ORGANIC LETTERS

2008
Vol. 10, No. 12
2601−2604

(1-Nosyl-5-nitroindol-3-yl)methyl Ester: A Novel Protective Group for Carboxylic Acids

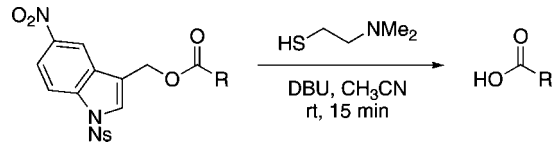
Takuya Nishimura, Kouhei Yamada, Tohru Takebe, Satoshi Yokoshima, and Tohru Fukuyama*

Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

fukuyama@mol.f.u-tokyo.ac.jp

Received April 15, 2008

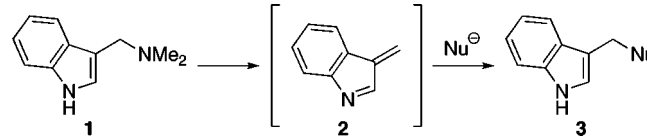
ABSTRACT



The usefulness of (1-nosyl-5-nitroindol-3-yl)methyl esters as a novel protective group for carboxylic acid is fully demonstrated. The novel protective group is stable under a broad range of conditions and can easily be deprotected under the mild conditions used for removal of the nosyl (Ns) group. It is orthogonal to the existing protective groups for carboxylic acids such as *t*-butyl and allyl esters.

Indole is known to show a variety of reactivities due to its electron-rich 10π-electron system.[1] *N*,*N*-Dimethyl-(1*H*-indol-3-yl)methylamine (**1**), also known as gramine, is a useful unit to synthesize 3-substituted indoles. Reactions of gramine or its methiodide with nucleophiles, such as cyanides, malonates, nitroalkanes, or boronic acid, proceed via the elimination of the dimethylamine or trimethylamine and subsequent addition to the resulting intermediate **2** to give the corresponding "substitution" product **3** (Scheme 1).[2] We reasoned that introduction of an electron-withdrawing group on the indole nitrogen would substantially slow down the elimination process. This led us to develop a novel protective method for carboxylic acids as (indol-3-yl)methyl esters.

Scheme 1. Reaction of Gramine



We first prepared a model compound **4a** and tested its potential as a protective group for carboxylic acids (Scheme 2). 2-Nitrobenzensulfonyl (Ns) group,[3] which can be removed under mild conditions such as exposure to thiolates, was selected as the electron-withdrawing group on the indole nitrogen. As expected, subjection of **4a** to the standard conditions for cleaving the Ns group gave the corresponding carboxylic acid **6a** in good yield. In addition, 3-(phenylthi-

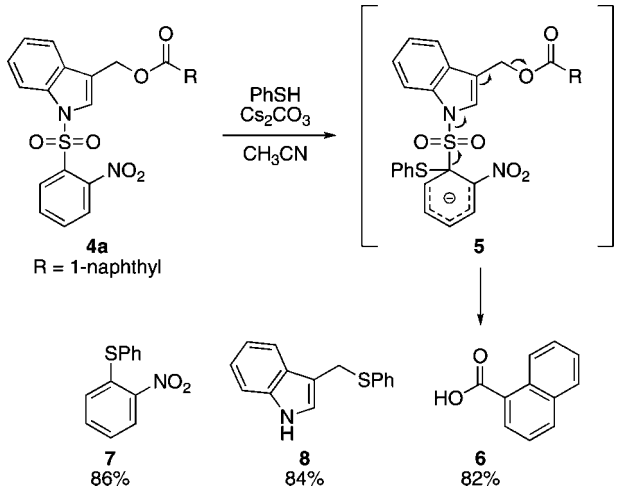
(1) (a) For recent representative reviews, see: Joule, J. A. In *Science of Synthesis*; Thomas, E. J., Ed.; Georg Thieme Verlag: Stuttgart, 2000; pp 361−652. (b) Jones, G. B.; Chapman, B. J.; Black, D. St. C.; Sundberg, R. J.; Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F., Eds.; Pergamon, Elsevier Science Ltd: Oxford, 1996; pp 1−258..

