Synthesis of 4-Azidoindole-3-acetic Acid, a Photoprobe Causing Sustained Auxin Activity

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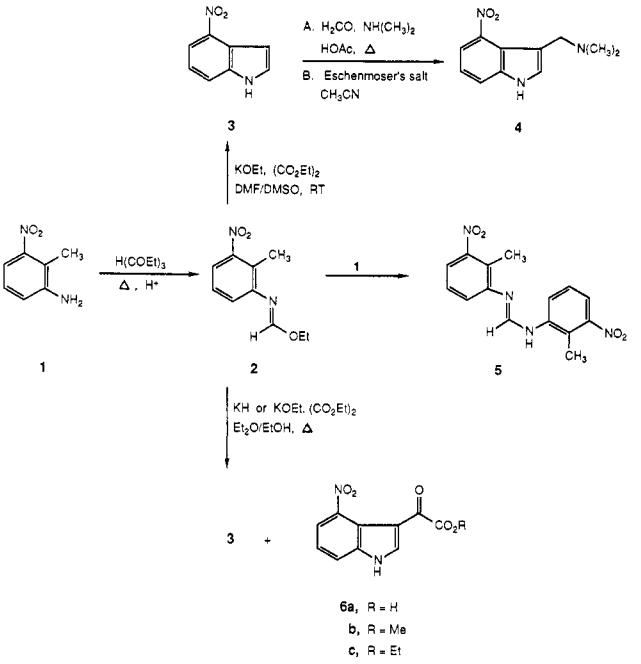
Earlier[2-4] we reported the synthesis of 4-, 5-, and 6-azidoindole-3-acetic acid (4-N_3IAA, 5-N_3IAA, and 6-N_3IAA), plant hormone analogues designed as photoaffinity labeling reagents[5] to be used for identification and isolation of auxin receptors. Extensive chemical and biochemical testing of these compounds[3,6-8] has demonstrated that, in the dark, they behave almost exactly like indole-3-acetic acid (IAA), the primary natural auxin, and that, on photolysis, they bind irreversibly to auxin-sensitive sites. Particularly exciting is the observation that irradiation of soybean hypocotyl tissue after 1 h of exposure to 4-N_3IAA (**10**) in the dark causes the tissue to grow during 11 h in auxin-free solution as much as tissue that is continuously exposed to 4-N_3IAA or to IAA in the dark for this period.[6] One interpretation is that the photoprobe has irreversibly activated a key auxin receptor.

Our efforts to examine this sustained auxin response in greater detail were limited by the difficulty of preparing adequate supplies of 4-N_3IAA, which was initially obtained in only 1.4% overall yield. By far the least efficient step in our original synthesis was the first one, conversion of gramine to a mixture of 4- and 6-nitrogramine by nitration, which yielded only 10–18% 4-nitrogramine (purified).[3,9]

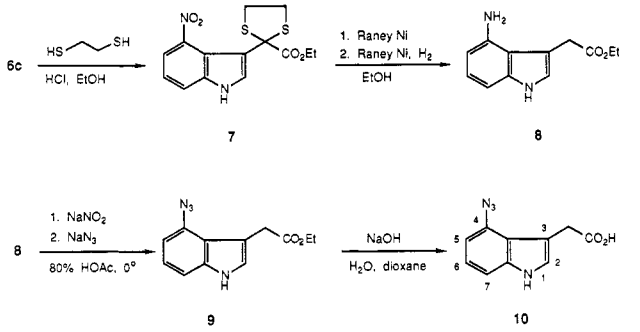
To circumvent this nonregiospecific, low-yield step, we explored a new synthesis of 4-nitroindole (**3**) reported by Bergman and Sand[10,11] that starts with 2-methyl-3-nitroaniline (**1**), as shown in Scheme I. Heating aniline **1** in excess triethyl orthoformate at reflux gave high yields of formimidate **2**, with either *p*-toluenesulfonic acid or aniline hydrochloride as catalyst,[12] but aniline hydrochloride led to a more easily purified product. Impurities remaining after fractional vacuum distillation were conveniently removed by recrystallization from hexane–diethyl ether (but not from absolute ethanol) with excellent recovery of the product. The formimidate **2** must be used promptly, for it decomposes quantitatively on standing, even when carefully purified and protected from moisture. The major decomposition product is not the aniline **1** expected from hydrolysis, but the amidine **5**, which apparently arises by attack of reverted aniline **1** on residual formimidate **2**.

