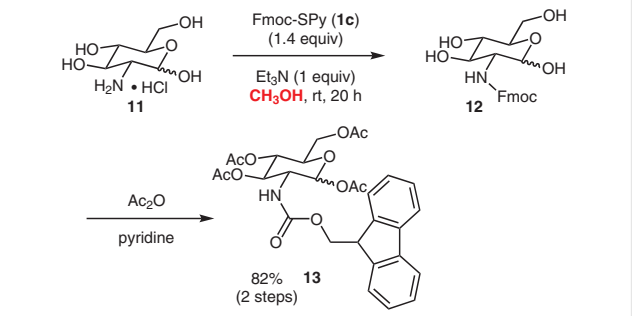
One of the features of $PySCO_2R$ **1** is high stability in the presence of hydroxyl groups. For example, *N*-protection of phenylalaninol (**4**) with the most electrophilic reagent TrocSPy (**1d**, 1.2 equiv) in methanol at room temperature

proceeded rapidly to give the *N*-protected product **5d** in 97% yield within 10 min (Scheme 2).[15,16] The acceleration of this reaction compared to that in CH_2Cl_2 (Table 2, entry 4) is probably due to activation of the acylating reagent by hydrogen bonding with methanol.[5a,b,d]

The observed stability of the present reagents in alcohol (Table 1 and Scheme 2) should be very useful for protecting highly polar amines that are insoluble in conventional solvents such as CH_2Cl_2. Furthermore, *N*-protection of glucosamine, which contains multiple hydroxyl groups, in methanol was conducted to confirm the *N*-selectivity of reagent **1** (Scheme 3). Thus, the reaction of glucosamine hydrochloride (**11**) with FmocSPy (**1c**) in the presence of Et_3N in methanol at room temperature proceeded to generate the *N*-selectively protected compound **12**, which, without isolation, was acetylated to afford **13** in 82% yield. Notably, compound **12** exhibits self-assembly on the surface of cancer cells.[17]



Scheme 2 *N*-Selective Troc-protection of phenylglycinol (**4**) in methanol



Scheme 3 *N*-Selective protection of glucosamine in methanol

In conclusion, the highly nitrogen-selective protecting reagents $PySCO_2R$ (**1a–g**) are readily available and storable. The reaction of **1** is operationally very simple, involving only the reaction of an amine with $PySCO_2R$ reagent in an appropriate solvent under air at room temperature. Although various reagents including ROCO-OSu and ROCO-NT for protection of amino groups have been explored, the present method provides a new option that should be especially useful for amines with limited availability, such as amine groups of intermediates in the late stages of natural product synthesis.

Funding Information

This work was supported by the Japan Society for the Promotion of Science (JSPS KAKENHI Grant Number 17K0821 to O.T.).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690856.

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(14) In addition to usual abbreviations for carbamates, Moc (methyloxycarbonyl) and Eoc (ethyloxycarbonyl) are used in this paper.

(15) **Typical Procedure**
To a stirred solution of phenylalaninol (**4**, 53.0 mg, 0.350 mmol) in methanol (1 mL) was added dropwise a solution of **1d** (121 mg, 0.422 mmol) in methanol (1 mL). After 10 min, completion of the reaction was confirmed by TLC. The mixture was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel (hexane–EtOAc, 5:1 to 2:1) to afford **5d** (111 mg, 97%). IR (KBr): 3422, 2953, 1720, 1541, 1252, 1092 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.17 (5 H, m), 5.44 (1 H, br d, *J* = 8.4 Hz), 4.72 (1 H, d, *J* = 12.3 Hz), 4.66 (1 H, d, *J* = 12.3 Hz), 4.03–3.91 (1 H, m), 3.75–3.64 (1 H, m), 3.63–3.51 (1 H, m), 2.89 (2 H, d, *J* = 6.9 Hz), 2.52–2.38 (1 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.5, 137.3, 129.2, 128.6, 126.7, 95.5, 74.4, 63.4, 54.2, 37.2. HRMS (ESI): *m/z* calcd for $C_{12}H_{14}Cl_3NNaO_3$ $[M + Na]^+$: 347.9937; found: 347.9948.

(16) Under similar conditions using *N*-(2,2,2-trichloroethoxycarbonyloxy)succinimide (Troc-OSu) or 2,2-trichloroethoxycarbonyl chloride (TrocCl), **5d** was obtained 93% or 27% yield, respectively.

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