Light-Sensitive Protecting Groups for Amines and Alcohols: The Photosolvolysis of N-Substituted 7-Nitroindolines

Alfred Hassner,*[a] Diana Yagudayev,[a] Tarun K. Pradhan,[a] Abraham Nudelman,[a] Boaz Amit[b]

[a] Department of Chemistry, Bar-Ilan University, Ramat-Gan 52900, Israel
Fax +972(3)7384053; E-mail: hassna@mail.biu.ac.il

[b] ProChon Biotech Ltd., Weizmann Science Park, Nes Ziona, 70400, Israel

Received 6 June 2007

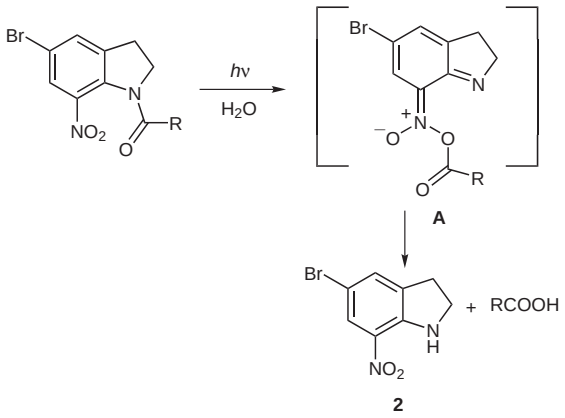
Abstract: Representative examples of primary and secondary amines were protected as urea derivatives **4** of 5-bromo-7-nitroindoline and even more efficiently as ureas **8** derived from 5,7-dinitroindoline, via high-yield reactions with carbamoyl chlorides **3** and **7**, respectively. Deprotection of **4** or **8** was achieved in high yields by UV irradiation at room temperature in Pyrex vessels under neutral conditions and exclusion of air. In a similar manner the dinitroindolines serve as protecting groups for alcohols and phenols; the derived carbamates **5** and **9** can likewise be deprotected photochemically in high yields.

Key words: alcohols, amines, protecting groups, photochemistry, ureas, carbamates, indolines

Facile protection and deprotection of functional groups are important steps in synthesis and manipulation of synthetic organic compounds and natural products. Frequently, only the proper selection of protecting groups combined with a good synthetic strategy can lead to a successful total synthesis.[1] Among various protecting groups, photochemical deprotection offers the important advantage of neutral conditions and absence of chemical reagents.[2]

In 1973, Amit and Patchornik reported the photolysis of amides, derived from N-substituted *o*-nitroanilides, to furnish free carboxylic acids in high yields.[3] The photocleavage of the above amides formally follows the known photoreduction reactions of aromatic nitro compounds bearing substituents at the *ortho* position, where an oxygen atom is transferred from the nitro group to the *ortho* substituents.[4] As a result of this rearrangement to the oxygenated *ortho* substituent, *o*-nitrosoaniline and often other photo side products were formed, which can interfere with the isolation and purity of the product. To improve the outcome of the photolysis, another light-sensitive protecting group of carboxylic acids was developed.[5] UV irradiation of amides, derived from 5-bromo-7-nitroindoline, in the presence of water, furnished the free carboxylic acids and the starting nitroindolines in good yields, as shown in Scheme 1.

By contrast with *o*-nitroanilides, the 7-nitroindoline amides were cleaved by photosolvolysis. Undeniably, the excited 7-nitro group activates the amide bond to nucleophilic attack. However, unlike *o*-nitrobenzyl derivatives, the photochemistry of the 7-nitroindoline group appears to involve hydrolysis of a very reactive acyl nitronate intermediate **A**[6–8] in the presence of water (Scheme 1). To achieve an efficient synthesis of the required 7-nitroindolines and to ensure regioselective nitration at the C-7 position, it is common to have a substituent at C-5, (usually Br, CH_2CO_2R, or NO_2), and in some cases also a methoxy group at C-4.[8]