4-Nitroindole (**3**) was obtained by addition of diethyl oxalate and potassium ethoxide in dimethylformamide to formimidate **2** in dimethyl sulfoxide, as described by

Scheme I



Scheme II



Bergman and Sand.[10] In our hands, an additional 0.5 equiv of potassium ethoxide was required to drive the reaction to completion, perhaps because we used commercial base. This modification was essential, because it is difficult to separate the product from residual starting material. Results with potassium hydride in absolute ethanol were variable, leading in some cases to 4-nitroindole (**3**) and in others to complex mixtures (see below).

We attempted introduction of the side chain at the 3-position of the indole ring by two methods: (1) Mannich condensation with dimethylamine and formaldehyde in aqueous acetic acid, a procedure reported previously,[13] and (2) modification of the procedure described by Kozikowski and Ishida[14] for converting indoles to gramines with dimethylmethyleneammonium chloride. Although both methods give the desired 4-nitrogramine (**4**), the improvement in overall yield to 4-N_3IAA (**10**) is less than twofold.

An alternative route shown in Scheme II was inspired by Bergman, Sand, and Tilstam's reports[10,11] of the conversion of 2-methyl-3-nitroaniline (**1**) to 4-nitroindole (**3**). When we ran this reaction in refluxing diethyl ether, generating potassium ethoxide from potassium hydride and absolute ethanol, and recrystallized the crude product from methanol, we obtained 4-nitroindole (**3**), mixed with substantial quantities of the methyl and ether esters of

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(4-nitroindol-3-yl)-2-oxoacetic acid (**6b,c**), the corresponding free acid **6a**, and starting material **2**. Bergman and Sand[11] had postulated **6c** as an intermediate in this reaction, without description, and Berti and Da Settimo[15,16] had prepared **6a** and **6c** in low yields (9% and 7.5%) by different routes; but these key intermediates had not otherwise been examined. Careful adjustment of reaction conditions (twofold excess of freshly opened commercial potassium ethoxide, a threefold excess of diethyl oxalate, and a 2:1 mixture of anhydrous diethyl ether–absolute ethanol as solvent) brought the yield of **6c** to 56% (purified). Flash chromatography provided a higher recovery and removed contaminating 4-nitroindole (**3**) and other side products more efficiently than recrystallization from absolute ethanol; sublimation favored decarboxylation.

The α-keto group on the side chain was reduced to a methylene group by conversion to the dithioketal **7** with 1,2-ethanedithiol in absolute ethanol using anhydrous hydrogen chloride as catalyst, a procedure employed for a related compound,[17] followed by treatment with Raney nickel in warm ethanol to produce ethyl 4-nitroindole-3-acetate. This reaction was accompanied by formation of some ethyl 4-aminoindole-3-acetate (**8**). Treatment with Raney nickel in refluxing ethanol caused decomposition to an unidentified product, which was judged by thin-layer chromatography and mass spectroscopy not to be the desired amine **8**. Complete conversion to amine **8** was accomplished by hydrogenation over fresh Raney nickel in a Parr hydrogenator. Since the corresponding free acid was difficult to purify on a small scale,[3] amine **8** was converted directly to ethyl 4-azidoindole-3-acetate (**9**) by diazotization in 80% acetic acid followed by displacement with sodium azide.[3,18] Saponification to the free acid **10** was accomplished in aqueous sodium hydroxide that contained dioxane to enhance solubility of the ester, giving 4-N_3IAA (**10**) identical in all respects with an authentic sample.[3] The overall yield from 2-methyl-3-nitroaniline (**1**) to the final product is 18%, more than tenfold higher than our previously reported synthesis of 4-N_3IAA (**10**).[3] The present synthesis has the additional advantage over the initial synthesis that regioisomers cannot be produced.

