was then added phytol (**10a**) or isophytol (**10b**) (620 mg, 2.09 mmol, both compounds (Aldrich) were used without purification). The solution was refluxed for 5 h, cooled, and poured onto crushed ice. Extraction with ether (50 mL) and washing of the ether extract with saturated $NaHCO_3$ (2 × 50 mL), water (2 × 50 mL), and saturated NaCl (2 × 50 mL) was followed by drying over anhydrous $MgSO_4$. The ether was removed under reduced pressure and the oily residue chromatographed with 5% ethyl acetate in hexane. The final product from both reactions was a yellow oil: yield, **5** + **10a** 415 mg (52%), **5** + **10b** 441 mg (55%). Anal. Calcd for $C_{29}H_{50}OS$: C, 77.96; H, 11.28; S, 7.17. Found (for **5** + **10a** only): C, 78.27; H, 11.48; S, 7.08. The literature[8] analysis was given only for the acetate.

**Condensation of 5 with 10b according to Ref 9.** Compound **5** (450 mg, 2.67 mmol) was dissolved in butyl acetate (1.5 mL) containing 100 mg of anhydrous, fused $ZnCl_2$ and 10 mg of $Na_2S_2O_4$. After heating for 10 min at 100 °C, isophytol (**10b**) (100 mg, 0.33 mmol) was added together with a drop of concentrated $H_2SO_4$. The solution was heated to 125 °C for 15 min and cooled, and a further 600 mg (2.02 mmol) of **10b** was added, followed by further heating at 125 °C for 10 min. After cooling, the oily product (yield, 1.0 g (82%)) was obtained by the addition of water. Isolation and purification were carried out as described above. Anal. Calcd for $C_{29}H_{50}OS$: C, 77.96; H, 11.28; S, 7.17. Found: C, 78.22; H, 11.48; S, 7.31. Lit.:[9] C, 77.27; H, 11.00.

**3,4-Dihydro-6-hydroxy-4,4,5,7,8-pentamethyl-2*H*-1-benzothiopyran (16).** The synthesis of this compound by reaction of **5** with 3-methyl-2-buten-1-ol under the conditions given in ref 8 has been reported previously.[7] Compound **2c** is a minor product (10% relative to **16**) in this reaction. The structure of **16** has been confirmed by X-ray analysis.[7]

***S*-(3,3-Dimethylallyl)-2,3,5-trimethyl-4-hydroxybenzenethiol (17).** This compound was synthesized by the condensation of **5** with isoprene essentially according to ref 21. To a heterogeneous mixture of anhydrous fused zinc chloride (0.05 g, 0.36 mmol) and of glacial acetic acid (5 mL) was added **5** (0.5 g, 2.9 mmol). The heterogeneous mixture was warmed slightly (50 °C) and cooled to 25 °C, and isoprene (2 mL, 17.6 mmol) was added at once. The reaction flask was stoppered well, and the solution was allowed to stand at 25 °C for 4 days, 1 drop of $H_2SO_4$ was added, and the solution was refluxed 10 min. The cooled solution was poured onto ice and extracted with ethyl acetate (2 × 20 mL). The organic phase was washed with saturated $NaHCO_3$ (20 mL), dried over $Na_2SO_4$, and filtered and the solvent removed under reduced pressure. The reaction mixture was subjected to column chromatography using 5% ethyl acetate in hexane as eluent. The white crystalline product had the following: yield, 350 mg (50%); mp 95.5–96.0 °C, $R_f$ 0.32 (19/1). Anal. Calcd for $C_{14}H_{20}OS$: C, 71.14; H, 8.53. Found: C, 70.85; H, 8.52. $^1H$ NMR $\delta$ 7.1 (s br, 1 H, Ar H), 5.4–5.0 (m, 1 H, =CH), 4.6 (s, 1 H),[20] 3.2 (d, 2 H, $SCH_2$), 2.4 (s, 3 H, $ArCH_3$), 2.25 (s, 6 H, $ArCH_3$), 1.85–1.4 (m, 6 H, $C(CH_3)_2$).

**Acknowledgment.** We thank H. Seguin for the elemental analyses and Dr. J. R. Brisson for the high-field NMR spectra. We also thank the National Foundation for Cancer Research and the Association for International Cancer Research for partial support of this work.

**Supplementary Material Available:** Figure showing 500-MHz $^1H$ NMR spectrum of the products formed by reaction of **5** with **10b**. (2 pages). Ordering information is given on any current masthead page.

(21) Smith, L. E.; Ungnade, H. E.; Hoehn, H. V.; Wawzonek, S. *J. Org. Chem.* **1939**, *4*, 311–317.

# α-Nitroarylation of Ketones and Esters: An Exceptionally Facile Synthesis of Indoles, 2-Indolinones, and Arylacetic Acids†

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Silyl enol ethers and ketene silyl acetals add to aromatic nitro compounds in the presence of fluoride ion sources to give dihydroaromatic nitronates which are readily oxidized to α-nitroaryl carbonyl compounds by DDQ or $Br_2$. These versatile intermediates are readily converted into indoles or 2-indolinones by reductive cyclization. Since halogen substituents on the aromatic ring are not displaced in the initial alkylation reaction, nucleophilic substitution of these groups, followed by functional group manipulations of the nitro group, permits easy access to indoles, 2-indolinones, and arylacetic acids with varied substitution patterns.

Because of the very potent and diverse biological activity exhibited by various indole derivatives, this heterocyclic system has attracted considerable attention in chemistry, biology, and medicine.[1] Understandably, a very large body of chemical literature has appeared dealing with various synthetic methods for the construction of the indole nucleus. The most versatile among these are the Fischer, Bischler, Madelung, Reissert, Nenitzescu, and Gassman procedures and their various modifications.[1a,b,2] Organometallic intermediates[2c,3] as well as 2-(dimethylamino)styrenes[4] have also served as precursors for indoles. Other fundamentally new methods based on $S_{RN}1$ reactions,[5] intramolecular amidoalkylations,[6] nucleophilic[7] and free radical[8] additions, 1,5-electrocyclization of zwitterionic intermediates,[9] and aromatization of alicyclic precursors[10] are also noteworthy. By comparison, only a few methods have been reported for the synthesis of the indolinone

† Contribution No. 3936.

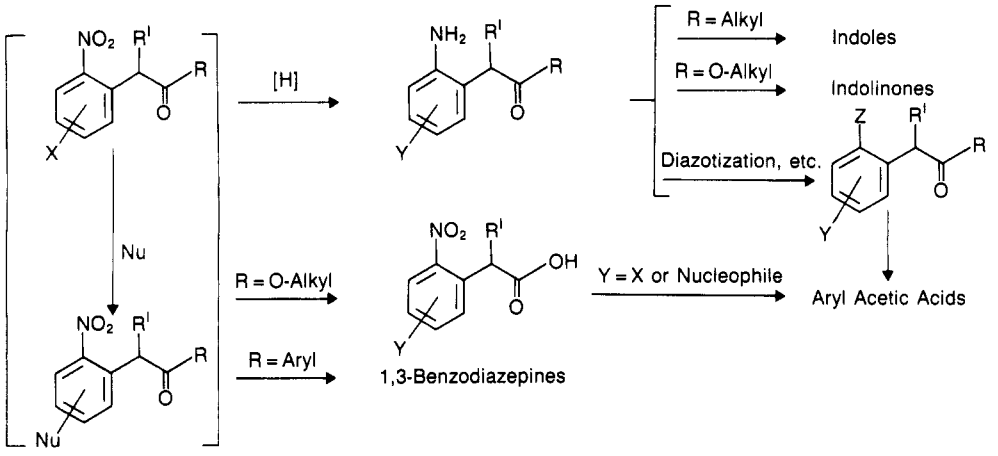
(1) (a) Sundberg, R. J. *Chemistry of Indoles*; Academic Press: New York, 1970. (b) Houlihan, W. J., Ed. *Indoles*; Wiley-Interscience: New York, 1972; Part 1; (c) Part 2; (d) Part 3, 1979. (e) Saxton, J. E., Ed. *Indoles*; Wiley-Interscience: New York, 1983; Part IV. (f) Windholz, M., Ed. *The Merck Index*; Merck and Co.: Rahway, NJ, 1979.

(2) (a) Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P.; Cue, B. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 5495. (b) Gassman, P. G.; Gruetzmacher, G.; van Bergen, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 5512. (c) For a compilation of the recent methods for indole synthesis, see: Wender, P. A.; White, A. W. *Tetrahedron* **1983**, *39*, 3767, ref 8.

(3) Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071. (b) Hegedus, L. S.; Allen, G. F.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 3583 and references cited therein. (c) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1979**, 1133. (d) Ames, D. E.; Ribeiro, O. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1073. (e) Kraus, G. A.; Frazier, K. *Tetrahedron Lett.* **1978**, *19*, 3195. (f) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1984**, *22*, 1347. (g) Larock, R. C.; Liu, C.-L.; Lau, H. H.; Varapath, S. *Tetrahedron Lett.* **1984**, *25*, 4459.

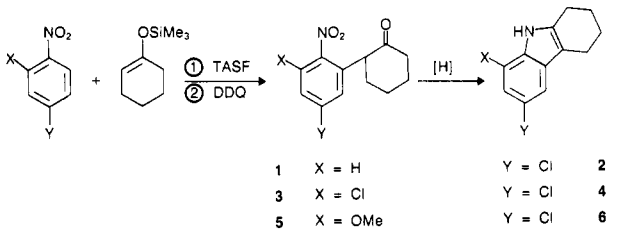
0022-3263/86/1951-1704$01.50/0 

**Scheme I. Transformations of α-Nitroaryl Carbonyl Compounds**

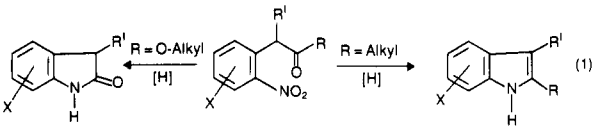


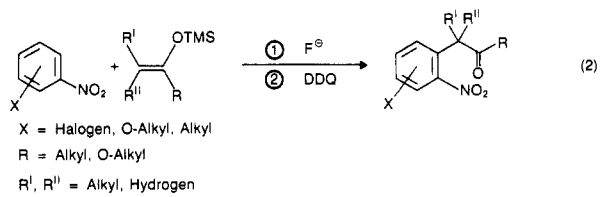

(oxindole) nucleus even though this heterocyclic system has been the focus of increasing attention because of its varied physiological properties.[11] Of these the variations of the Lewis acid mediated cyclization of α-haloacetanilides, cyclization of (*o*-aminophenyl)acetic acid derivatives and the Gassman procedure are the most general.[12,13] Several other new reaction schemes have also been reported since 1974.[14] With the notable exception of the Gassman method all these routes call for the use of an appropriate aromatic precursor often times not readily available, except for the most simple indolinones. The scope of these methods is further limited by the incompatibility of the key bond-forming reactions with a variety of aromatic substituents. These limitations also apply to a number of reported indole syntheses.