(2) (a) For recent examples of gramines, see: Artman, G. D., III; Grubbs, A. W.; Williams, R. M. *J. Am. Chem. Soc.* **2007**, *129*, 6336. (b) de la Herrán, G.; Segura, A.; Csáky, A. G. *Org. Lett.* **2007**, *9*, 961. (c) Wada, Y.; Nagasaki, H.; Tokuda, M.; Orito, K. *J. Org. Chem.* **2007**, *72*, 2008. (d) Jones, D. T.; Artman, G. D., III; Williams, R. M. *Tetrahedron Lett.* **2007**, *48*, 1291. (e) Grubbs, A. W.; Artman, G. D., III; Tsukamoto, S.; Williams, R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2257. (f) Shchekotikhin, A. E.; Dezhenkova, L. G.; Susova, O. Y.; Glazunova, V. A.; Luzikov, Y. N.; Sinkevich, Y. B.; Buyanov, V. N.; Shtil, A. A.; Preobrazhenskaya, M. N. *Bioorg. Med. Chem.* **2007**, *15*, 2651. (g) Attia, M. I.; Güclü, D.; Hertlein, B.; Julius, J.; Witt-Enderby, P. A.; Zlotos, D. P. *Org. Biomol. Chem* **2007**, *5*, 2129.

(3) (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. (b) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353. (c) Kan, T.; Fukuyama, T. *J. Synth. Org. Chem., Jpn.* **2001**, *59*, 779.

10.1021/ol8008655 CCC: $40.75
Published on Web 05/17/2008

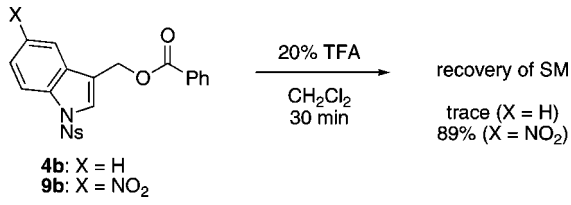
Scheme 2. Attempted Cleavage of Indol-3-ylmethyl Ester



omethyl)indole (**8**) was also isolated, which might be formed via a reaction of the intermediate **2** with thiophenol.

Although the high reactivity of (1-Ns-indol-3-yl)methyl ester to liberate the corresponding carboxylic acid was confirmed, it turned out that the ester is too labile under acidic conditions to serve as a good protecting group. Upon treatment with trifluoroacetic acid, for example, only a trace amount of **4b** could be recovered (Scheme 3). To increase

Scheme 3. Stability of the Esters under Acidic Conditions

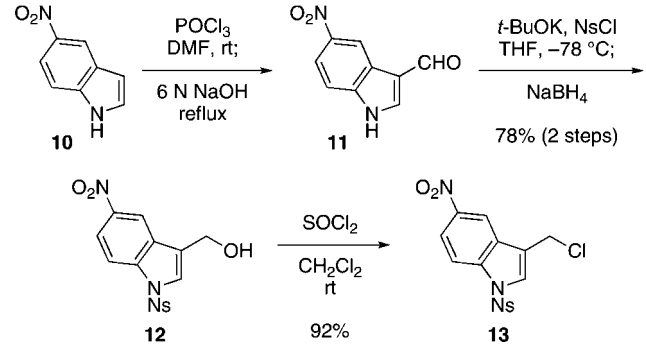


the stability under acidic conditions, we attempted to introduce an additional electron-withdrawing group[4] and found that a nitro group at the 5-position of indole greatly increased the stability of the corresponding ester. Under the aforementioned acidic conditions, **9b** was recovered in 89% yield. Hence, we decided to employ the (1-Ns-5-nitroindol-3yl)methyl group as a protective group for carboxylic acids.