Scheme 1

Over the years 5-bromo-7-nitroindoline (BNI) has been used in a wide range of reactions including peptide synthesis.[9] Corrie et al. used the BNI group as a photocleavable (caged) precursor for releasing of neuroactive amino acids, such as L-glutamate, in neutral aqueous solution.[10] Furthermore, Corrie's group examined the mechanism of photolysis of *N*-acyl-7-nitroindolines and the finding that in aqueous solution the photoproduct was 7-nitrosoindole, implying a change in mechanism.[6,11] Nicolaou et al.[7] carried out the photocleavage of the carboxyl functionality in the presence of primary and secondary amines, which led to amides in high yields. They also demonstrated for the first time an intramolecular photo-induced cyclorelease with a number of resins based on BNI urea derivatives.[7] Bochet et al.[8] described a photochemical protection of amines as amides or as carbamates in neutral medium using 7-dinitroindolines as substrates. Despite this comprehensive research and development in the use of the photocleavable 7-nitroindoline group, its use was focused mostly on protecting and/or activating the carboxylic acid function.

SYNLETT 2007, No. 15, pp 2405–2409
Advanced online publication: 13.08.2007
DOI: 10.1055/s-2007-985580; Art ID: G18107ST

Amino functions are generally protected by conversion into amides and carbamates, which often do not provide sufficient resistance to basic or acidic reaction conditions. Therefore a stronger bond, such as found in ureas, would be advantageous as a protecting group for the amino moiety. On the other hand, the stability of ureas towards solvolytic conditions requires the use of rather vigorous conditions for its chemical cleavage. Hence, photolytic cleavage of ureas would provide a specific and mild method for their deprotection under neutral conditions. This may be of particular importance in photoresists or UV curing of polymers.[12] Except for the study by Nicolaou et al.,[7] using diamines, there have been no attempts for protection and deprotection of simple amines via urea derivatives. Furthermore, there apparently are no comprehensive reports where 7-nitroindoline carbamates were used as photolabile protecting groups of alcohols.

We describe herein the efficient use of the 7-nitroindoline group as a photocleavable protecting group of amines or alcohols, under neutral conditions, via urea or carbamate derivatives, respectively.

Initial studies to obtain BNI ureas **4** from corresponding carbamates **5** by reaction with amines were disappointing. When we tried direct functionalization of BNI **2** under mild conditions by means of 4-nitrophenyl chloroformate at room temperature mainly starting material was obtained.[13] This is apparently because the 7-nitro substituent diminishes reactivity at the indoline N, both by electron withdrawal and steric hindrance. This was also apparent by the fact that carbamate **5a**, which we finally obtained by reaction of 5-bromoindoline with 4-nitrophenyl chloroformate, followed by nitration, reacted only sluggishly with benzylamine. Since subsequent nitration of carbamates or ureas derived from 5-bromoindoline is not a desirable pathway for protection of alcohols or amines, we adopted carbamoyl chloride **3** as our starting point for the preparation of ureas **4** (see Scheme 2), in spite of the fact that reaction of **3** with ethylene diamine[7] required 50 equivalents of the diamine.

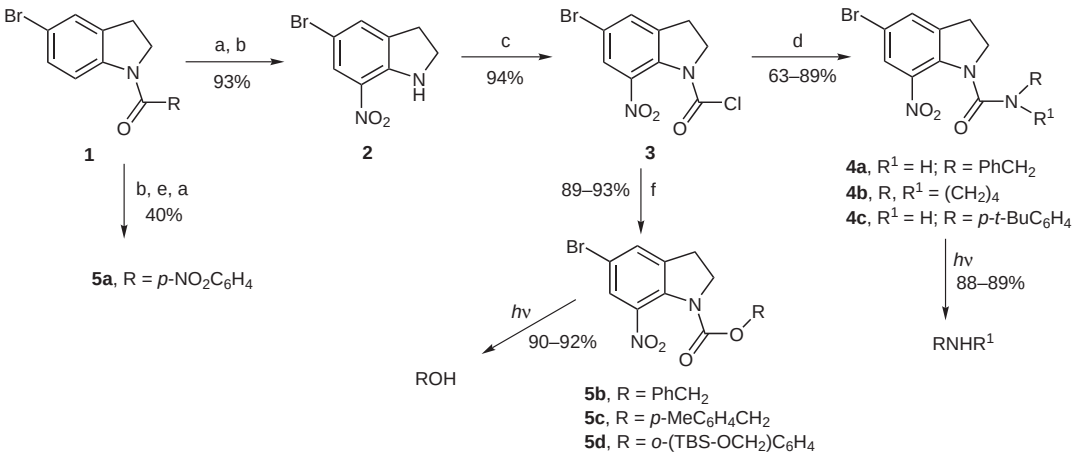
First, the BNI group **2**, prepared by hydrolysis of *N*-acetyl-5-bromoindoline **1**,[3] was coupled via its carbamoyl chloride **3** with amines and alcohols (Scheme 2). The urea derivatives **4a** and **4b** were obtained in good yields (Scheme 2, Table 1) from benzylamine and pyrrolidine, respectively, and we were able to cut down significantly the amounts of amine and DMAP to 10 equivalents. Still the aromatic amine, *p-tert*-butylaniline, was not nucleophilic enough to react with **3** and had to be converted first into its amide anion by means of *n*-BuLi. Ureas **4** were stable to dilute acid or base at room temperature.