**Scheme II. Synthesis of Tetrahydrocarbazoles**




Conceptually one of the most attractive and general methods for the synthesis of indoles and indolinones would be reductive cyclization of α-nitroaryl carbonyl compounds (eq 1). This reaction has indeed been one of the oldest

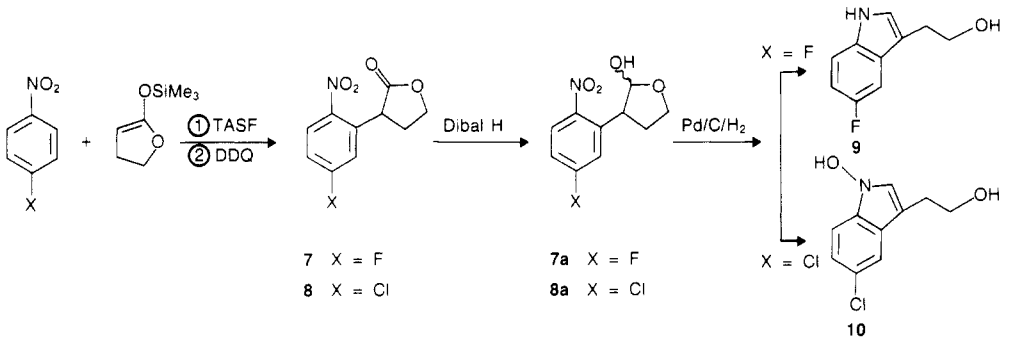


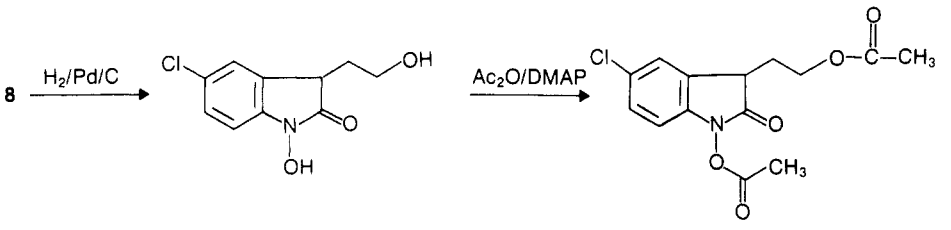

methods[1a,b,3d-f] for the synthesis of indoles and indolinones even though the availability of starting materials[15] has severely limited its utility. Recently we have reported[16] a new and general synthesis of α-nitroaryl carbonyl compounds starting from readily available aromatic nitro compounds and silyl enol ethers derived from ketones and esters (eq 2). In this paper we report our results on the use of these compounds for the synthesis of indoles and indolinones. In addition, this nitroaromatic alkylation sequence is conveniently adapted to the synthesis of ary-

(4) Hengartner, U.; Batcho, A. D.; Blount, J. F.; Leimgruber, W.; Larscheid, M. E.; Scott, J. W. *J. Org. Chem.* **1979**, *44*, 3748.
(5) (a) Beugelmans, R.; Roussi, G. *J. Chem. Soc., Chem. Commun.* **1979**, 950. (b) Bard, R. R.; Bunnett, J. F. *J. Org. Chem.* **1980**, *45*, 1546.
(6) (a) Ben-Ishai, D. *J. Chem. Soc., Chem. Commun.* **1980**, 687. (b) Ben-Ishai, D.; Peled, N.; Sataty, I. *Tetrahedron Lett.* **1980**, *21*, 569. (c) Nordlander, J. E.; Catalane, D. B.; Kotian, K. D.; Stevens, R. M.; Haky, J. E. *J. Org. Chem.* **1981**, *46*, 778.
(7) (a) Germain, C.; Bourdais, J. *J. Heterocycl. Chem.* **1976**, *13*, 1209. (b) Fleming, I.; Woolias, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 827, 829. (c) Ito, Y.; Kobayashi, K.; Saegusa, T. *J. Am. Chem. Soc.* **1977**, *99*, 3532; (d) *J. Org. Chem.* **1979**, *44*, 2030. (d) For an intramolecular Wittig approach, see: Corre, M. L.; Hercouet, A.; Baron, H. L. *J. Chem. Soc., Chem. Commun.* **1981**, 14.
(8) Ueno, Y.; Chino, K.; Okawara, M. *Tetrahedron Lett.* **1982**, *23*, 2575.
(9) (a) Speckamp, W. N.; Veenstra, S. J.; Dijkink, J.; Fortgens, R. *J. Am. Chem. Soc.* **1981**, *103*, 4643. (b) Veenstra, S. J.; Speckamp, W. N. *J. Am. Chem. Soc.* **1981**, *103*, 4645. (c) For a photochemical cyclization route, see: Schultz, A. G.; Hagmann, W. K.; *J. Org. Chem.* **1978**, *43*, 3391.
(10) (a) Baiocchi, L.; Giannangeli, M. *J. Heterocycl. Chem.* **1982**, *19*, 891. (b) Trost, B. M.; Reiffen, M.; Crimmin, M. *J. Am. Chem. Soc.* **1979**, *101*, 257.
(11) For leading references to the biological activity of 2-indolinones, see: (a) Canas-Rodriguez, A.; Leeming, P. R. *J. Med. Chem.* **1972**, *15*, 762. (b) Kornet, M. J.; Thio, A. P. *J. Med. Chem.* **1976**, *19*, 892. (c) Fischer, W.; Schilling, E.; Schmiedel, R.; Muller, M. *Pharm.* **1982**, *37*, 12. (d) Hardtmann, G. E. U.S. Pat. 4 160 032, 1979.
(12) (a) Reference 1a, p 357. (b) Hardegger, E.; Corrodi, H.; *Helv. Chim. Acta* **1956**, *39*, 514. (c) Romeo, H.; Corrodi, H.; Hardegger, E. *Helv. Chim. Acta* **1955**, *38*, 46. (d) Beckett, A. H.; Daisley, R. W.; Walker, J. *Tetrahedron* **1968**, *24*, 6093.
(13) Gassman, P. G.; van Bergen, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 5508. See also ref 2b.
(14) For representative examples, see: (a) Mori, M.; Hashimoto, Y.; Ban, Y. *Tetrahedron Lett.* **1980**, *21*, 631. (b) Reference 3c. (c) Mori, M.; Ban, Y. *Tetrahedron Lett.* **1976**, *17*, 1803, 1807. (d) Schultz, A. G.; Hagmann, W. K. *J. Org. Chem.* **1978**, *43*, 4231. (e) Reference 6a,b. (f) Wolfe, J. F.; Sleevi, M. C.; Goehring, R. R. *J. Am. Chem. Soc.* **1980**, *102*, 3646. See also: Goehring, R. R.; Sachdeva, Y. P.; Pisipati, J. S.; Sleevi, M. C.; Wolfe, J. F. *J. Am. Chem. Soc.* **1985**, *107*, 435. (g) Reisch, J.; Muller, M.; Labitzke, H. *Arch. Pharm.* **1984**, *317*, 639. (h) Kikugawa, Y.; Kawase, M. *J. Am. Chem. Soc.* **1984**, *106*, 5728.
(15) For some of the recent methods of their synthesis, see: (a) Via nuclear substitution of halogen, ref 7a. (b) From (nitroaryl)acetic acids, Geyer, H. M., III; Martin, L. L.; Crichlow, C. A.; Dekow, F. W.; Ellis, D. B.; Kruse, H.; Setescak, L. L.; Worm, M. *J. Med. Chem.* **1982**, *25*, 340. (c) From nitrotoluenes, ref 4 and Garcia, E. E.; Fryer, R. K. *J. Heterocycl. Chem.* **1974**, *11*, 219. (d) From 2-aminonitro compounds, Raucher, S.; Koolpe, G. A. *J. Org. Chem.* **1983**, *48*, 2066. (e) See also ref 3d–f.
(16) (a) RajanBabu, T. V. *Abstract of Papers*, 188th National Meeting of the American Chemical Society, Philadelphia, PA, August 1984; American Chemical Society: Washington, DC, 1984; ORGN 256. (b) RajanBabu, T. V.; Fukunaga, T. *J. Org. Chem.* **1984**, *49*, 4571. (c) RajanBabu, T. V.; Reddy, G. S.; Fukunaga, T. *J. Am. Chem. Soc.* **1985**, *107*, 5473.

**Scheme III. Synthesis of 3-(2-Hydroxyethyl)indoles**




**Scheme IV. Synthesis of 5-Chloro-1-hydroxy-3-(2-hydroxyethyl)-2-indolinone**




lacetic and arylpropionic acids. We describe here our simple entry into these medicinally important classes of compounds.[17]

## Results and Discussion

Addition of silyl enol ethers and ketene silyl acetals to aromatic nitro compounds in the presence of tris(dimethylamino)sulfonium difluorotrimethylsiliconate (TASF) followed by oxidation of the intermediate nitronate gives $\alpha$-nitroaryl ketones and esters, respectively (eq 2). This coupling reaction makes use of two of the most readily available classes of organic compounds and it tolerates a wide variety of functional groups on the aromatic partner.[16] In addition, the reaction is applicable to the synthesis of a variety of $\alpha$-(nitroheteroaromatic) carbonyl compounds. Aromatic halogen is not displaced under the alkylation conditions and hence it can be replaced with other nucleophiles. The nitro or carbonyl group can be reduced with or without concomitant reduction of other nuclear substituents. The masked amino group can be transformed into other functionalities via the diazotization reaction. This combination of reactions (Scheme I) thus provides a unique opportunity for the synthesis of variously substituted aromatic compounds. Arylacetic acids, indoles, indolinones, and other heterocycles[18] can now be prepared from these intermediates. Classical methods for the preparation of several of these compounds, wherever feasible, would be very circuitous.

**Indoles.** Several examples of reduction of $\alpha$-nitroaryl ketones to indoles have been reported[19] previously and the examples below illustrate the synthesis of various tetrahydrocarbazoles from 1-(trimethylsiloxy)cyclohexene and the appropriate aromatic nitro compounds in two steps (Scheme II). Note that in the nucleophilic alkylation step no halogen displacement occurs.

Indoles can also be synthesized from $\alpha$-nitroaryl esters and lactones if these compounds are first reduced to the aldehyde (Scheme III). In the $\gamma$-butyrolactone adducts **7** and **8**, selective reduction of the lactone to the isomeric lactols (**7a** and **8a**, respectively) is carried out with diisobutylaluminum hydride (Dibal-H). Subsequent catalytic reduction yields the indoles. While the reduction of the 4-fluoro compound **7** proceeds smoothly to give **9**, the 4-chloro derivative yielded the 1-hydroxyindole **10** as the major product. Recently such products have been observed in the reductions of 2-(dimethylamino)styrenes carrying electron-withdrawing substituents in the 5- or 6-position.[20]

Nitrobenzyl ketones readily prepared from silyl enol ethers of acetophenone and aromatic nitro compounds can be converted into 2-substituted indoles.[15c]

**2-Indolinones.** The few reported examples of reductive cyclization of $\alpha$-(nitroaryl)acetic acid derivatives to indolinones indicate the reaction to be capricious at times.[12,21] We find that various $\alpha$-(2-nitroaryl)acetic acid derivatives undergo clean reductive cyclization in 20% ethyl acetate in ethanol at 40–50 psi of hydrogen to give moderate to good yields of indolinone derivatives (Table I). With chlorinated substrates depending on the catalyst some dechlorination has been observed. For example, in entry 5 varying amounts of 3-methyl-2-indolinone are obtained as an impurity when 10% Pd/C is used as the catalyst. This can be circumvented by the use of sulfided platinum[4] as the catalyst or by reduction with iron and acetic acid. Note also that catalytic reduction of the $\gamma$-butyrolactone adducts gives 3-(2-hydroxyethyl)-2-indolinones (Table II).