Experimental Section

Melting points were determined on a Thomas-Hoover Uni-Melt or a Büchi capillary apparatus and are corrected. ^{1}H NMR spectra were recorded on a Varian EM-390 or a Varian XL-200 spectrometer. Samples were dissolved in $(CD_3)_2SO$, using tetramethylsilane (Me_4Si) as an internal standard. Mass spectra were obtained by J. Carter Cook and his staff at the University of Illinois. Electron-impact mass spectra (EIMS) were recorded on a Varian-MAT CH-5 double-focusing spectrometer. Field desorption mass spectra (FDMS) were obtained on a Varian-MAT Model 731 double-focusing mass spectrometer. Microanalyses were performed by Josef Nemeth and his staff at the University of Illinois. Thin-layer chromatography (TLC) was conducted on Merck silica gel plastic-backed plates with fluorescent indicator, eluted with chloroform–ethyl acetate (3:1) (solvent A), ethyl acetate–2-propanol–water (65:25:10) (solvent B), chloroform–methanol (9:1) (solvent C), or methylene chloride (solvent D). Visualization was under 254- or 365-nm light or in iodine vapor. The adsorbent for flash column chromatography was Alfa large-pore (58 μm) silica gel. Raney nickel (no. 28), diethyl oxalate, 2-methyl-3-nitroaniline (**1**), and 1,2-ethanedithiol were purchased from Aldrich. Potassium ethoxide was purchased from Alfa. Triethyl orthoformate (98%, Aldrich) was redistilled through a 45-cm Podbilniak column. Acetonitrile (Mallinckrodt) was dried over K_2CO_3 and then P_2O_5, distilled from fresh P_2O_5, and stored over 3-Å molecular sieves, as described by Burfield, Lee, and Smithers.[20] *All manipulations involving azides were carried out under red light or in the dark.*

Ethyl *N*-(2-Methyl-3-nitrophenyl)formimidate (2). 2-Methyl-3-nitroaniline (**1**) was converted to formimidate **2** with triethyl orthoformate and *p*-toluenesulfonic acid, as described by Bergman and Sand[10] except that the pale yellow solid (92%) obtained by fractional vacuum distillation (Kugelrohr) was further purified by recrystallization from hexane–diethyl ether (97% recovery) to remove impurities visible by TLC, giving white crystals: mp 58–59 °C (lit.[10] mp 57–58 °C); TLC, solvent A, R_f 0.68, solvent B, R_f 0.55; ^{1}H NMR (90 MHz) δ 1.40 (t, 3, $J_{CH_3CH_2}$ = 6.3 Hz, CH_3), 2.38 (s, 3, $ArCH_3$), 4.34 (q, 2, $J_{CH_2CH_3}$ = 6.3 Hz, CH_2), 7.21 and 7.40 [dd and t (overlapping), 2, $J_{3,4}$ = 7.8 Hz, $J_{3,5}$ = 1.8 Hz, $J_{4,5}$ = $J_{4,3}$ = 7.8 Hz, 3-H and 4-H], 7.65 (dd, 1, $J_{5,4}$ = 7.8 Hz, $J_{5,3}$ = 1.8 Hz, 5-H), 7.97 (s, 1, N=$CHOCH_2CH_3$); EIMS (10 eV) *m/e* (relative intensity) 208 (M^+, 100).

Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.45. Found: C, 57.44; H, 5.70; N, 13.32.

Because the formimidate **2** decomposes on storage, even when desiccated or refrigerated, it must be used promptly. Decomposition under these conditions is detectable by melting point and TLC within a few days of preparation and purification.

4-Nitroindole (3). Method A. Ethyl *N*-(2-methyl-3-nitrophenyl)formimidate (**2**) was converted to 4-nitroindole (**3**) on addition of excess potassium ethoxide and diethyl oxalate in dimethyl sulfoxide and dimethylformamide as reported by Bergman and Sand.[10] After 1 h, an additional 0.5 equiv of potassium ethoxide was added, and stirring was continued for 1 h to drive the reaction to completion. The crude product (85%, mp 185–195 °C) was purified by sublimation [160 °C (8 mmHg), 63% recovery] or by recrystallization (methanol, 15% recovery) affording, in each case, bright yellow crystals: mp 200–202 °C (lit.[10] mp 204–205 °C); TLC, solvent D, R_f 0.39; ^{1}H NMR (90 MHz) δ 7.03 (m, 1, 2-H, collapses to dd with D_2O, $J_{2,3}$ = 3 Hz, $J_{2,7}$ = 1 Hz), 7.28 (t, 1, $J_{6,7}$ = $J_{6,5}$ = 8.1 Hz, 6-H), 7.72 (m, 1, 3-H, collapses to d with D_2O, $J_{3,2}$ = 3 Hz), 7.85 (d of pseudo t, 1, $J_{7,6}$ = 8.1 Hz, $J_{7,5}$ = 1.7 Hz, $J_{7,2}$ = 1 Hz, 7-H), 8.03 (d, 1, $J_{5,6}$ = 8.1, $J_{5,7}$ = 1.7 Hz, 5-H), 12.17 (br s, 1, NH, exchanges with D_2O).