The carbamate derivatives **5a**–**d** were synthesized in over 90% yield by reaction of **3** with 2 equivalents of alcohols by the same method as the urea derivatives **4** (Scheme 2, Table 1).

Photolysis of ureas **4a**–**c**, first attempted as reported[3] for amides **1**, in a Rayonet apparatus with 350 nm lamps, required several days. Much more efficient for us was a 150 W UV Hanau lamp, placing the samples in Pyrex tubes approximately 1–1.5 cm from the UV lamp. Furthermore, removal of air prior to the irradiation was important and was carried out by bubbling argon for one hour into the solution of the urea in degassed dichloromethane–dioxane–water ($8\cdot10^{-2}$ M). The photoreactions were monitored by UV, since the product BNI **2** displays a maximum at much longer wavelengths (ca. 440 nm) than the parent ureas or carbamates (ca. 360 nm) as shown in Figure 1 and Figure 2.

After the irradiation, the products were purified by chromatography to furnish indoline **2** (no nitroso product was detected) and the free amines RNR^1H or alcohols ROH in high yields as shown in Table 1. Photolysis of carbamates **5** required less time (7–9 h) than photolysis of ureas **4** (12–14 h).

Though we had been able to scale down the large excess of amine as well as of DMAP from 50 to 10 equivalents in the synthesis of the ureas **4**, we felt that the more electron-poor and more readily prepared 5,7-dinitroindoline **6**[13] may offer an advantage. Indeed, reaction of the acid



Scheme 2 *Reagents*: (a) $NaNO_3$, TFA; (b) 20% HCl, MeOH; (c) triphosgene, pyridine, CH_2Cl_2; (d) RR^1NH, CH_2Cl_2, 4-DMAP or BuLi; (e) $ClCOOC_6H_4NO_2$; (f) ROH, CH_2Cl_2, 4-DMAP.

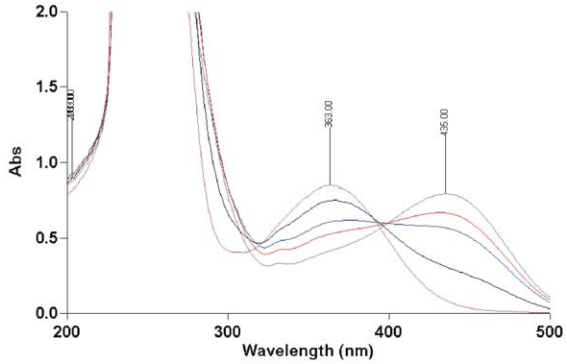


Figure 1 UV Spectra of the irradiation product of urea **4** at various reaction times ($2.6 \cdot 10^{-5}$ M, CH_2Cl_2).