As in the case of the indole synthesis, direct reduction of 3-(5-chloro-2-nitrophenyl)oxacyclopentan-2-one (**8**) gave a 1-hydroxy-2-indolinone **23** as the major product under catalytic reduction conditions (Scheme IV). Clean reduction to the normal product **24** is best carried out with Fe/acetic acid.

(17) Arylacetic and -propionic acids are among the most potent anti-inflammatory and analgesic agents. For leading references, see: (a) Giordano, C.; Castaldi, G.; Uggeri, F. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 413. (b) Walsh, D. A.; Shamblee, D. A.; Welstead, W. J., Jr.; Sancilio, L. F. *J. Med. Chem.* **1982**, *25*, 446. (c) See also: Ueda, I.; Kitaura, Y.; Konishi, N. E.P.O. Patent Application 0 008 226, July 8, 1979.

(18) For the synthesis of 1,3-benzodiazepines, see ref 15b.

(19) For a compilation of recent methods, see ref 15d.

(20) Clark, R. D.; Repke, D. B. *J. Heterocycl. Chem.* **1985**, *22*, 121 and references cited there. See also ref 21 for other examples of 1-hydroxyindoles.

(21) (a) Daisley, R. W.; Hanbali, J. R. *J. Heterocycl. Chem.* **1983**, *20*, 999 and references cited therein. (b) Wright, W. B., Jr.; Collins, K. H. *J. Am. Chem. Soc.* **1956**, *78*, 221. (c) See also ref 1d, p 163.

**Scheme V. Synthesis of 2-Indolinone-7-sulfonamide**

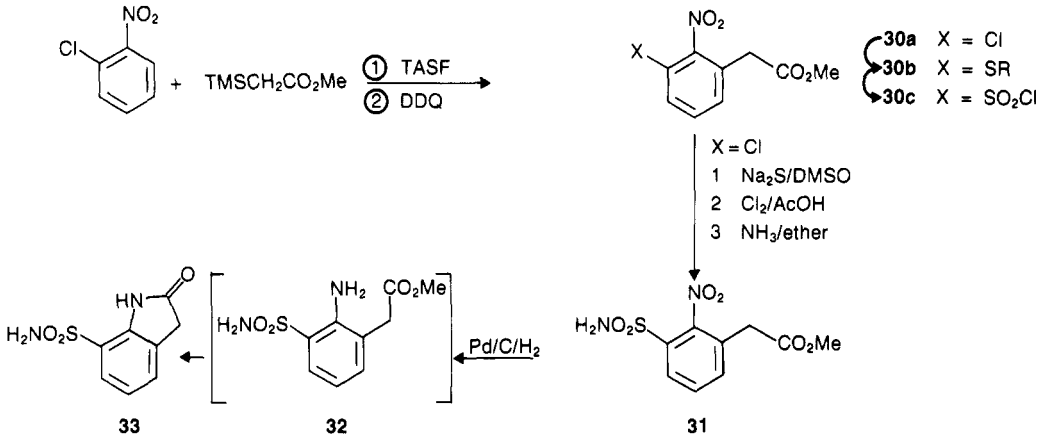
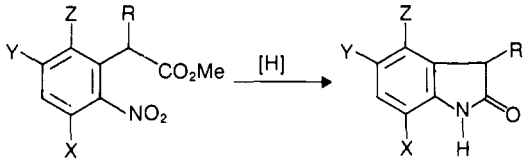


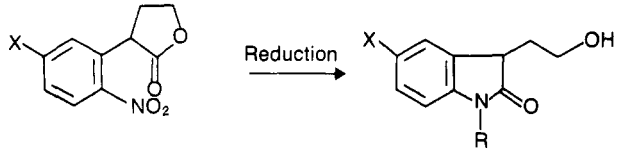

**Table I Synthesis of 2-Indolinones**




| Entry | Starting Material X | Y | Z | R | Method* | 2-Indolinone(Yield, %) |
|---|---|---|---|---|---|---|
| 1 | H | H | Cl | H | A | **11** (76) |
| 2 | H | Cl | H | H | A | **12** (80) |
| 3 | Cl | H | H | H | A | **13** (60) |
| 4 | H | H | H | Me | B | **14** (50) |
| 5 | H | Cl | H | Me | B | **15** (74) |
| 6 | Cl | Cl | H | Me | B | **16** (54) |
| 7 | H | Me | H | Me | B | **17** (95) |
| 8 | H | OMe | H | Me | B | **18** (68) |

*Method A. $Pt/S/C/H_2$ B. $Pd/C/H_2$

**Table II. Synthesis of 3-(2-Hydroxyethyl)-2-indolinones**



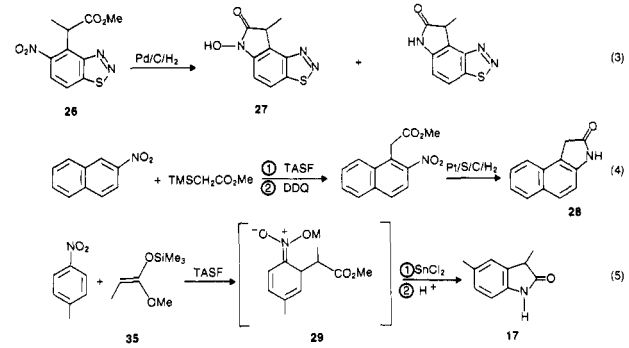

| Entry | Starting Material X | | Method | Indolinone(Yield*, %) R | |
|---|---|---|---|---|---|
| 1 | H | **19a** | $Pd/C/H_2$ | H | **20** (52) |
| 2 | Me | **19b** | $Pd/C/H_2$ | H | **21** (45) |
| 3 | F | **7** | $Pd/C/H_2$ | H | **22** (37) |
| 4 | Cl | **8** | $Pd/C/H_2$ | OH | **23** (63) |
| 5 | Cl | **8** | Fe/AcOH | H | **24** (28) |

*Isolated product. Yield of Crude product (by $^1H$ NMR) is 80 ~ 95% in the hydrogenation experiments.

The structure of this rather uncommon heterocyclic system[21,22] was proved by various spectroscopic techniques as well as subsequent chemical transformations. For example, in the high resolution $^1H$ NMR spectrum of **23** the exchangeable proton at δ 10.80 ($CDCl_3$) is characteristic of the N–OH. In addition to the parent peak, the high resolution mass spectrum shows prominent ($M^+$·–OH) peak usually seen in this type of compounds. Treatment of **23** with acetic anhydride and 4-(dimethylamino)pyridine gave bis-acetate **25** whereas only a monoacetate is formed under these conditions from the normal indolinone **22**. The bis-acetate **25** has diagnostic absorptions at 1805 and 1740 $cm^{-1}$ in the infrared spectrum.

Methyl α-methyl-5-nitro-1,2,3-benzothiadiazole-4-acetate (**26**) upon catalytic reduction also gives a 1-hydroxyindolinone **27** in addition to the expected product (eq 3).

The simplicity of this procedure is further illustrated by a two-step synthesis of benzo[4,5]indolin-2-one (**28**) from 2-nitronaphthalene and methyl (trimethylsilyl)acetate (eq 4).




At least in one instance, 2-indolinone has been synthesized, albeit in low (24%) yield, by the direct reduction of the in situ generated nitronate adduct **29** by anhydrous stannous chloride (eq 5).

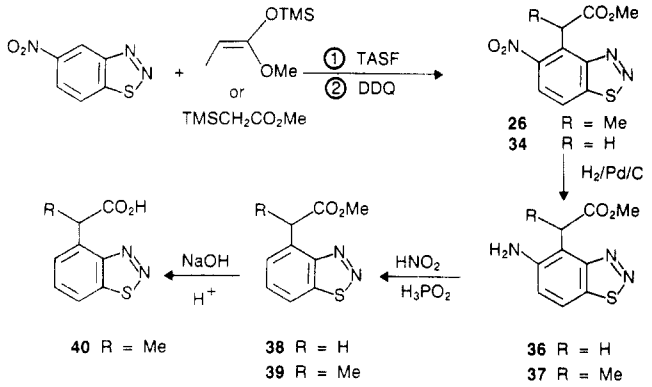
Further reduction of indolinones to indolines or indoles has been reported in the literature.[23]

An illustration of the utility of the primary adduct of nucleophilic alkylation of a halogenated nitroaromatic is shown in Scheme V with the synthesis of a deceptively simple 2-indolinone-7-sulfonamide (**33**). Methyl (trimethylsilyl)acetate is coupled with 2-chloronitrobenzene and the resulting product **30a** is subjected to nucleophilic aromatic substitution of the chlorine by sulfur. Oxidative chlorination and amination yields the nitro sulfonamide **31** in very high yield. Catalytic reduction in ethanol with 10% Pd on carbon yields the sulfonamide **32** in quantitative yield. By the appropriate choice of solvents for the reaction this reduction can be controlled to give the uncyclized amino ester **32** or the indolinone **33**. For example, by increasing the amount of ethyl acetate the cyclization

(22) For a similar compound, see: Dopp, D. *J. Chem. Soc., Chem. Commun.* **1968**, 1284.

(23) (a) McEvoy, F. J.; Allen, G. R., Jr. *J. Org. Chem.* **1973**, *38*, 3350. (b) Wierenga, W.; Griffin, J.; Warpehoski, M. A. *Tetrahedron Lett.* **1983**, *24*, 2437 and references cited therein. (c) Kubo, A.; Takai, T. *Synthesis* **1980**, 365.

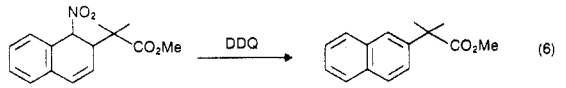
**Scheme VI. Synthesis of 1,2,3-Benzothiadiazole-4-acetic Acids**



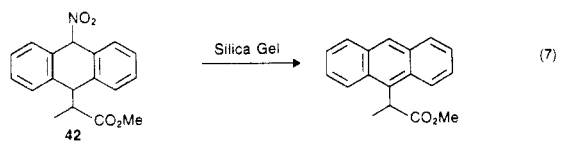

of the in situ formed amino compound is slowed down. We have also observed this behavior in the reductions of **26** and **34** (see Experimental Section). Attempts to prepare **33** by several of the classical methods described earlier failed. It is also noteworthy that in this situation the Gassman procedure cannot be employed since the reaction conditions are incompatible with oxidatively unstable (e.g., sulfur-containing groups on the aromatic nucleus) groups. Also, the alternate route of displacement by sulfur nucleophiles on a preformed haloindolinone would be equally difficult.