Method B. Numerous attempts to obtain 4-nitroindole (**3**) from ethyl *N*-(2-methyl-3-nitrophenyl)formimidate (**2**) using excess potassium ethoxide or excess potassium hydride in absolute ethanol and diethyl oxalate in diethyl ether, as suggested by Bergman, Sand, and Tilstam,[11] produced complex mixtures containing unreacted formimidate **2** (~20%), the desired nitroindole **3** (~10%), the methyl and ethyl esters of (4-nitroindol-3-yl)-2-oxoacetate (**6b** and **6c**) (~30%, combined), and the corresponding free acid **6a** (~30%). Constituents were detected by neutralization of an aliquot of the reaction mixture with 6 M hydrochloric acid, followed by TLC (solvents B and D) against authentic standards. Composition of these mixtures (slightly variable) is reported above in parentheses as percent of total isolated weight. Separation of components within the crude product collected by suction filtration[11] was achieved by fractional sublimation [0–200 °C (5 mmHg)] or flash chromatography [silica gel, methylene chloride followed by methylene chloride–methanol (9:1) as eluants], yielding in both cases **2**, **3**, and **6c**. When the basic filtrate[11] was neutralized with concentrated hydrochloric acid, cooled in ice, filtered, washed in water, and air-dried, the resulting hard cake was found to be nearly pure **6a**. Except for the esters, identification of isolated compounds was confirmed by comparison of melting points, TLC behavior, and ^{1}H NMR spectra with those of corresponding samples reported elsewhere in this paper. The esters were demonstrated to be a mixture of **6b** and **6c** by ^{1}H NMR, for which the spectrum contained a singlet at δ 3.88 in addition to peaks matching those of the ethyl ester. Comparison of the integration for the singlet with the integration for the triplet appearing at δ 1.33 indicated that the esters were present in approximately equal amounts. Identities of the esters were confirmed by mass spectroscopy: EIMS (10 eV) *m/e* (relative

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intensity) 262 (M^+ for **6c**, 1), 248 (M^+ for **6b**, 1), 189 ($M^+ - CO_2Et$ or CO_2Me, 100).

4-Nitrogramine (4). Method A. A (dimethylamino)-methylene side chain was introduced onto 4-nitroindole (**3**) by condensation with formaldehyde and dimethylamine in aqueous acetic acid, according to the procedure of Hsing and King.[13]

Method B. This reaction is a modification of the one described by Kozikowski and Ishida,[14] in which Eschenmoser's salt and acetonitrile are substituted for dimethylmethyleneammonium chloride and dichloromethane. For both methods, crude product was purified by precipitation of 4-nitrogramine (**4**) from dilute HCl with concentrated NH_4OH, giving orange crystals (74% for method A and 24% for method B), mp 125–127 °C (lit.[10] mp 127.5–129.5 °C). TLC and ^1H NMR were identical with those for an authentic sample obtained by nitration of gramine and separation from 6-nitrogramine.[3,9]