(1-Ns-5-Nitroindol-3-yl)methyl esters can be prepared either by condensation with alcohol or by alkylation, as described below. Preparation of the requisite alcohol **12** and chloride **13** is shown in Scheme 4. Commercially available 5-nitroindole (**10**) was subjected to the Vilsmeier reaction to give formylindole **11**.[5] Introduction of the Ns group on the indole nitrogen followed by reduction with $NaBH_4$ afforded (1-Ns-5-nitroindol-3yl)methanol (**12**) in good yield

(4) Schwarz, H.; Arakawa, K. *J. Am. Chem. Soc.* **1959**, *81*, 5691.
(5) Noland, W. W.; Rieke, R. D. *J. Org. Chem.* **1962**, *27*, 2250.

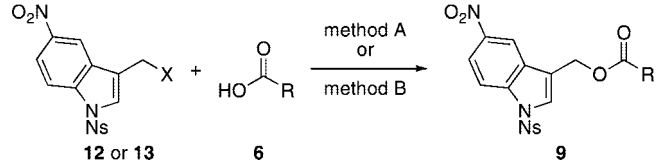
Scheme 4. Preparation of Alcohol **12** and Chloride **13**

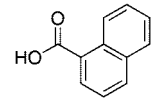
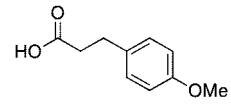
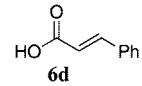
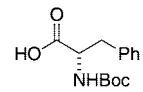


without any chromatographic separations. Alcohol **12** was readily transformed into its chloride **13** by treatment with thionyl chloride.

The esters of aryl, aliphatic, α,β-unsaturated, and α-amino caboxylic acids with alcohol **12** were prepared by treatment with EDCI and a catalytic amount of DMAP in dichloromethane (Table 1, method A). Alkylation of the carboxylic acids with chloride **13** also proceeded in the presence of

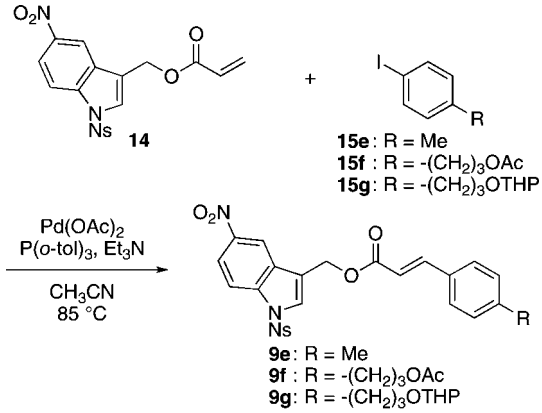
Table 1. Preparation of (1-Ns-5-nitroindol-3-yl)methyl Esters[a]



entry	carboxylic acid	product	yield (%) method A	yield (%) method B
1	 6a	**9a**	64	93
2	 6b	**9b**	88	90
3	 6c	**9c**	90	98
4	 6d	**9d**	83	99
5	 6h	**9h**	84	96

[a] Method A: **12** (X = OH, 1.2 equiv), EDCI (1.5 equiv), DMAP (cat), CH_2Cl_2. Method B: **13** (X = Cl, 1.2 equiv), Cs_2CO_3 (3.0 equiv), NaI (3.0 equiv), CH_3CN, 40 °C.

Scheme 5. Heck Reaction

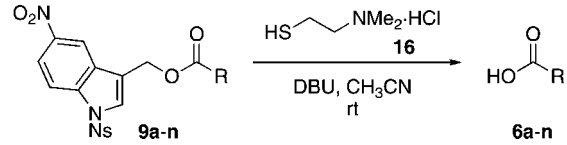


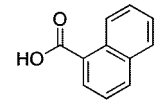
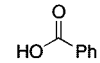
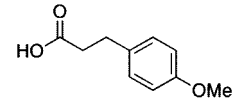
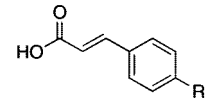
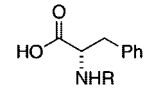
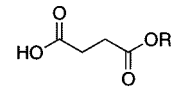
cesium carbonate and sodium iodide in acetonitrile to furnish the corresponding (1-Ns-5-nitroindol-3yl)methyl esters in good yields (method B). In addition, we found that acrylate **14** is a suitable substrate for the Mizoroki−Heck reaction.[6,7] Treatment with aryl iodide **15e**−**g** under the standard conditions furnished the corresponding α,β-unsaturated esters **9e**−**g** in moderate to high yields (Scheme 5).