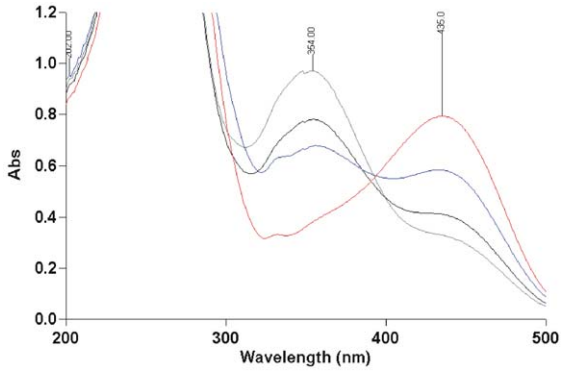


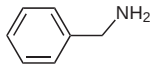
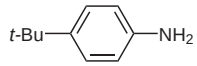
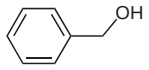
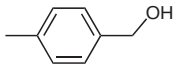
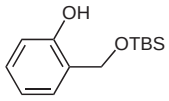
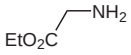
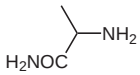
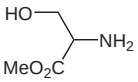
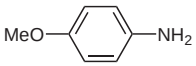
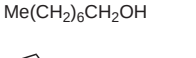
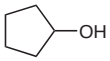
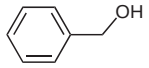
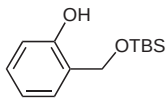
Figure 2 UV Spectra of the irradiation product of carbamate **5** at various reaction times ($2.6 \cdot 10^{-5}$ M, CH_2Cl_2).

chloride **7**, the analogue of **3** synthesized from **6** and triphosgene, proceeded readily with a number of amines, including amino acid derivatives, requiring only 1 equivalent of amine and 1.5–2.5 equivalents of DMAP and producing ureas **8a**–**e** in high yield (Scheme 3, Table 1). The reaction proceeded even with an aromatic amine (*p*-methoxyaniline) without requiring conversion into its lithio derivative. In a similar manner we obtained carbamates **9a**–**d** by reaction of a number of alcohols and a phenol in high yield. It is noteworthy that the amino alcohol, serine methyl ester, furnished exclusively the urea derivative **8c** via reaction of the more nucleophilic amine.

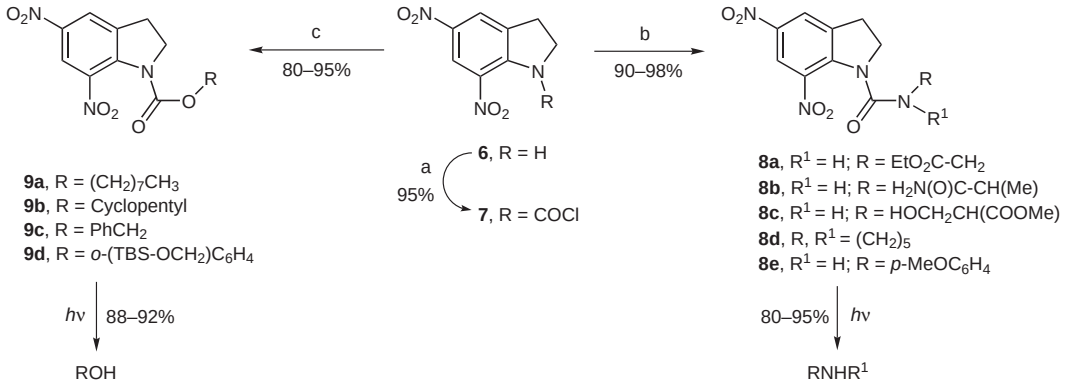
Photocleavage of the 5,7-dinitroindoline ureas **8a**–**e** and carbamates **9a**–**d** proceeded under neutral conditions at room temperature for 2–7 h in Pyrex tubes in the presence of water and was followed by UV as described for analogues **4** and **5** to provide pure free amines and alcohols, respectively, in excellent yields (see Table 1). Furthermore, the photolysis of the 5,7-dinitro derivatives required less time than for the 5-bromo-7-nitro derivatives.

In conclusion, the 5-bromo-7-nitroindoline moiety **2** was successfully used to protect primary and secondary aliphatic amines and an aromatic amine, in good yields, as urea derivatives **5**. Deprotection of **4** was achieved photochemicaly in high yield at room temperature in Pyrex vessels under neutral conditions and exclusion of air. In a similar manner protection and deprotection of alcohols was carried out via carbamates **5**. However, since formation of the urea derivatives **4** necessitated 10 equivalents of the amine, a more efficient protecting group was found to be 5,7-dinitroindoline **7**, which required only one

Table 1 Synthesis and Photolysis of **4**, **5**, **8**, and **9** by Protection and Photodeprotection of Amines and Alcohols in the Presence of Water at Room Temperature[a]

Protection			Deprotection (*hv*)	
Compound	PR^1NH or ROH	Yield (%)	Time (h)	Yield (RNR^1H or ROH)
4a		89	13	89
4b		87	12	88
4c		63	14	88
5b		93	8	90
5c		91	9	90
5d		89	7	92
8a		98	5	95
8b		96	5	93
8c		95	6	90
8d		90	4	87
8e		87	7	80
9a		80	3	92
9b		87	3	90
9c		85	2	88
9d		95	2	90

[a] Compounds **4** were prepared using 10 equiv of amine, **5** using 2 equiv of alcohol, while for **8** or **9** 1 equiv of amine or alcohol was used.