***N*^{1},*N*^{2}-Bis(2-methyl-3-nitrophenyl)amidine (5).** Compound **5** was obtained from a sample of ethyl *N*-(2-methyl-3-nitrophenyl)formimidate (**2**) that had been stored in a tightly sealed brown glass bottle for 6 months. Although the stored formimidate was pure when fresh, melting point, color, TLC, and ^1H NMR all indicated that substantial decomposition had occurred. Recrystallization from ethanol–ethyl acetate (93% recovery) gave pale yellow needles: mp 170 °C; TLC, solvent B, R_f 0.72, solvent D, R_f 0.30; ^1H NMR (200 MHz) δ 2.35 (s, 6, 2 $ArCH_3$), 7.40 (t, 2, $J_{5,4} = J_{5,6} = 8.1$ Hz, 5-H), 7.56 (dd, 4, $J_{4,5} = J_{6,5} = 8.1$ Hz, $J_{4,6} = J_{6,4} = 1.0$ Hz, 4-H and 6-H), 8.02 (s, 1, ArN=C*H*NHAr), 9.58 (br s, 1, NH, exchanges with D_2O); EIMS (10 eV) *m/e* (relative intensity) 314 (M^+, 11), 152 ($M^+ - 162$, 100).

Anal. Calcd for $C_{15}H_{14}N_4O_4$: C, 57.32; H, 4.49; N, 17.83. Found: C, 57.19; H, 4.70; N, 17.77.

(4-Nitroindol-3-yl)-2-oxoacetic Acid (6a). A modification of the procedure suggested by Bergman, Sand, and Tilstam[11] for making 4-nitroindole (**3**) was followed. After the evaporated reaction mixture was dissolved in methanol and poured with stirring into ice water saturated with potassium carbonate, the yellow precipitate was removed by suction filtration. The red filtrate was acidified with concentrated hydrochloric acid, yielding an orange solid, which was collected by suction filtration, washed with water, and air-dried. The hard cake was dissolved in 25 mL of hot 2 N sodium hydroxide, treated with charcoal, filtered, and cooled to room temperature. After extraction with methylene chloride, the aqueous layer was acidified to pH 3 with 6 M hydrochloric acid, giving an orange precipitate, which was collected by suction filtration, washed with water, and air-dried. From 2.08 g (10 mmol) of **2** was obtained 0.450 g of crystals of the free acid **6a** (19%): mp 193 °C dec (lit.[16] mp 177 °C, dec[19]); TLC, solvent B, R_f 0.35, solvent D, R_f 0.03; ^1H NMR (90 MHz) δ 7.4 (t, 1, $J_{6,5} = J_{6,7} = 7.8$ Hz, 6-H), 7.72 (dd, 1, $J_{7,6} = 7.8$ Hz, $J_{7,5} = 1.2$ Hz, 7-H), 7.88 (dd, 1, $J_{5,6} = 7.8$ Hz, $J_{5,7} = 1.2$ Hz, 5-H), 8.53 (d, 1, $J_{2,NH} = 3$ Hz, 2-H, collapses to s with D_2O), 12.8 (s, 1, CO_2H, exchanges with D_2O); FDMS *m/e* 234 (M^+).

Ethyl (4-Nitroindol-3-yl)-2-oxoacetate (6c). A 250-mL three-necked round-bottomed flask was charged with 1.26 g (15 mmol) of potassium ethoxide, whereupon 17 mL of absolute ethanol was added immediately under moisture-free conditions. After the mixture was stirred to solubilize the solid, 33 mL of anhydrous diethyl ether was added, followed by 2.92 g (20 mmol) of diethyl oxalate. After 5 min, 2.08 g (10 mmol) of formimidate **2** was added to the deep yellow suspension, and the reaction mixture was stirred and refluxed for 24 h. To drive the reaction to completion, additional diethyl oxalate (1.0 equiv) and potassium ethoxide (0.5 equiv) were added, and refluxing and stirring were continued for another 10 h. The deep red solution was evaporated under reduced pressure, and the residue was dissolved in boiling absolute ethanol. The resulting solution was poured onto about 400 mL of ice-cold water, with stirring, and the crude product was collected by suction filtration and washed with cold water, yielding 1.83 g (70%) of **6c** as a dull yellow solid. The crude product was purified by flash column chromatography on silica gel with chloroform–ethyl acetate (3:1) as eluant, giving 1.46 g of **6c** (80% recovery) as pale yellow crystals: mp 188–189 °C (lit.[15] mp 184–186 °C); TLC, solvent A, R_f 0.19; ^1H NMR (90 MHz) δ 1.33 (t, 3, $J_{CH_3,CH_2} = 7.5$ Hz, CH_3), 4.29 (q, 2, $J_{CH_2,CH_3} = 7.5$ Hz, CH_2), 7.40 (t, 1, $J_{6,7} = J_{6,5} = 7.8$ Hz, 6-H), 7.76 and 7.90 [dd (overlapping), 3, $J_{7,6} = J_{5,6} = 7.8$ Hz, 7-H and 5-H], 8.50 (s, 1, 2-H), 12.8 (br s, 1, NH); EIMS (10 eV) *m/e* (relative intensity) 262 (M^+, 3), 189 ($M^+ - CO_2Et$, 100).