**Arylacetic and Arylpropionic Acids.** The α-nitroaryl esters obtained by the nucleophilic addition of silyl ketene acetals to aromatic nitrocompounds (eq 2) are readily hydrolyzed under mildly basic conditions to afford the corresponding acids. Synthesis of α-(2-nitrophenyl)-, α-(4-nitrophenyl)-, α-(5-chloro-2-nitrophenyl)-, α-(3,5-dichloro-2-nitro-phenyl)-, and α-(5-fluoro-2-nitrophenyl)-propionic acids are described in the Experimental Section. The nitro group in the initially formed adducts can be replaced by reduction and subsequent diazotization.[24] This provides a unique entry into aromatic and heteroaromatic acetic/propionic acids inaccessible by classical methods. This is illustrated in Scheme VI by the synthesis of benzothiadiazole-4-acetic and -propionic acids from the parent nitro compound. In addition, several examples of the preparation of (aminophenyl)acetic/propionic acids from indolinones have also been described in the literature.[17b,c]

We have previously shown[16c] that some dihydro aromatic adducts (**41** and **42**, for example) prepared by similar routes can be converted into esters of arylacetic acids directly by elimination of $HNO_2$ (eq 6, 7).

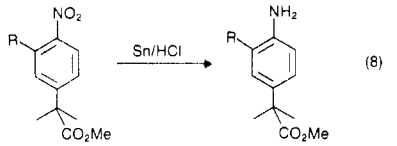



(6)

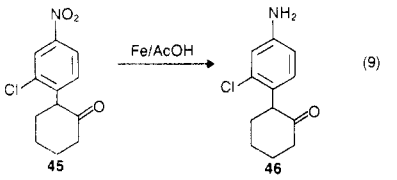



(7)

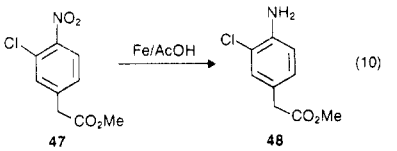
Finally, nitroaryl carbonyl compounds which cannot cyclize upon reduction (i.e., the $NO_2$ group in positions other than ortho) can be readily reduced to the corresponding aminoaryl esters or ketones. Three prototypical examples are shown in eq 8–10.




(8)




(9)




(10)

**Conclusion.** The nucleophilic alkylation of aromatic nitro compounds with silyl enol ethers is an exceptionally general reaction that provides wide variety of α-nitroaryl carbonyl compounds. These versatile intermediates can be easily converted into arylacetic acids, propionic acids, indoles, 2-indolinones and other heterocyclic compounds. The applications described in this paper are *illustrative* rather than *exhaustive* and these types of compounds derived from various aromatic and heteroaromatic systems are now readily accessible by the chemistry described here.

## Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 21 double beam Acculab 8 or Nicolet Model 7199FT spectrometer. UV spectra were recorded on a Cary 17 spectrophotometer. NMR spectra were obtained on a Varian EM-390, IBM NR80, or Nicolet 360WB spectrometer and chemical shifts are reported relative to tetramethylsilane and were recorded in $CDCl_3$ solutions unless otherwise indicated. Gas chromatography was done on a Hewlett Packard 5710A instrument. Unless otherwise specified a glass column (6 ft × $^1/_8$ in., 3% SP2100 on Supelcoport 60/80 support) was used with temperature programming.

All solvents were purified by standard procedures and were freshly distilled. Acetonitrile was refluxed with calcium hydride and was distilled fresh for each reaction. It was further dried over 3-Å sieves.

The ketene silyl acetals and silyl enol ethers were prepared according to procedures reported in the literature.[25] Aromatic nitro compounds were purchased commercially and were purified by either recrystallization or distillation. We have previously disclosed[16] the synthesis of various α-nitroaryl carbonyl compounds used in this study.

TASF[26] is extremely hygroscopic: rigorous exclusion of water from all solvents and reagents was followed in all experiments involving TASF and/or silyl enol ethers. TASF was weighed out in a dry polyethylene glovebag. Unless otherwise mentioned all experiments were carried out under nitrogen atmosphere.

**Iron–Acetic Acid Reduction[15d] of α-(2-Nitro-5-chlorophenyl)cyclohexanone (1).** A mixture of 0.784 g of iron, 1.62 mL of glacial acetic acid, 0.544 g of sodium acetate, and 1 g of the starting nitro compound[16c] was refluxed in 80 mL of 1:4 (v/v) ethanol/water for 2 h. The mixture was cooled, ethanol was evaporated, and the residue was extracted into methylene chloride. The usual workup followed by column chromatography on silica gel (1/4 $CCl_4/CH_2Cl_2$) yielded 0.160 g (20%) of 6-chloro-

(24) See for example: Tamura, Y.; Yoshimoto, Y.; Kunimoto, K.; Tada, S.; Matsumura, S.; Murayama, M.; Shibata, Y.; Enomoto, H. *J. Med. Chem.* **1981**, *24*, 43. For an example of hydrolysis and diazotization of 2-indolinone, see: Bartl, V.; Protiva, M. Czeck. CS 187, 099; *Chem. Abstr.* **1982**, *96*, 34882m.

(25) (a) Ainsworth, C.; Chen, F.; Kuo, Y.-N. *J. Organomet. Chem.* **1972**, *46*, 59. (b) Ainsworth, C.; Kuo, Y.-N. *Ibid.* **1972**, *46*, 73. (c) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, 34, 2324.

(26) Middleton, W. J. U.S. Pat. 3940402, 1976; *Org. Synth.* **1985**, *64*, 221.

1,2,3,4-tetrahydrocarbazole: mp (hexane) 140 °C (lit.[27] 143–145 °C); IR (kBr) 3410, 2940, 2860, 2840, 1620, 1600, 1470 $cm^{-1}$; $^1H$ NMR δ 1.50–2.00 (m, br, 4 H), 2.45–2.90 (m, br, 4 H), 7–7.50 (4 H, aromatic and NH; intensity reduced to 3 H upon $D_2O$ exchange); HRMS found 205.0629 ($M^+$), calcd for $C_{12}H_{12}NCl$ 205.0659.

**Catalytic Reduction of 1 Using 10% Pd on Carbon.** An ethanolic solution of 0.600 g of the title compound containing 100 mg of 10% Pd on carbon was hydrogenated using a Parr hydrogenator at 32 psi starting pressure of hydrogen. At the end of the reaction the catalyst was filtered off and the product (0.483 g, 99%) was isolated by evaporation of the solvent and was identified by comparison of properties with an authentic sample prepared by Fe/acetic acid reduction of the same starting nitro ketone. HPLC analysis of the product revealed that partial dechlorination (~10%) had occurred during the hydrogenation. This dechlorination can be avoided completely by the use of sulfided platinum on carbon (see below) as the catalyst for reduction.

**Catalytic Reduction of 2-(3,5-Dichloro-2-nitrophenyl)-cyclohexanone (3) with Sulfided Platinum on Carbon: Preparation of 6,8-Dichloro-1,2,3,4-tetrahydrocarbazole (4).** To 0.30 g of the nitro compound **3** dissolved in 20 mL of 3:1 THF/methanol was added 0.100 g of sulfided platinum on carbon (Alfa), and the mixture was subjected to hydrogenation at 1500 psi for 21 h at room temperatures. The catalyst was filtered off with the aid of Celite and the product was isolated as a crystalline solid by column chromatography on silica gel using 15% ethyl acetate/hexane as eluant: yield (0.150 g) (54%); mp 115–118 °C; IR (KBr) 3400 $cm^{-1}$; $^1H$ NMR (360 MHz) δ 1.65–1.85 (m, 4 H), 2.45–2.70 (m, 4 H), 6.32 (s, br, 1 H exchangeable with $D_2O$), 6.92 (d, $J$ = 2 Hz, 1 H), 7.13 (d, $J$ = 2 Hz, 1 H); HRMS, found 234.9960 ($M^+$), calcd for $C_{12}H_7NCl_2$ 234.9954.

Chemical reductions (Fe/acetic acid and aluminum amalgam[3e]) gave, in addition to **4**, another product exhibiting similar $^1H$ NMR spectra with a low field broad signal at δ 7.85. The structure of this air-sensitive compound has not been confirmed even though based on literature precedents (vide infra) it could most likely be the 1-hydroxy derivative of **4**.

**6-Chloro-8-methoxy-1,2,3,4-tetrahydrocarbazole (6)**: 56% (Pt/S/$H_2$); mp 61–63 °C; IR (neat) 3430 $cm^{-1}$; $^1H$ NMR (360 MHz) δ 1.80–1.95 (m, 4 H), 2.61 (t, m, $J$ = 6 Hz, 2 H), 2.68 (t, m, $J$ = 6 Hz, 2 H), 3.90 (s, 3 H), 6.56 (d, $J$ = 1 Hz, 1 H), 7.04 (d, $J$ = 1 Hz, 1 H), 7.90 (s, br, exchangeable $D_2O$, 1 H); HRMS, found 235.0758 ($M^+$), calcd for $C_{13}H_{14}NOCl$ 235.0764.

**3-(5-Fluoro-2-nitrophenyl)oxacyclopentan-2-one (7).** To a flame-dried 500-mL round-bottomed flask equipped with magnetic stirrer, dropping funnel, and a thermocouple well were added 5.30 mL (50 mmol) of 4-fluoronitrobenzene, 9.70 mL (52.5 mmol) of 4,5-dihydro-2-(trimethylsiloxy)furan, and 250 mL of anhydrous THF. The mixture was cooled to −78 °C and 13.75 g of TASF (50 mmol) in 10 mL of anhydrous acetonitrile was added dropwise (exothermic reaction; temperature was kept below −75 °C). The dropping funnel was rinsed with 5 mL more of acetonitrile and the solution was stirred for 30 min. The dry ice bath was removed and the mixture was brought to −20 °C and was further stirred for 1 h. The solution was then cooled to −78 °C and 2.43 mL (48 mmol) of bromine in 25 mL of cyclohexane was added dropwise in 15 min; stirring was continued for 10 min and the bath was removed. Fifty milliliters of saturated $KH_2PO_4$ was added and the product was extracted with three 50-mL portions of ether. The organic phase was washed with brine, dried over anhydrous magnesium sulfate, and concentrated. Column chromatography on silica gel using 1:1 ethyl acetate/hexane as solvent yielded 8.920 g (79.3%) of an off-white solid. **7**: mp (EtOH) 130–133 °C; UV (EtOH) 340 (380), 262 (5180) nm; IR (KBr) 1775, 1585, 1480, 1535, 1360 $cm^{-1}$; $^1H$ NMR δ 2.15–3.05 (m, 2 H), 4.30–4.80 (m, 3 H), 7.05–7.45 (m, 2 H), 8.00–8.45 (m, 1 H); $^{19}F$ NMR 102.69 (m); HRMS found 226.0502 ($M^+$ + 1), calcd for $C_{10}H_9NO_4F$ 226.0516, 179.0513 ($M^+ - NO_2$), calcd 179.0508.