Scheme 3 *Reagents*: (a) triphosgene, pyridine, CH_2Cl_2; (b) RR^1NH, 4-DMAP, CH_2Cl_2; (c) ROH, 4-DMAP, CH_2Cl_2.

equivalent of amine. In this manner 5,7-dinitroindoline urea and carbamate derivatives **8** and **9** were readily prepared. Photolysis of ureas **8** and carbamates **9** furnished free amines, amino acid derivatives, and alcohols, respectively, in high yield under mild and neutral conditions.

5-Bromo-7-nitroindoline-1-carbonyl Chloride (3)

To a solution of nitroindoline **2** (1.00 g, 4.1 mmol) and pyridine (0.66 mL, 2 equiv) in CH_2Cl_2 (15 mL) at 0 °C, triphosgene (0.40 g, 1/3 equiv) was added. The mixture was then allowed to warm to r.t. for ca. 30 min and was washed with 1 N HCl, diluted with CH_2Cl_2, dried over $MgSO_4$, and concentrated to give **3** as an orange powder (1.18 g, 94% yield), mp 121–122 °C. ^{1}H NMR ($CDCl_3$): δ = 7.75 (m, 1 H), 7.53 (m, 1 H), 4.40 (t, *J* = 5.9 Hz, 2 H), 3.20 (t, *J* = 5.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ = 146.8, 139.1, 132.6, 132.6, 132.36, 125.9, 118.2, 53.3, 28. Due to the high moisture sensitivity of **3**, no HRMS was obtained.

General Procedure for the Synthesis of Ureas 4

To a solution of **3** (1.10 g, 3.6 mmol) in CH_2Cl_2 (15 mL), amine (10 equiv), and 4-DMAP (10 equiv) were added and the mixture was stirred in the dark overnight at r.t. It was then washed with 3% HCl and 3% $NaHCO_3$ solution, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated in vacuo. The residue was crystallized from $CHCl_3$ to get pure compound **4**.

1-(Benzylcarbamoyl)-5-bromo-7-nitroindoline (4a)

Synthesized from **3** and benzylamine in 89% yield; mp 182–183 °C. ^{1}H NMR ($CDCl_3$): δ = 7.82 (m, 1 H), 7.46 (m, 1 H), 7.36–7.31 (m, 5 H), 5.02 (br s, 1 H, NH), 4.48 (d, *J* = 6.5 Hz, 2 H), 4.13 (t, *J* = 8.1 Hz, 2 H), 3.24 (t, *J* = 8.1 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ = 161.3, 142.4, 142.2, 138.3, 131.7, 128.9, 127.9, 127.84, 125.8, 120.5, 50.58, 45, 28.8. HRMS: *m/z* calcd for $C_{16}H_{14}BrN_3O_3$: 375.0232; found: 375.023 $[M]^+$.

General Procedure for the Synthesis of Carbamates 5

To a solution of **3** (1.10 g, 3.6 mmol) in CH_2Cl_2 (15 mL), alcohol (2 equiv), and 4-DMAP (2 equiv) were added and the reaction mixture was left in the dark overnight at r.t. It was then washed with 3% HCl and 3% $NaHCO_3$ solution, extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated.

1-Benzyloxycarbonyl-5-bromo-7-nitroindoline (5b)

Synthesized from **3** and benzyl alcohol. The crude carbamate was chromatographed on silica gel (EtOAc–hexane, 7:1) to get **5b** as a yellow oil (93% yield). ^{1}H NMR ($CDCl_3$): δ = 7.76 (m, 1 H), 7.49 (m, 1 H), 7.38–7.34 (m, 5 H), 5.19 (s, 2 H, CH_2O), 4.24 (t, *J* = 7.7 Hz, 2 H, CH_2N), 3.15 (t, *J* = 7.7 Hz, 2 H, CH_2CH_2N). ^{13}C NMR ($CDCl_3$): δ = 154.1, 143.5, 139.9, 136.5, 135.1, 130.3, 128.5, 127.9, 127.6, 123.4, 116.5, 65.9, 45.6, 24.3. HRMS: *m/z* calcd for $C_{16}H_{13}BrN_2O_4$: 377.1921; found: 377.191 $[M]^+$.