Anal. Calcd for $C_{12}H_{10}N_2O_5$: C, 54.97; H, 3.84; N, 10.68. Found: C, 54.86; H, 3.85; N, 10.33.

A small sample of the ethyl ester **6c** was converted to the free acid **6a** in hot 2 N sodium hydroxide. Acidification with 6 N hydrochloric acid, cooling in ice, collection by suction filtration, washing with water, and air-drying gave orange crystals identical with those of authentic free acid **6a**, as judged by melting point, TLC (solvents B and D), and ^1H NMR.

Ethylene Dithioketal of Ethyl (4-Nitroindol-3-yl)-2-oxoacetate (7). The procedure for preparing the ethylene dithioketal **7** is based on Plieninger and Müller's method for preparing a related compound.[17] To a suspension of 1.66 g (6.33 mmol) of the ketoacetate **6c** in 75 mL of absolute ethanol acidified with anhydrous HCl gas was added 0.898 g (9.50 mmol) of 1,2-ethanedithiol. After the reaction mixture was stirred under dry nitrogen at 60 °C for 3 h, the volume was reduced to a few milliliters in a fume hood under a stream of nitrogen, and the solid was collected by suction filtration, giving 1.79 g (84%) of dithioketal **7** as yellow crystals: mp 208–209 °C; TLC, solvent A, R_f 0.38; ^1H NMR (200 MHz) δ 1.13 (t, 3, $J_{CH_3,CH_2} = 7.2$ Hz, CH_3), 3.49 (m, 4, CH_2CH_2), 4.05 (q, 2, $J_{CH_2,CH_3} = 7.2$ Hz, ethyl CH_2), 7.27 (t, 1, $J_{6,7} = J_{6,5} = 7.8$ Hz, 6-H, collapses to d on broad-band irradiation of dd at δ 7.81–7.84), 7.81 (d, 1, $J_{7,6} = 8.0$ Hz, 7-H, collapses to s on broad-band irradiation of t at δ 7.27), 7.84 (d, 1, $J_{5,6} = 7.8$ Hz, 5-H, collapses to s on broad-band irradiation of t at δ 7.27), 8.05 (d, 1, $J_{2,NH} = 2.6$ Hz, 2-H, collapses to s on broad-band irradiation of NH at δ 12.0), 12.0 (br s, 1, NH); EIMS (10 eV) *m/e* (relative intensity) 338 (M^+, 1), 265 ($M^+ - CO_2Et$, 100).

Anal. Calcd for $C_{14}H_{14}N_2O_4S_2$: C, 49.69; H, 4.17; N, 8.27; S, 18.95. Found: C, 49.61; H, 4.27; N, 8.13; S, 18.74.

Ethyl 4-Aminoindole-3-acetate (8). In a 250-mL three-necked round-bottomed flask were placed 0.400 g (1.18 mmol) of the dithioketal **7**, 40 mL of absolute ethanol, and about a teaspoonful of wet Raney nickel catalyst. After the mixture was stirred at 35 °C for 24 h under dry nitrogen, the catalyst was removed by filtration and washed with absolute ethanol. Fresh catalyst (about 0.5 teaspoon) was added to the combined washings and filtrate and the suspension was shaken on a Parr apparatus for 1 h at room temperature under hydrogen at 40 psi. Catalyst was again removed by filtration and washed with absolute ethanol, and the combined, colorless filtrate and washings were evaporated to dryness under reduced pressure at 35 °C. The resulting brown residue **8** weighed 0.336 g (95%): TLC, solvent A, R_f 0.36; EIMS (10 eV) *m/e* (relative intensity) 218 (M^+, 68). Amine **8** was converted directly to ethyl 4-azidoindole-3-acetate (**9**).