**2-Hydroxy-3-(5-fluoro-2-nitrophenyl)oxacyclopentane (7a).** To 75 mL of an anhydrous THF solution of the lactone **7** (2.25 g, 10 mmol) at −30 °C was added 12 mL of 1 M diisobutylaluminum hydride (Dibal-H) in toluene solution over 5 min. The mixture was stirred at −30 °C for 2 h, 20 mL of sodium potassium tartrate was added, and the mixture was further stirred for 30 min. Extraction with ether, drying over magnesium sulfate, and concentration yielded 2.23 g (98%) of the product which when chromatographed on silica gel (ethyl acetate/hexane) gave pure material. The diastereomeric nature of the product was revealed by GLPC (3% SP 2100 on Supelcoport) analysis: IR (neat) 3300, 3000, 1650, 1550 $cm^{-1}$; $^1H$ NMR δ 1.80–3.00 (m, 2 H), 3.40–4.50 (m, 4 H), 5.40 (s, br), 5.60 (d, $J$ = 4 Hz), together 5.40–5.60 integrates to 1 H, diasteretopic, 6.90–7.50 (m, 2 H), 7.70–8.00 (m, 1 H); HRMS found 180.0457 ($M^+ - CH_2OH$), calcd for $C_9H_7NO_2F$ 180.0461. A minor impurity (<10%) occasionally resulted from overreduction and was identified as 2-(5-fluoro-2-nitrophenyl)-butane-1,4-diol: IR (KBr) 3360, 3080, 2930, 2880, 1620, 1520, 1480, 1360 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) δ 2.00 (m, 2 H), 3.25–4.60 (m, 7 H), 6.95–8.00 (m, 3 H); HRMS 212.0730 ($M^+$ − OH), calcd for $C_{10}H_{11}NO_3F$ 212.0723.

**5-Fluorotryptophol (9).** A solution of 2.24 g (9.86 mmol) of lactol **7a** in 30 mL of 20% ethyl acetate in ethanol was hydrogenated at 50 psi using 500 mg of 5% Pd/C. After filtration and concentration, 1.730 g (98%) of product was isolated. The crude product was recrystallized from benzene: mp 89–91 °C; IR (KBr) 3400–2800, 1620, 1580, 1545, 1530, 1050 $cm^{-1}$; $^1H$ NMR δ 2.90 (t, $J$ = 7 Hz, 2 H), 3.65 (t, $J$ = 7 Hz, 2 H), 4.50 (s, br, 1 H, exchangeable with $D_2O$), 7.20–7.90 (m, 4 H), 11.30 (s, br, 1 H, exchangeable with $D_2O$); HRMS, found 180.0934 ($M^+$ + 1), calcd 180.0825, 179.0848 ($M^+$), calcd for $C_{10}H_{10}NOF$ 179.0746.

***O*-(*tert*-Butyldimethylsilyl)-5-fluorotryptophol.** A mixture of 1.141 g (6.38 mmol) of **9**, 0.456 g (6.70 mmol) of imidazole, and 1.005 g (6.70 mmol) of *tert*-butyldimethylsilyl chloride in 20 mL of DMF was stirred at 0 °C to room temperature for 20 h. Fifty milliliters of water was added and the product was extracted into ether. The ether layer was washed with water, dried, and concentrated to yield 1.832 g (98%) of the product: IR (neat) 3430, 2960, 2860, 1630, 1615, 1585, 1255, 1100, 840 $cm^{-1}$; $^1H$ NMR δ 0.05 (s, 6 H), 0.90 (s, 9 H), 2.90 (t, $J$ = 7 Hz, 2 H), 3.80 (t, $J$ = 7 Hz, 2 H), 6.50–7.30 (m, 4 H), 9.00 (s, br, 1 H, exchangeable with $D_2O$); HRMS, found 293.1614 ($M^+$), calcd for $C_{16}H_{24}NOSiF$ 293.1611.

**2-Hydroxy-3-(5-chloro-2-nitrophenyl)oxacyclopentane (8a).** To a flame-dried 100-mL flask, equipped with magnetic stirring bar and a septum was added 0.241 g (1 mmol) of 3-(5-chloro-2-nitrophenyl)oxacyclopentan-2-one[16c] in 10 mL of anhydrous THF. The solution was cooled to −30 °C and 1.2 mL of 1 M Dibal-H solution in toluene was added. The mixture was warmed to 0 °C. The reaction was followed by GC (3% SP2100 on Supelcoport $^1/_8$ in. × 6 ft glass column, programmed run, 130 °C to 240 °C, increment of 32°/min). After 3 h, 10 mL of saturated sodium potassium tartrate was added, and the ice bath was removed and stirring was continued for 30 min. The product was extracted into ether and the ether extracts were combined and dried. Chromatography on silica gel yielded 0.145 (60%) g of the product: IR (neat) 3350, 3000, 1625, 1580, 1520 $cm^{-1}$; $^1H$ NMR δ 1.70–3.00 (m, 2 H), 3.45 (s, br, 1 H), 3.50–4.45 (m, 3 H), 5.40–5.70 (two m, 1 H), 7.20–7.80 (m, 3 H); HRMS, found 242.0231 ($M^+$ − H), calcd for $C_{10}H_9NO_4Cl$ 242.0220, 226.0277 ($M^+$ − OH), calcd 226.0271.

**1-Hydroxy-5-chlorotryptophol (10).** The lactol **8a** (0.94 g) was hydrogenated in 20% ethyl acetate/ethanol and the product was chromatographed on silica gel using 1:1 ethyl acetate/hexanes containing 5% methanol to get 0.391 g (48%) of a solid which was recrystallized from hexane/benzene: mp 127–133 °C dec; UV (EtOH) 303 (3610), 288 (3650), 233 (32 370) nm; IR (KBr) 3400, 2800, 1610, 1560, 1540, 1060 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$/$CDCl_3$) δ 2.90 (t, $J$ = 6 Hz, 2 H), 3.80 (t, $J$ = 6 Hz, 2 H), 3.60–3.90 (s, br, 1 H, exchangeable with $D_2O$), 7.00–7.70 (m, 4 H), 10.67 (s, 1 H, exchangeable with $D_2O$); HRMS, found 211.0398 ($M^+$), calcd for $C_{10}H_{10}NO_2Cl$ 211.0400, 193.0282 ($M^+ - H_2O$), calcd 193.0294. Also present are trace amounts of ions corresponding to the indole: HRMS, found 195.0438 ($M^+$), calcd for $C_{10}H_{10}NOCl$ 195.0451. Anal. for **10**: C, 56.76 (calcd 56.87), H, 4.74 (5.06), N, 6.68 (6.63).

**Catalytic Reduction of α-(2-Nitroaryl) Carbonyl Compounds: Synthesis of 2-Indolinones.** The following compounds were also prepared by catalytic hydrogenation over 5% Pd/C at 40–50 psi in 20–25% ethyl acetate/ethanol at room temperature. The catalyst was filtered off with the aid of Celite and the filter

(27) Campaigne, E. E.; Lake, R. D. *J. Org. Chem.* **1959**, *24*, 478.

cake was washed with boiling ethyl acetate. Crude yields of essentially pure material (TLC, NMR) were 90–95%. The reported yields are for isolated crystallized material. Column chromatography was done on silica gel using ethyl acetate/hexane mixtures or the same solvent mixture containing 5–10% methanol.

**3-Methyl-2-indolinone (14)**: yield 50%; mp (benzene) 118 °C (lit.[28] 123 °C); IR (KBr) 3200, 1715, 1075, 1620 $cm^{-1}$; $^1H$ NMR $\delta$ 1.50 (d, $J$ = 7 Hz, 3 H), 3.50 (q, $J$ = 7 Hz, 1 H), 7.10 (m, 4 H), 9.10 (s, br, 1 H) exchangeable with $D_2O$).

**5-Chloro-3-methyl-2-indolinone (15)**: yield 74%; mp 199–201 °C; IR (KBr) 3200, 2960, 2920, 2860, 1725, 1670, 1620 $cm^{-1}$; $^1H$ NMR $\delta$ ($Me_2SO$-$d_6$) 1.43 (d, $J$ = 7 Hz, 3 H), 3.37 (q, $J$ = 7 Hz, 1 H), 6.77 (d, $J$ = 9 Hz, 1 H), 7.13 (m, 2 H), 9.70 (s, br, 1 H); (360 MHz) $\delta$ 1.45 (d, $J$ = 9 Hz, 3 H), 3.45 (q, $J$ = 9 Hz, 1 H), 6.82 (d, $J$ = 9 Hz, 1 H), 7.19 (s, br, 1 H), 7.20 (s, br, 1 H), 8.50 (s, br, 1 H exchangeable with $D_2O$); HRMS, found 181.0286 ($M^+$), calcd for $C_9H_8NOCl$ 181.0295.

**5,7-Dichloro-3-methyl-2-indolinone (16)**: yield 54%; mp (ether/hexanes) 159–161 °C; IR (KBr) 3200, 1725, 1620, 1580 $cm^{-1}$; $^1H$ NMR $\delta$ 1.50 (d, $J$ = 8 Hz, 3 H), 3.53 (q, $J$ = 8 Hz, 1 H), 7.06 (s, br, 1 H), 7.20 (m, 1 H), 8.50–9.20 (s, br, 1 H, exchangeable with $D_2O$); HRMS, found 214.9916 ($M^+$), calcd for $C_9H_7NOCl_2$ 214.9905. Anal. C, H, N, Cl.

**3,5-Dimethyl-2-indolinone (17)**: yield >95%; mp 153–156 °C; vide infra for physical data.

**7-Chloro-2-indolinone (13).** Methyl (2-nitro-3-chlorophenyl)acetate (0.722 g,) dissolved in 15 mL of ethanol/ethyl acetate (8:1, v/v) was hydrogenated by using a Parr hydrogenator to get a solid which showed two spots on TLC. Trituration with methylene chloride gave 0.210 g of a solid identified as 7-chloro-2-indolinone, mp 223–225 °C (lit.[29] mp 214–217 °C). The minor product (0.070 g) was identified as 2-indolinone by comparison of properties with those of an authentic sample. **7-Chloro-2-indolinone**: IR (KBr) 3200, 3080, 2940, 1700, 1620, 1585, 480 $cm^{-1}$; $^1H$ NMR (360 MHz) $\delta$ 3.61 (s, 2 H), 6.97 (t, $J$ = 8 Hz, 1 H), 7.12 (dd, $J$ = 8 Hz, 2 Hz, 1 H), 7.21 (dd, $J$ = 8 Hz, 2 Hz, 1 H), 7.92 (s, br, exchangeable $D_2O$, 1 H).

Reduction with Fe/acetic acid gave some free amine (30%) as well as clean 7-chloro-2-indolinone (23%). No trace of dechlorination was observed (vide infra).

**5-Methoxy-3-methyl-2-indolinone (18)**: yield 68%; mp 125–126 °C; IR (KBr) 3200–2800, 1700, 1605, 1485, 1210 $cm^{-1}$; $^1H$ NMR (360 MHz) $\delta$ 1.49 (d, $J$ = 8 Hz, 3 H), 3.45 (q, $J$ = 8 Hz, 1 H), 3.79 (s, 3 H), 6.72 (dd, $J$ = 8 Hz, 2 Hz, 1 H), 6.81 (d, $J$ = 8 Hz, 1 H), 6.84 (s, 1 H) 8.63 (s, br, 1 H); HRMS, found 177.0776 ($M^+$), calcd for $C_{10}H_{11}NO_2$ 177.0789.

**3-(2-Hydroxyethyl)-2-indolinone (20)**: yield 52%; mp ($CHCl_3$) 109–110 °C; (lit.[23] mp 107–110 °C); (KBr) 3400–3000, 1695, 1620, 1600, 1490 $cm^{-1}$; $^1H$ NMR $\delta$ 1.60–2.30 (m, 2 H), 3.13 (s, br, 1 H), 3.60 (t, $J$ = 5 Hz), 1 H), 3.90 (t, $J$ = 5 Hz, 2 H), 6.73–7.33 (m, 4 H), 8.67 (s, br, 1 H, exchangeable with $D_2O$); HRMS, found 177.0806 ($M^+$), calcd for $C_{10}H_{11}NO_2$ 177.0790.