5,7-Dinitroindoline-1-carbonyl Chloride (7)

A solution of dinitroindoline **6**[8] (1.05 g, 5 mmol), pyridine (0.8 mL, 10 mmol), and triphosgene (1 g, 5 mmol) in anhyd CH_2Cl_2 (50 mL) was stirred for 24 h at r.t. The mixture was washed with 5% HCl (3 × 30 mL), H_2O, and dried (Na_2SO_4). The residue left after removal of solvent under reduced pressure was sufficiently pure for the next step. Yield 95%; mp 158–159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 1.8 Hz, 1 H), 8.28 (d, *J* = 1.8 Hz, 1 H), 4.59 (t, *J* = 8.4 Hz, 2 H, CH_2N), 3.44 (t, *J* = 8.4 Hz, 2 H, CH_2CH_2). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 147.0, 143.8, 139.4, 139.4, 138.0, 124.0, 120.0, 53.8, 27.9. HRMS (CI, CH_4): *m/z* (%) calcd for $C_9H_6ClN_3O_5$: 271.000; found: 270.998 (82) $[M]^+$, 209.023 (100) $[MH - COCl]^+$.

General Procedure for the Synthesis of Dinitrocarbamates 8

An amine (1 equiv) was added to the stirred mixture of **7** (1 equiv) and 4-DMAP (1.5–2.5 equiv) in anhyd CH_2Cl_2. The mixture was stirred at r.t. for 1–5 h, then washed with 5% HCl solution, H_2O, and dried (Na_2SO_4).

2-[(1-Carbamoyl-5,7-dinitroindoline)]-3-hydroxypropionic Acid Methyl Ester (8c)

Synthesized from L-serine methyl ester hydrochloride (1.55 g, 10 mmol), compound **7** (2.71 g, 10 mmol), and 4-DMAP (3 g, 25 mmol) in anhyd CH_2Cl_2 (30 mL). The residue after removal of solvent afforded pure **8c** in 95% yield; mp 169 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ = 8.46 (d, *J* = 2.4 Hz, 1 H), 8.30–8.29 (m, 1 H), 6.95 (d, *J* = 7.8 Hz, 1 H, NHCH), 4.57–4.42 (m, 3 H), 4.29 (s, 1 H, OH), 3.97 (dd, *J* = 11.0, 4.5 Hz, 1 H, CH_2O), 3.87 (dd, *J* = 11.0, 4.5 Hz, 1 H, CH_2O), 3.71 (s, 3 H, CH_3O), 3.50–3.41 (m, 2 H, CH_2CH_2). ^{13}C NMR (300 MHz, acetone-d_6): δ = 171.5, 155.4, 143.3, 142.5, 139.6, 137.9, 123.9, 120.4, 62.9, 57.1, 52.5, 52.2, 28.7. HRMS (CI, CH_4): *m/z* (%) calcd for $C_{13}H_{14}N_4O_8$: 354.081; found: 355.087 (12) $[MH]^+$.

General Procedure for the Synthesis of Dinitrocarbamates 9

A respective alcohol (1 equiv) was added to the stirred solution of **7** (1 equiv) and 4-DMAP (1.2 equiv) in anhyd CH_2Cl_2. The mixture was stirred at r.t. for 3–8 h, then washed with 5% HCl solution, H_2O, and dried (Na_2SO_4).