Ethyl 4-Azidoindole-3-acetate (9). Conversion of amine **8** to azide **9** was accomplished by diazotization in 80% acetic acid followed by displacement with sodium azide, as described by Melhado and Leonard.[3,18] The brown residue obtained by evaporation of the reaction mixture at 35 °C under reduced pressure was washed with water, collected by suction filtration, and dried overnight in air. The crude product was dissolved in ethyl acetate, adsorbed onto silica gel, and purified by flash column chromatography on silica gel, utilizing chloroform–ethyl acetate (3:1) as eluant. From 42 mg of ethyl 4-aminoindole-3-acetate (**8**) was obtained 27 mg (57%) of ethyl 4-azidoindole-3-acetate (**9**) as orange crystals: mp 127–128 °C dec (evacuated, sealed tube); TLC, solvent A, R_f 0.55; ^1H NMR (200 MHz) δ 1.20 (t, 3, $J_{CH_3,CH_2} = 6.8$ Hz, CH_3), 3.82 (s, 2, CH_2CO), 4.11 (q, 2, $J_{CH_2,CH_3} = 7.2$ Hz, ethyl CH_2), 6.84 (d, 1, $J_{7,6} = 7.4$ Hz, 7-H), 7.10 (d, 1, $J_{5,6} = 7.0$ Hz, 5-H), 7.19 and 7.22 [t and d (overlapping), 2, $J_{6,7} = J_{6,5} = 5.0$ Hz, $J_{2,1} = 2.2$ Hz, 6-H and 2-H, d collapses to s on broad-band irradiation of NH at δ 11.1), 11.1 (br s, 1, NH); EIMS (10 eV) *m/e* (relative intensity) 244 (M^+, 14), 216 ($M^+ - N_2$, 4), 143 ($M^+ - N_2 - CO_2Et$, 100).

4-Azidoindole-3-acetic Acid (10). The free acid **10** was obtained by saponification of the ester **9**. To 0.050 g (0.2 mmol) of **9** were added 5 mL of 1 M sodium hydroxide and 5 mL of dioxane, and the mixture was stirred at room temperature for 5 h. The solution was reduced to 2 mL on a rotary evaporator at 30 °C under reduced pressure and filtered by suction, and the filtrate was acidified with 2 M hydrochloric acid until turbidity persisted. After cooling on ice, the orange crystals were collected

by suction filtration, washed twice with 2-mL portions of cold water, and dried in air. Weight of the free acid 10 was 0.035 g (79%): mp 176 °C (lit.[3] mp 177 °C); TLC, IR, ^{1}H NMR, and EIMS were identical with those of an authentic standard.[3]

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Registry No. 1, 603-83-8; 2, 115118-93-9; 3, 4769-97-5; 4, 7150-46-1; 5, 115118-94-0; 6a, 90947-20-9; 6b, 115118-95-1; 6c, 91974-30-0; 7, 115118-96-2; 8, 115118-97-3; 9, 115118-98-4; 10, 79473-09-9; H_2CO, 50-00-0; $NH(CH_3)_2$, 124-40-3; Eschenmoser's salt, 33797-51-2; 1,2-ethanedithiol, 540-63-6.

Synthesis of 2-(((*p*-Nitrophenyl)sulfonyl)oxy) Esters from Ketene Silyl Acetals and Bis((*p*-nitrophenyl)sulfonyl) Peroxide

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We recently reported that the reactions of enol derivatives of ketones (enol acetates, silyl enol ethers, and enamines) with bis(arylsulfonyl) peroxides provide a very efficient and regiospecific route to 2-((arylsulfonyl)oxy) ketones.[1] These analogues of 2-halo ketones have a much simpler and more selective reactivity pattern than the 2-halo ketones, and they can be readily converted to 2-hydroxy ketals and acetals and 2-amino ketones in high yields.[2]

Since 2-oxygenated carboxylic acids and esters have a great deal of utility in synthesis,[3] it seemed that 2-((arylsulfonyl)oxy) esters might likewise provide useful starting materials for the synthesis of 2-substituted esters and acids. Only a few reports of 2-(sulfonyloxy) esters can be found in the literature. Creary has prepared a few 2-mesyl and 2-triflyl esters as solvolysis substrates.[4] Several reports have appeared that show that 2-triflyl esters are reactive alkylating agents toward nucleophiles.[5] While it has been stated that 2-(mesyloxy) and 2-(tosyloxy) esters are much less useful than the triflates,[5d] to our knowledge no specific compounds or data are available in the literature relevant to this claim.