**3-(2-Hydroxyethyl)-5-methyl-2-indolinone (21)**: yield 45%; mp 116–118 °C; IR (KBr) 3400, 1695, 1625, 1490 $cm^{-1}$; $^1H$ NMR $\delta$ 2.10 (m, 2 H), 2.27 (s, 3 H), 3.53 (t, $J$ = 6 Hz, 1 H), 3.87 (s, br, 3 H, upon adding $D_2O$ sharpens to a triplet, $J$ = 6 Hz, 2 H), 6.73 (d, $J$ = 10 Hz, 1 H), 6.96 (d, $J$ = 10 Hz, 1 H), 7.03 (s, 1 H), 9.50 (s, br, 1 H, exchangeable with $D_2O$); HRMS, found 191.0914 ($M^+$), calcd for $C_{11}H_{13}NO_2$ 191.0946. Anal. C, H, N.

**3-(2-Hydroxyethyl)-5-fluoro-2-indolinone (22)**: yield 37%; mp ($CHCl_3$/hexane) 115.5–116.5 °C; IR (KBr) 3400–3000, 1700, 1630, 1610, 1490 $cm^{-1}$; $^1H$ NMR ($CD_3COCD_3$, 360 MHz) $\delta$ 2.18 (m, 2 H), 3.62 (t, $J$ = 7 Hz, 1 H), 3.79 (m, 2 H, sharpens to t upon addition of $D_2O$, $J$ = 6 Hz), 4.05 (t, $J$ = 4 Hz, 1 H, exchangeable with $D_2O$), 6.82–7.00 (m, 2 H), 7.10–7.20 (m, 1 H), 9.58 (s, br, 1 H, exchangeable with $D_2O$); ($Me_2SO$-$d_6$) $\delta$ 1.05 (m, 2 H), 2.60 (m, 2 H), 3.55 (s, br, 2 H), 6.00 (m, br, 3 H), 9.45 (s, br, 1 H); $^{19}F$ NMR ($CD_3COCD_3$) -122.2 (q, m); HRMS, found 195.0695 ($M^+$), calcd for $C_{10}H_{10}NO_2F$ 195.0696, 177.0588 ($M^+ - H_2O$), calcd 177.0589. Anal. C, 60.42 (calcd 61.32), H, 5.14 (5.17), N, 6.85 (7.18).

**1-Hydroxy-3-(2-hydroxyethyl)-5-chloro-2-indolinone (23)**: yield 63%; mp 179–182 °C; IR (KBr) 3420, 3260, 1695, 1620, 1475, 1070, 1030 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 360 MHz) $\delta$ 1.90 (m, 1 H), 2.05 (m, 1 H), 3.52 (m, 2 H), 3.62 (t, $J$ = Hz, 1 H), 4.67 (t, br, $J$ = 4 Hz, 1 H, exchangeable with $D_2O$), 7.40 (s, br, 1 H), 7.32 (dd, $J$ = 8 Hz, 2 Hz, 1 H), 6.86 (d, $J$ = 8 Hz, 1 H), 10.80 (s, br, 1 H, exchangeable with $D_2O$); ($Me_2SO$-$d_6$) (360 MHz) $\delta$ 1.90 (m, 1 H), 2.05 (m, 1 H), 3.52 (m, br, 2 H), 3.62 (t, $J$ = 6 Hz, 1 H, exchangeable with $D_2O$), 4.67 (t, br, $J$ = 4 Hz, 1 H, exchangeable with $D_2O$), 6.86 (d, $J$ = 8 Hz, 1 H), 7.32 (dd, $J$ = 8 Hz, 2 Hz, 1 H), 7.40 (s, br, 1 H), 10.80 (s, br, 1 H, exchangeable with $D_2O$); HRMS, found 227.0342 ($M^+$), calcd for $C_{10}H_{10}NO_3Cl$ 227.0349. Anal. C, 53.38 (calcd 52.85), H, 4.59 (4.43), N, 5.07 (6.16). HRMS and TLC of the crude reaction product indicated the presence of 3-(2-hydroxyethyl)-5-chloro-2-indolinone (**24**) as the major side product, a compound which was also prepared by Fe/acetic acid reduction of **8** (see below).

**Catalytic Reduction of $\alpha$-Nitroaryl Esters in the Presence of Sulfided Platinum on Carbon.** The following indolinones containing chlorine substituents are best prepared by catalytic reduction of the corresponding nitrobenzeneacetates. Typically 0.300 g of the starting material dissolved in 20 mL of 3:1 THF/methanol was charged in a glass liner of a pressure vessel containing 100 mg of 10% sulfided platinum on carbon. The vessel was subjected to 1500 psi of $H_2$ and maintained at that pressure at room temperature for 18 h. Evaporation of the solvent followed by chromatography on silica gel (ethyl acetate/hexane as the solvent) yielded the indolinones in 65–90% yield. The crude product was recrystallized from acetone/hexane.

**4-Chloro-2-indolinone (11)**: mp 216–218 °C (lit.[21b] mp 217–218 °C); $^1H$ NMR (360 MHz) $\delta$ 3.55 (s, 2 H), 6.80 (d, $J$ = 7 Hz, 1 H), 7.00 (d, $J$ = 8 Hz, 1 H), 7.17 (dd, $J$ = 8 Hz, 7 Hz, 1 H), 8.70 (s, br, exchangeable with $D_2O$, 1 H).

**5-Chloro-2-indolinone (12)**: mp 198–199 °C (lit.[21b] mp 195–196 °C); $^1H$ NMR (360 MHz) $\delta$ 3.53 (s, 2 H), 6.80 (d, $J$ = 8 Hz, 1 H), 7.19 (d, $J$ = 8 Hz, 1 H), 7.20 (s, 1 H), 8.66 (s, br, exchangeable with $D_2O$, 1 H). A significant proportion of the uncyclized amine was obtained in this case. This can be readily cyclized to the indolinone by treatment with triethylamine in $CH_2Cl_2$/methanol.

**7-Chloro-2-indolinone (13)**: mp 223–225 °C (lit.[29] mp 214–217 °C); vide supra for data.

**Benzo[4,5]indolin-2-one (28)**: mp 237–241 °C dec; IR (KBr) 3200, 1710, 1635 $cm^{-1}$; $^1H$ NMR (360 MHz) $\delta$ 3.81 (s, 2 H), 7.18 (d, $J$ = 8 Hz, 1 H), 7.37 (t, m, $J$ = 8 Hz, 1 H), 7.51 (t, m, $J$ = 8 Hz, 1 H), 7.65 (d, $J$ = 8 Hz, 1 H), 7.79 (d, $J$ = 8 Hz, 1 H), 7.83 (d, $J$ = 8 Hz, 1 H), 8.12 (s, br, exchangeable with $D_2O$, 1 H); HRMS, found 183.0677 ($M^+$), calcd for $C_{12}H_9NO$ 183.0684.

**5-Chloro-3-(2-hydroxyethyl)-2-indolinone (24) via Reduction of 8 with Fe/Acetic Acid.** A mixture of 0.482 g (2 mmol) of **8** 0.392 g of iron powder, 0.800 mL of acetic acid, and 0.272 g of sodium acetate in 50 mL of 4:1 (v/v) ethanol/water was refluxed for 2 h under nitrogen. The reaction mixture was cooled and the solvent was evaporated. The residue was extracted into methylene chloride (30 mL × 4), and the combined organic layer was washed with saturated sodium chloride. Concentration of the dried extract followed by chromatography on silica gel using 1:1 ethyl acetate/hexane containing 5% methanol yielded 0.120 g (28%) of product identified as the desired 2-indolinone: mp 145–148 °C dec; IR (KBr) 3440, 2960, 2930, 2880, 1700, 1620, 1480, 1040 $cm^{-1}$; $^1H$ NMR (360 MHz, $Me_2SO$-$d_6$) $\delta$ 2.05 (m, 1 H), 2.25 (m, 1 H), 3.65–3.85 (m, br, 3 H), 4.85 (t, $J$ = 5 Hz, 1 H, exchangeable with $D_2O$), 7.05 (d, $J$ = 8 Hz, 1 H), 7.42 (d, m, $J$ = 8 Hz, 1 H), 7.54 (s, br, 1 H), 10.65 (s, br, 1 H, exchangeable with $D_2O$); HRMS, found 211.0398 ($M^+$), calcd for $C_{10}H_{10}NO_2Cl$ 211.0400. No trace of the corresponding 1-hydroxy-2-indolinone (**23**) (vide supra, catalytic reduction) was observed.

**Iron–Acetic Acid Reduction of Methyl (3-Chloro-2-nitrophenyl)acetate.** Following the standard procedure reported in the previous experiment, methyl (2-amino-3-chlorophenyl)-acetate (30%) and 7-chloro-2-indolinone (23%) were prepared by reduction of the title compound. **Methyl (2-amino-3-chlorophenyl)acetate**: IR (neat) 3420, 3350, 3080, 3030, 2990, 2950, 1710, 1640, 1600, 1500, 1220 $cm^{-1}$; $^1H$ NMR (360 MHz) $\delta$ 3.68 (s, 2 H), 3.70 (s, 3 H), 4.52 (s, br, exchangeable with $D_2O$, 2 H), 6.65 (t, $J$ = 8 Hz, 1 H), 7.00 (dd, $J$ = 8 Hz, 2 Hz, 1 H), 7.20 (dd, $J$ = 8 Hz, 2 Hz, 1 H); HRMS, found 199.0395 ($M^+$), calcd for $C_9H_{10}NO_2Cl$ 199.0399. 7-Chloro-2-indolinone: mp 223–225 °C (lit.[29] mp 214–217 °C).

(28) Brunner, K. *Monatsh. Chem.* **1897**, *18*, 527.
(29) Nakashima, T.; Suzuki, I. *Chem. Pharm. Bull.* **1969**, *17*, 2293. U.S. Pat. 3 883 236; *Chem. Abstr.* **1970**, *72*, 55145.

**1-Acetoxy-3-(2-acetoxyethyl)-5-chloro-2-indolinone (25).** A methylene chloride solution of 0.250 g of **23** and 0.230 g of (dimethylamino)pyridine was treated with 0.200 mL of acetic anhydride at 0 °C. Upon disappearance of starting material the product was extracted into $CH_2Cl_2$ after adding 10 mL of 1 N HCl and was chromatographed on silica gel using ethyl acetate/hexane as solvent: yield, 0.053 g (19%); IR (KBr) 1805, 1740, 1610, 1235 $cm^{-1}$; $^1H$ NMR δ 1.96 (s, 3 H), 2.37 (m, superimposed on s (δ 2.39, 3 H), total 5 H), 3.67 (t, $J$ = 5 Hz, 1 H), 4.20 (d, t, $J$ = 6 Hz, 1 Hz, 2 H), 6.70 (d, $J$ = 9 Hz, 1 H), 7.20 (d, m, $J$ = 9 Hz, 1 H), 7.30 (m, 1 H); HRMS, found 269.0450 ($M^+ - CH_2CO$), calcd for $C_{12}H_{12}NO_4Cl$ 269.0454.