5,7-Dinitroindoline-1-carboxylic Acid 2-(*tert*-Butyldimethylsilanyloxymethyl)phenyl Ester (9d)

Synthesized from 2-(*tert*-butyldimethylsilanyloxy-methyl)phenol[14] (2.38 g, 10 mmol), **7** (2.71 g, 10 mmol), and 4-DMAP (1.46 g, 12 mmol) in anhyd CH_2Cl_2 (30 mL) at r.t. for 3 h. The residue afforded after removal of solvent pure **9d** in 95% yield; mp 161–162 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 1.5 Hz, 1 H), 8.28 (d, *J* = 1.5 Hz, 1 H), 7.54–7.51 (m, 1 H), 7.33–7.26 (m, 2 H), 7.16–7.12 (m, 1 H), 4.73 (s, 2 H, CH_2O), 4.57 (t, *J* = 8.4 Hz, 2 H, CH_2N), 3.41 (t, *J* = 8.4 Hz, 2 H, CH_2CH_2), 0.91 (s, 9 H, CCH_3), 0.084 (s, 6 H, $SiCH_3$). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 150.8, 147.4, 143.3, 140.2, 138.3, 133.2, 128.2, 128.2, 126.7, 123.5, 123.3, 121.6, 120.2, 60.4, 50.8, 28.1, 25.8, 18.3, –5.3. HRMS (CI, CH_4): *m/z* (%) calcd for $C_{22}H_{27}N_3O_7Si$: 473.162; found: 473.168 (13) $[M]^+$, 416.091 (66) $[M - {}^tBu]^+$.

General Procedure for Deprotection of Urea and Carbamate Derivatives 4, 5, 8, or 9 by Irradiation

The respective carbamate or urea derivative (300–400 mg) in CH_2Cl_2–dioxane–H_2O (5:10:1) at a concentration of $8 \cdot 10^{-2}$ M was deoxygenated by bubbling argon into the mixture for 1 h followed by irradiation at r.t. with a 150 W UV Hanau lamp in Pyrex tubes at a distance of 1–1.5 cm from the UV lamp for the time indicated in Table 1. Free amines, alcohols, and nitroindolines (no nitrosoindole derivatives were observed) were isolated by silica gel chromatography of the crude products, after removal of solvent under reduced pressure, and identified by comparison with authentic compounds.

Acknowledgment

Support of this research by the Marcus Center for Medicinal and Pharmaceutical Chemistry at Bar-Ilan University is gratefully acknowledged.

References and Notes

(1) (a) Kocienski, P. J. *Protecting Groups*, 3rd ed.; Thieme: New York, **2004**. (b) Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, **1999**, 369. (c) Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, **1999**, 494.
(2) See: Bochet, C. G. *J. Chem. Soc., Perkin Trans. 1* **2002**, 125; and references cited therein.
(3) Amit, B.; Patchornik, A. *Tetrahedron Lett.* **1973**, *24*, 2205.
(4) Morisson, H. A. *The Chemistry of the Nitro and Nitroso Groups*, Part 1; Feuer, H., Ed.; Interscience: New York, **1970**, 185.
(5) Amit, B.; Ben-Efraim, D. A.; Patchornik, A. *J. Am. Chem. Soc.* **1976**, *98*, 843.
(6) Papageorgiou, G.; Ogden Barth, A.; Corrie, J. E. T. D. C. *J. Am. Chem. Soc.* **1999**, *121*, 6503.
(7) Nicolaou, K. C.; Safina, B. S.; Winssinger, N. *Synlett* **2001**, 900.
(8) (a) Helgen, C.; Bochet, C. G. *J. Org. Chem.* **2003**, *68*, 2483. (b) Helgen, C.; Bochet, C. G. *Synlett* **2001**, 1968.
(9) Papageorgiou, G.; Corrie, J. E. T. *Tetrahedron* **2000**, *56*, 8197.
(10) Pass, S.; Amit, B. *J. Am. Chem. Soc.* **1981**, *103*, 7674.
(11) Morrison, J.; Wan, P.; Corrie, J. E. T.; Papageorgiou, G. *Photochem. Photobiol. Sci.* **2002**, *1*, 960.
(12) See, for instance: (a) Frechet, J. M. J.; Cameron, J. F.; Chung, C. M.; Haque, S. A.; Willson, C. G. *Polym. Bull. (Berlin)* **1993**, *30*, 369. (b) Beecher, J. E.; Cameron, J. F.; Frechet, J. M. J. *J. Mat. Chem.* **1992**, *2*, 811.
(13) Previously, carbamate derivatives of 7-nitroindolines have been obtained by prior deprotonation with NaH (ref. 8).
(14) Sefkow, M.; Kaatz, H. *Tetrahedron Lett.* **1999**, *40*, 6561.