2-(Sulfonyloxy) esters are invariably made by reaction of the 2-hydroxy ester with a sulfonylating agent. While this route provides high yields and can be used for the preparation of optically active 2-(sulfonyloxy) esters, the 2-hydroxyl group must be already present in the starting material. We wish to report that 2-(((*p*-nitrophenyl)sulfonyl)oxy) (nosyl) esters can be prepared directly from esters by conversion to ketene silyl acetals and reaction with bis((*p*-nitrophenyl)sulfonyl)) peroxide (pNBSP).

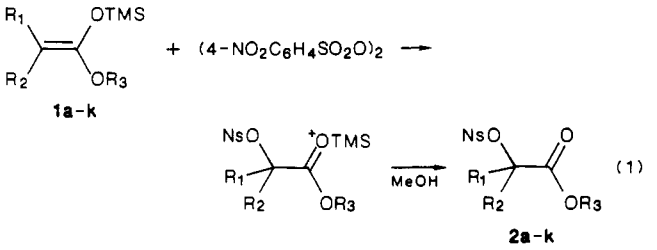
Table I. Preparation of 2-(((*p*-Nitrophenyl)sulfonyl)oxy) Esters from *O*-Trimethylsilyl Ketene Acetals and pNBSP

		yield,[a] %	
ketene acetal	product	method A	method B
1a	**2a**	75	88
1b	**2b**	77	79
1c	**2c**	low	82
1d	**2d**	54	84[b]
1e	**2e**	67	
1f	**2f**	78	79[c]
1g	**2g**	68	
1h	**2h**		67
1i	**2i**		69
1j	**2j**	low	73
1k	**2k**	very low	61

[a] Yields are isolated yields of pure products. [b] This experiment utilized 1.0 equiv of the *O*-trimethylsilyl ketene acetal. [c] The yield with 1.0 equiv of *O*-trimethylsilyl ketene acetal is 79%.

Results and Discussion

A series of *O*-trimethylsilyl ketene acetals, **1a–k**,[6] was reacted with pNBSP (1.0 equiv) and methanol (5 equiv) in ethyl acetate solution at 0 °C (method A). Simple aqueous workup gave the 2-nosyl esters, **2a–k**, isolated by flash chromatography in good to high yields (Table I). The methanol was needed to trap the oxonium ion produced from the electrophilic addition of pNBSP to the silyl ketene acetal double bond (eq 1).[1] If methanol is omitted,



a, R_1 = H; R_2, R_3 = Me
b, R_1 = H; R_2 = Me; R_3 = Et
c, R_1 = H; R_2 = Me; R_3 = *t*-Bu
d, R_1 = H; R_2 = Et; R_3 = Et
e, R_1 = H; R_2 = Et; R_3 = *i*-Bu
f, R_1 = H; R_2 = C_6H_5; R_3 = Me
g, R_1, R_2 = H; R_3 = *i*-Pr
h, R_1, R_2, R_3 = Me
i, R_1, R_2 = $-(CH_2)_5-$; R_3 = Me
j, R_1 = H; R_2, R_3 = $-(CH_2)_3-$
k, R_1 = H; R_2, R_3 = $-(CH_2)_2-$

the product mixtures are much more complex. Too much methanol (>20 equiv) also gave reduced yields because the silyl ketene acetal begins to degrade noticeably. While the stoichiometry of eq 1 indicates a 1:1 ratio of trimethylsilyl ketene acetal to pNBSP, in practice an excess (1.2–1.5 equiv) of the ketene acetal was normally used to ensure complete reaction of the peroxide. Comparable yields were obtained, however, when a 1:1 ratio of reactants was employed for several examples (Table I).

Several *O*-trimethylsilyl ketene acetals failed to give products under these conditions or gave low yields of products that were components of a complex product mixture. It was surmised that the high acidity of the *p*-nitrobenzenesulfonic acid byproduct was causing hydrolysis and/or degradation of the ester function. A simple change (method B) was to use sodium methoxide (1.5

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