**3-(2-Acetoxyethyl)-5-fluoro-2-indolinone.** To a solution of 0.288 g (1.48 mmol) of **22** in 10 mL of methylene chloride were added 0.142 mL (1.75 mmol) of pyridine, 0.220 g (0.18 mmol) of 4-(dimethylamino)pyridine, and 0.165 mL (1.75 mmol) of acetic anhydride. The mixture was stirred at 0 °C to room temperature for 2 h. The reaction mixture was extracted with 10 mL of $CH_2Cl_2$ after adding 5 mL of 1 N HCl. After washing with saturated sodium chloride, the organic layer was dried and concentrated to give 0.296 g (84%) of the acetate: IR (KBr) 3260, 1720, 1625, 1605, 1485, 1235 $cm^{-1}$; $^1H$ NMR δ 1.98 (s, 3 H), 2.38 (m, 2 H), 3.55 (t, $J$ = 5 Hz, 1 H), 4.15 (dt, $J$ = 2 Hz, 7 Hz, 2 H), 6.80–7.05 (m, 3 H), 9.20 (s, br, 1 H); HRMS found 237.0802 ($M^+$), calcd for $C_{12}H_{12}NO_3F$ 237.0801.

**3,5-Dimethyl-2-indolinone via in Situ Reduction of an Aromatic Nitronate (29): Preparation of 17.** A three-necked flask fitted with a 25-mL addition funnel was charged with 1.08 g (7.88 mmol) of 4-nitrotoluene and 1.716 g (9.85 mmol) of (*E*)-1-methoxy-1-(trimethylsiloxy)-1-propene (**35**)[25] in 10 mL of THF. From the addition funnel 2.73 g (10 mmol) of TASF in 2 mL of freshly distilled acetonitrile was added dropwise to the reaction flask at −10 °C. The mixture was warmed to 0 °C and maintained at 0 °C for 3 h and 1.90 g of anhydrous $SnCl_2$ dissolved in 15 mL of dry THF was added slowly. The mixture was stirred for 10 min and 2 mL of concentrated HCl was added followed by 8 mL of water. After being refluxed for 30 min the solution was basified to pH 10. The aqueous layer was extracted into ether, dried, and concentrated. Chromatography on silica gel yielded 0.302 g (24%) of **17**: IR (KBr) 3210, 3020, 2960, 2920, 2860, 1710, 1625, 1490, $cm^{-1}$; $^1H$ NMR δ 1.50 (d, $J$ = 8 Hz, 3 H), 2.30 (s, 3 H), 3.45 (q, $J$ = 8 Hz, 1 H), 6.90 (m, 3 H), 8.50 (s, br, 1 H, exchangeable with $D_2O$); HRMS, found 161.0837 ($M^+$), calcd for $C_{10}H_{11}NO$ 161.0840.

**Sn/HCl Reductions of α-Nitroaryl Carbonyl Compounds. Methyl α,α-Dimethyl-4-aminobenzene-1-acetate (44a) by Reduction of Methyl 4-Nitrobenzene-1-acetate (43a) with Sn and Concentrated HCl.** To 0.250 g of the nitro compound **43a** in 5 mL of methanol was added 0.360 g of tin granules. From the top of a condenser connected to the flask was added 2 mL of concentrated HCl, 0.3 mL at a time. After the addition was complete, the mixture was warmed on a water bath for 30 min. After cooling, sufficient 10% sodium hydroxide was added to get the medium to pH 13. The product was extracted into ether, and the combined ether layer was dried and concentrated. Chromatography using 20% acetone/petroleum ether gave the product identified as its benzoyl derivative: $^1H$ NMR δ 1.50 (s, 6 H), 3.55 (s, 3 H), 3.50–3.57 (s, br, exchangeable with $D_2O$, 2 H), 6.55 (d, $J$ = 8 Hz, 2 H), 7.10 (d, $J$ = 8 Hz, 2 H). The benzoyl derivative: mp 80–84 °C; IR (KBr) 3270, 3050, 2980, 2950, 1730, 1645, 1600, 1590, 1575, 1535, 1520, 1140 $cm^{-1}$; $^1H$ NMR δ 1.05 (s, 6 H), 3.60 (s, 3 H), 7.25–8.00 (m, 10 H); HRMS, found 297.1371 ($M^+$), calcd for $C_{18}H_{19}NO_3$ 297.1365.

**3-Methyl-2-indolinone via Sn/HCl Reduction.** The title compound can be prepared by the same procedure as described in the previous experiment by the reduction of methyl α-methyl-2-nitrobenzeneacetate.

**Methyl 2-Nitro-3-sulfonamidobenzene-1-acetate (31).** A mixture of 2.29 g (10 mmol) of methyl 3-chloronitrobenzene-1-acetate (**30a**)[16c] and 0.86 g (11 mmol) of sodium sulfide in 20 mL of $Me_2SO$ was stirred under nitrogen for 18 h. A check of the reaction by TLC showed it to be incomplete. An additional 0.100 g of sodium sulfide was added and the reaction was stirred for 4 more h. Thirty milliliters of 1.5 N HCl and 70 mL of methylene chloride were added and the organic layer was separated. The aqueous layer was further extracted with three portions of 50 mL each of methylene chloride. The combined $CH_2Cl_2$ layer was washed with saturated sodium chloride and concentrated. Last traces of the solvents were removed on a high vacuum pump to get a semisolid. Trituration with ether deposited a solid (1.50 g, 66%), identified as 3-(carbomethoxymethyl)-2-nitrophenyl disulfide (**30b**), which was used for the next step without further purification: $^1H$ NMR (360 MHz) δ 3.73 (s, 6 H), 3.86 (s, 4 H), 7.15–7.65 (m, 4 H), 7.83 (dd, $J$ = 7 Hz, 2 Hz, 2 H); HRMS, found 226.0164 ($M^+ - C_9H_8NO_4S$), calcd 226.0174.

The disulfide **30b** was dissolved in 15 mL of 4:1 acetic acid/water and chlorine gas was passed through the solution for approximately 20 min. The reaction flask was well stoppered and stirred for 30 min and was then added to 50 mL of water. The product was extracted into ether, and the combined ether extract was washed with saturated sodium chloride, dried, and concentrated. It was further dried by azeotroping with benzene. Crude yield of the sulfonyl chloride **30c**: 1.87 g (90%); IR (neat) 1740, 1550, 1385, 1365, 1200, 1175 $cm^{-1}$; $^1H$ NMR δ 3.76 (s, 5 H), 7.80–8.10 (m, 2 H), 8.30 (dd, $J$ = 8 Hz, 3 Hz, 1 H).

The sulfonyl chloride **30c** was dissolved in 100 mL of anhydrous ether. Approximately 5 mL of ammonia was condensed into the reaction mixture with the aid of a cold finger, and the reaction was stirred at 0 °C to room temperature for 2 h. Excess ammonia was removed by warming the reaction mixture on a warm water bath. Ether was removed on the rotary evaporator and 30 mL of saturated potassium dihydrogen phosphate solution was added to the residue. The product was extracted into methylene chloride, washed, and dried. Evaporation of the solvent and chromatography on silica gel (1:1 ethyl acetate/hexane with 5% methanol as solvent) gave the expected product **31**: yield 0.950 g (54%); IR (KBr) 3400–3000, 2960, 2900, 2840, 1735, 1600, 1540, 1340, 1370, 1170 $cm^{-1}$; $^1H$ NMR δ 3.77 (s, 3 H), 3.83 (s, 2 H), 5.40 (s, br, exchangeable with $D_2O$, 2 H), 7.73 (d, $J$ = 5 Hz, 1 H), 7.74 (d, $J$ = 5 Hz, 1 H), 8.16 (t, $J$ = 5 Hz, 1 H); HRMS, found 228.0322 ($M^+ - NO_2$), calcd for $C_9H_{10}NO_4S$ 228.0330.

**2-Oxoindoline-7-sulfonamide (33).** An ethanolic solution of 0.60 g of **31** was hydrogenated in a Parr shaker using 200 mg of 10% Pd on C at 40 psi of hydrogen. The catalyst was filtered off with the aid of Celite. The filter cake was washed with excess boiling ethanol. The ethanolic solution was refluxed for 1 h to promote cyclization of the amino ester. The solvent was removed and the product was isolated by chromatography on silica gel (1:1 ethyl acetate/hexane containing 5% methanol): yield 0.45 g (97%); IR (KBr) 3340, 3240, 1710, 1615, 1590, 1310, 1130 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3/Me_2SO$-$d_6$) δ 3.60 (s, 2 H), 7.10 (t, $J$ = 8 Hz, 1 H), 7.41 (d, $J$ = 8 Hz, 1 H), 7.42 (s, br, exchangeable with $D_2O$, 2 H), 7.57 (d, $J$ = 8 Hz, 1 H), 9.90 (s, br, exchangeable with $D_2O$, 1 H). HRMS, found 212.0237 ($M^+$), calcd for $C_8H_8N_2O_3S$ 212.0255.

Reduction in ethyl acetate containing varying amounts of ethanol (20–80%) gave significant amounts of uncyclized amino ester **32** which can be separated from minor amounts of the product by column chromatography. **32**: IR (neat) 3400, 1720, 1635, 1595, 1580, 1550, 1325, 1140 $cm^{-1}$; $^1H$ NMR ($CDCl_3/Me_2SO$-$d_6$) δ 3.67 (s, 2 H), 3.76 (s, 3 H), 5.56 (s, br, exchangeable with $D_2O$, 2 H), 6.80 (t, $J$ = 8 Hz, 1 H), 7.10 (s, br, exchangeable with $D_2O$, 2 H), 7.33 (d, $J$ = 8 Hz, 1 H), 7.80 (d, $J$ = 8 Hz, 1 H); HRMS, found 244.0518 ($M^+$), calcd for $C_9H_{12}N_2O_4S$ 244.0518.

**Methyl 5-Nitro-1,2,3-benzothiadiazole-4-acetate (34).** To a dry three necked flask fitted with a magnetic stirring bar, a thermocouple lead, and an addition funnel with a nitrogen inlet were added 5-nitro-1,2,3-benzothiadiazole (10 g, 55.2 mmol), dry THF (850 mL), and methyl (trimethylsilyl)acetate (9.05 mL, 55.2 mmol). The solution was chilled to −55 °C and TASF (15.2 g, 55.2 mmol) dissolved in dry acetonitrile (100 mL) was added dropwise over 1 h while maintaining the temperature at −55 °C to −50 °C. The precipitate which formed redissolved on warming to −3 °C. The solution was cooled to −38 °C and DDQ (12.54 g, 55.2 mmol) was added in portions over 2 min. The mixture was allowed to warm to ambient temperature and the solvent was evaporated at reduced pressure (40 °C). The residue was flash chromatographed on silica gel to give 0.95 g of recovered 5-nitro-1,2,3-benzothiadiazole on elution with 10% ether–hexane. Continued elution with 25% ether–hexane gave 10.57 g (75%) of **34** as a pale yellow solid: mp 96–98 °C; IR (KBr) 1734, 1521, 1345, 1200, 1180 $cm^{-1}$; $^1H$ NMR δ 3.80 (s, 3 H), 5.07 (s, 2 H), 8.35

(AB q, $\Delta\nu_{1-3}$ = 24 Hz, $J$ = 8 Hz, 2 H). Anal. C, H, N (sublimed at 85 °C/0.03 mm).