With a variety of (1-Ns-5-nitroindol-3-yl)methyl esters in hand, we next tried to cleave the esters.[8] Upon treatment with 2-(dimethylamino)ethanethiol hydrochloride (**16**, 2 eq) and DBU (4 eq) in acetonitrile at room temperature, the esters underwent a facile cleavage of the Ns group to give the deprotected carboxylic acids by way of elimination. The whole process was completed within 15 min. As shown in Scheme 2, two byproducts **7** and **8**, which arose from the Ns group and the indole core, respectively, were obtained in the deprotection with thiophenol. Using aminothiol **16** as a nucleophile, all the byproducts and the reagents can easily be removed by washing with aqueous hydrochloric acid, leaving the practically pure carboxylic acids in the organic phase.

The cleavage of the aryl, aliphatic, and α,β-unsaturated esters proceeded in good yields (Table 2, entries 1−7). The deprotection of the α,β-unsaturated esters occurred without forming the Michael adducts. A variety of protective groups, such as Ac, THP, Boc, Alloc, and Cbz, remained intact under these conditions (entries 6−10). Racemization of amino acids was not observed during the deprotection.[9] Although the base-labile Fmoc group did not tolerate the above conditions, treating **9k** with thiophenol and potassium carbonate in acetonitrile gave the desired product in good yield (entry 11). Typical esters of carboxylic acids, including *t*-butyl, allyl, and benzyl esters, were also stable under these conditions (entries 12−14).

Table 2. Cleavage of (1-Ns-5-nitroindol-3-yl)methyl Esters[a]



entry	substrate	product	yield (%)
1	**9a**	 **6a**	99
2	**9b**	 **6b**	quant
3	**9c**	 **6c**	95
			
4	**9d**	**6d**: R = H	95
5	**9e**	**6e**: R = Me	quant
6	**9f**	**6f**: R = $(CH_2)_3OAc$	96
7	**9g**	**6g**: R = $(CH_2)_3OTHP$	92
			
8	**9h**	**6h**: R = Boc	88
9	**9i**	**6i**: R = Alloc	92
10	**9j**	**6j**: R = Cbz	quant
11	**9k**	**6k**: R = Fmoc	96[b]
			
12	**9l**	**6l**: R = *t*-Bu	89
13	**9m**	**6m**: R = Allyl	86
14	**9n**	**6n**: R = Bn	quant

[a] Reaction conditions: $HSCH_2CH_2NMe_2$·HCl (2.1 equiv), DBU (4.2 equiv), CH_3CN, rt. [b] PhSH (2.0 equiv), K_2CO_3 (3.0 equiv), CH_3CN, rt.

Next, we examined the stability of (1-Ns-5-nitroindol-3-yl)methyl esters. Removal of the protective groups on nitrogen, such as Boc, Alloc, and Fmoc, could be conducted under the standard conditions (Table 3, entries 1, 2 and 4).[10] Additionally, the Cbz group was also removed by treatment

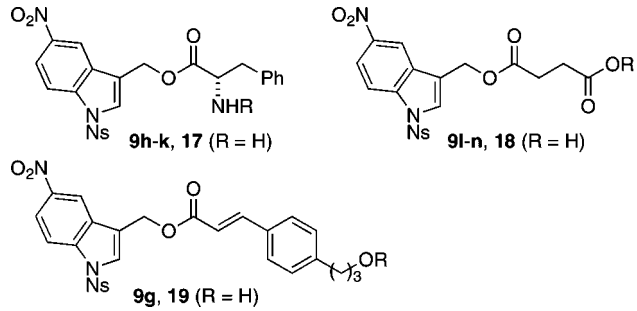
(6) (a) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (b) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320.

(7) Ester **14** was prepared by a reaction of **12** with acryloyl chloride.