**Methyl α-Methyl-5-nitro-1,2,3-benzothiadiazole-4-acetate (26).** To a dry three-necked flask equipped with mechanical stirring, a thermo couple, and an addition funnel with nitrogen inlet were added 5-nitro-1,2,3-benzothiadiazole (3.6 g, 20 mmol), dry THF (350 mL), and (*E*)-1-methoxy-1-(trimethylsilyloxy)-propene (4.0 mL, 20 mmol). The solution was chilled to −50 °C and TASF (5.5 g, 20 mmol) in dry acetonitrile (60 mL) was added dropwise over 1 h while maintaining the mixture at −55 °C to −50 °C. DDQ (4.6 g, 20 mmol) was added in portions over 1 min. The reaction was then allowed to warm to ambient temperature. The solvent was evaporated at reduced pressure (40 °C) and the residue was flash chromatographed on silica gel (20% ether–hexane) to give first 0.1 g of recovered 5-nitro-1,2,3-benzothiadiazole and then 2.46 g (46%) of **26** as a pale yellow solid: mp 87.5–90 °C; IR (KBr) 1743, 1720, 1523, 1341 cm$^{-1}$; $^1$H NMR δ 1.90 (d, $J$ = 7 Hz, 3 H), 3.60 (s, 3 H), 5.40 (q, $J$ = 7 Hz, 1 H), 8.25 (AB q, $\Delta\nu_{1-3}$ = 17 Hz, $J$ = 9 Hz, 2 H). Anal. C, H, N (sublimed at 70 °C/0.03 mm).

**Methyl 5-Amino-1,2,3-benzothiadiazole-4-acetate (36).** A Parr bottle rinsed twice with ethanol was charged with absolute ethanol (100 mL), 5% Pd/C (0.6 g), and a solution of **34** (2.0 g, 7.9 mmol) in ethyl acetate (100 mL). The mixture was hydrogenated until hydrogen uptake ceased. The mixture was filtered through a Celite pad and concentrated to give 1.74 g (82%) of **36** which was suitable for further reaction. Recrystallization from ethanol (100 mL boiled down to 35 mL and cooling) gave 1.45 g of fluffy yellow needles: mp 138–139 °C; IR (KBr) 3420, 3349, 1722 cm$^{-1}$; $^1$H NMR δ 3.71 (s, 3 H), 4.45 (s, 4 H, integration reduces to 2 H with $D_2O$ wash), 7.55 (AB q, $\Delta\nu_{1-3}$ = 53 Hz, $J$ = 9 Hz, 2 H). Anal. C, H, N.

**Reduction of 26 to 27.** The hydrogenation bottle rinsed twice with ethanol was charged with absolute ethanol (100 mL), 5% Pd/C (0.2 g), and a solution of **26** (1.0 g, 3.8 mmol) in ethyl acetate (50 mL). The mixture was hydrogenated until hydrogen uptake ceased. The mixture was filtered through Celite and the filtrate was concentrated at reduced pressure and chromatographed on silica gel (200 g). Elution with 2:1 ethyl acetate–hexane gave a yellow oil which was not stable and quickly darkened. Continued elution with 1:1 ethyl acetate–hexane gave 0.37 g of crude **27** as a pale yellow solid which was recrystallized from ethyl acetate (74 mL boiled down to 25 mL). In this manner 0.24 g (28%) of **27** as a white solid was obtained: mp 213–215 °C; IR (KBr) 3430, 1712, 1687, 1288, 830 cm$^{-1}$; $^1$H NMR ($CD_3COCD_3$) δ 1.78 (d, $J$ = 8 Hz, 3 H), 2.75 (br, s, 1 H), 4.15 (q, $J$ = 8 Hz, 1 H), 7.96 (AB q, $\Delta\nu_{1-3}$ = 60 Hz, $J$ = 8 Hz, 2 H). Anal. C, H, N.

**Methyl 1,2,3-Benzothiadiazole-4-acetate (38).** An Erlenmeyer flask equipped with a magnetic stirring was charged with **36** (1.5 g, 6.7 mmol) and 6 N HCl (20 mL), and the resulting slurry was chilled to −10 °C. Sodium nitrite (0.6 g, 8.7 mmol) dissolved in water (3 mL) was added dropwise over 5 min. The mixture darkened and became nearly homogeneous and it was stirred for an additional 5 min. This diazonium solution was added dropwise over 20 min to a vigorously stirred 50% aqueous solution of $H_3PO_2$ (60 mL, precooled to −10 °C). After an induction period of about 10 min, nitrogen evolution was steady. The mixture was stirred for 2 h at −10 °C to 0 °C; then it was extracted three times with ether. This organic phase was washed with water, 5% $NaHCO_3$, and brine; then it was dried by filtration through a cone of calcium sulfate. Evaporation of the solvent left a residue which was chromatographed on silica gel (100 g, 15% ether–hexane) to give 0.75 g (53%) of **38** as the first component off the column: white solid; mp 59–62 °C; IR (KBr) 1737, 1194, 1176, 765 cm$^{-1}$; $^1$H NMR δ 3.72 (s, 3 H), 4.50 (s, 2 H), 7.45–7.75 (m, 2 H), 8.00 (dd, $J$ = 9 Hz, 2 Hz, 1 H). Anal. C, H, N (sublimed at 50 °C/0.06 mm).

**Methyl α-Methyl-1,2,3-benzothiadiazole-4-acetate (39).** Methyl α-methyl-5-nitro-1,2,3-benzothiadiazole-4-acetate[16c] (**26**, 2.0 g, 7.5 mmol) was hydrogenated as described above in ethyl acetate (200 mL) and ethanol (10 mL). Low alcohol concentrations favored amine formation. The crude amine product obtained after filtration through Celite and concentration was immediately diazotized and deaminated as described above. Flash chromatography on silica gel (15% ether–hexane) gave 0.69 g (41% overall) of methyl α-methyl-1,2,3-benzothiadizole-4-acetate (**39**) as a clear oil: IR (neat) 1738, 1200 cm$^{-1}$; $^1$H NMR δ 1.75 (d, $J$ = 7 Hz, 3 H), 3.72 (s, 3 H), 5.10 (q, $J$ = 7 Hz, 1 H), 7.50–7.80 (m, 2 H), 8.05 (dd, $J$ = 7 Hz, 2 Hz, 1 H); HRMS, found 222.0470 (M$^+$), calcd for $C_{10}H_{10}N_2O_2S$ 222.0463.

**α-Methyl-1,2,3-benzothiadiazole-4-acetic Acid (40).** A solution of methyl α-methyl-1,2,3-benzothiadizole-4-acetate (**39**) (0.2 g, 0.9 mmol) was dissolved in THF (10 mL) and methanol (5 mL) was added followed by a solution of NaOH (0.1 g) in water (3 mL). The homogeneous solution was stirred for 1 h, then the solvent was removed in vacuo. The residue was partitioned between ethyl acetate and water. Phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with brine, dried over calcium sulfate, and concentrated to leave 0.19 g of the crude acid. Recrystallization from boiling water (20 mL) gave 0.13 g (69%) of **40** as hard white crystals: mp 125–127 °C; IR (KBr) 1708 cm$^{-1}$; $^1$H NMR ($CD_3COCD_3$) δ 1.75 (d, $J$ = 8 Hz, 3 H), 5.05 (q, $J$ = 8 Hz, 1 H), 7.60–8.00 (m, 2 H), 8.30 (br, d, 1 H); HRMS, found 208.0283 (M$^+$), calcd for $C_9H_8N_2O_2S$ 208.0306.

**Preparation of α-(2-Nitrophenyl)propionic Acid from Methyl α-(2-Nitrophenyl)propionate.** One gram of methyl α-(2-nitrophenyl)propionate was stirred with 1 mL of 1 N KOH in 1 mL of methanol and 10 mL of THF for 6 h. To the mixture was added 50 mL of ether, and the product was extracted into 5% sodium hydroxide (40 mL × 3) as the sodium salt. The aqueous layer was separated and acidified to pH 1 with concentrated HCl and then the acid product was extracted into ether (60 mL × 3). Concentration and drying gave a solid (0.81 g) identified as α-(2-nitrophenyl)propionic acid: IR (KBr) 1710, 1610, 1580, 1528, 1352 cm$^{-1}$; $^1$H NMR (360 MHz) δ 1.63 (d, $J$ = 6 Hz, 3 H), 4.35 (q, $J$ = 6 Hz, 1 H), 7.47 (m, 2 H), 7.63 (m, 1 H), 7.95 (dd, $J$ = 8 Hz, 2 Hz, 1 H); HRMS, found 195.0536 (M$^+$), calcd for $C_9H_9NO_4$ 195.0531.

The following acids were prepared by a similar route: α-(4-nitrophenyl)propionic acid, α-(5-chloro-2-nitrophenyl)propionic acid, α-(3,5-dichloro-2-nitrophenyl)propionic acid, α-(5-fluoro-2-nitrophenyl)propionic acid.

**Methyl α,α-Dimethyl-3-methyl-4-aminobenzene-1-acetate (44b).** The title compound was prepared by the procedure outlined earlier using Sn/HCl reduction of **43b**: mp 69–70 °C; $^1$H NMR δ 1.50 (s, 6 H), 2.15 (s, 3 H), 3.40–3.70 (m, br, exchangeable with $D_2O$, 2 H), 3.55 (s, 3 H), 6.60 (m, 1 H), 7.00 (m, br, 2 H).

**2-(4-Amino-2-chlorophenyl)cyclohexanone (46).** This compound was prepared by Fe/acetic acid reduction of **45**: IR (KBr) 3420, 1705 cm$^{-1}$; $^1$H NMR (360 MHz) δ 1.73–2.30 (m, 6 H), 2.45–2.57 (m, 2 H), 3.66 (s, br, 2 H), 3.98 (dd, $J$ = 12 Hz, 6 Hz, 1 H), 6.57 (dd, $J$ = 8 Hz, 2 Hz, 1 H), 6.71 (d, $J$ = 2 Hz, 1 H), 6.97 (d, $J$ = 8 Hz, 1 H); HRMS, found 223.0749 (M$^+$), calcd for $C_{12}H_{14}NOCl$ 223.0763.

**Methyl 4-Amino-3-chlorobenzene-1-acetate (48).** This compound was prepared by Fe/acetic acid reduction of methyl 4-nitro-3-chlorobenzene-1-acetate (**47**): IR (neat) 3470, 3380, 1730, 1630, 1570, 1510 cm$^{-1}$; $^1$H NMR (360 MHz) δ 3.49 (s, 2 H), 3.68 (s, 3 H), 4.05 (s, br, exchangeable with $D_2O$, 2 H), 6.70 (d, $J$ = 8 Hz, 1 H), 6.97 (dd, $J$ = 8 Hz, 2 Hz, 1 H), 7.16 (d, $J$ = 2 Hz, 1 H); HRMS, found 199.0397 (M$^+$), calcd for $C_9H_{10}NO_2Cl$ 199.0400.

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