(8) Esters **9i**−**k** were prepared by condensation of the corresponding carboxylic acids with **12** or by acylation of amine **17**. On the other hand, Esters **9l**−**n** were obtained by reaction of **12** with succinic anhydride, followed by esterification of the resulting carboxylic acid. For experimental details, see the Supporting Information.

(9) The optical purity of the product **6j** was determined as 99% ee by HPLC (CHIRALCEL OD, hexane/2-propanol = 90:10, 1.0 mL/min) after transformation into its methyl ester ($SOCl_2$, MeOH, rt).

Table 3. Compatibility of (1-Ns-5-nitroindol-3-yl)methyl Esters [a]

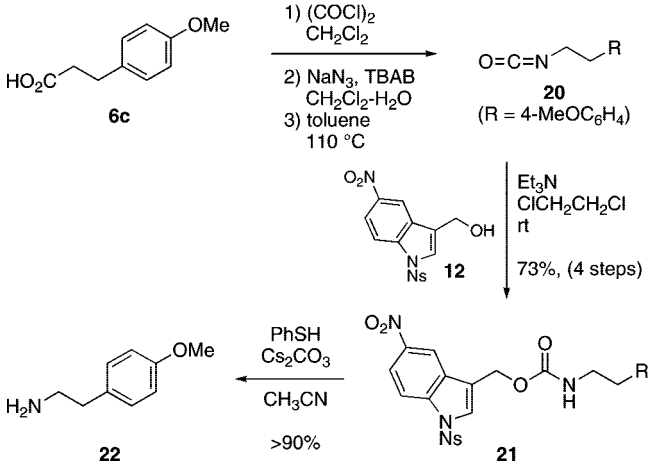


entry	substrate	conditions	product	yield (%)
1	**9h**: R = Boc	20% TFA CH_2Cl_2	**17**	91
2	**9i**: R = Alloc	$Pd(PPh_3)_4$ $TMSNEt_2$ CH_2Cl_2	**17**	87
3	**9j**: R = Cbz	TMSCl, NaI CH_3CN	**17**	86
4	**9k**: R = Fmoc	20% piperidine DMF	**17**	90
5	**9l**: R = *t*-Bu	HCO_2H	**18**	98
6	**9m**: R = Allyl	$Pd(PPh_3)_4$ Pyrrolidine CH_3CN	**18**	71
7	**9n**: R = Bn	–	–	–[b]
8	**9g**: R = THP	CSA MeOH-CH_2Cl_2	**19**	quant

[a] Reactions were performed under the conditions provided in the Table. [b] The desired product was not obtained.

with TMSCl and sodium iodide in acetonitrile without using hydrogenolysis conditions (entry 3).[11] Although selective cleavage of benzyl ester could not be achieved even by employing Lewis acids, *t*-butyl and allyl esters were cleaved under the typical conditions (entries 5−7). On the other hand, a THP ether was easily removed by treatment with CSA in methanol (entry 8).

Scheme 6



For further application of (1-Ns-5-nitroindol-3-yl)methanol, trapping an isocyanate was attempted. Reaction of isocyanate **20**, derived from carboxylic acid **6c**, with (1-Ns-5-nitroindol-3-yl)methanol (**12**) proceeded to furnish carbamate **21** in good yield. Upon treatment with thiolate, the carbamate was smoothly cleaved to generate the corresponding amine **22**, which was isolated in good yield as its Boc amide (Scheme 6).

In summary, we have demonstrated the utility of (1-Ns-5-nitroindol-3-yl)methyl esters as a novel protective method for carboxylic acids. Cleavage of the Ns group under mild conditions liberated the corresponding carboxylic acids in excellent yields. This novel protective group is stable under acidic or basic conditions and is orthogonal to existing protective groups for carboxylic acid, such as *t*-butyl and allyl esters.

Acknowledgment. This work was financially supported in part by a Grant-in-Aid (15109001, 16073205 and 19590004) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8008655

(10) Merzouk, A.; Guibé, F.; Loffet, A. *Tetrahedron Lett.* **1992**, *477*, 35.

(11) Jung, M. E.; Lyster, M. A. *J. Chem. Soc., Chem. Commun.* **1978**, 315.