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1,3-Dipolar Cycloaddition Reactions with Isatin-*N*-acetic Acids. Synthesis of Dimethyl 9-Oxo-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylates

Wayne K. Anderson* and Paul F. Corey

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14214

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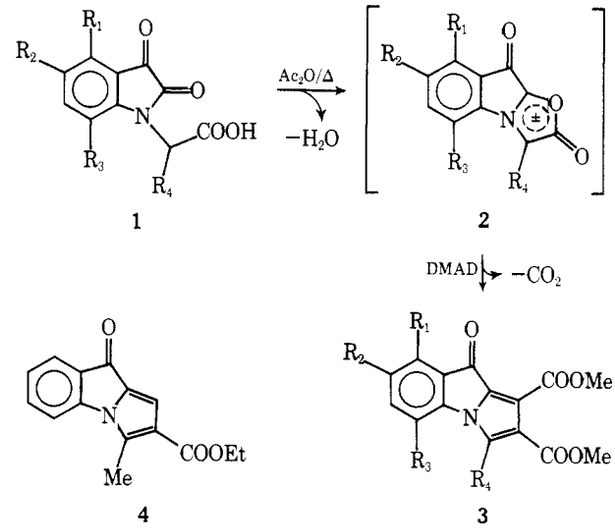
The 9*H*-pyrrolo[1,2-*a*]indole skeleton, first recognized in 1955,[1] has been encountered during the course of investigations directed toward the synthesis of the antitumor agent mitomycin.[2-5] More recently, derivatives of 9-oxo-9*H*-pyrrolo[1,2-*a*]indole have been shown to possess hypoglycemic[6] and anticancer[7] activities. The most commonly applied synthesis of 9-oxo-9*H*-pyrrolo[1,2-*a*]indoles involves an intramolecular Friedel–Crafts acylation of an appropriately substituted *N*-phenylpyrrole, generating the central ring through formation of a second bridge between the two aromatic moieties.[5,8,9]

Current work in our laboratory required a versatile synthesis of dimethyl 9-oxo-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylates (**3**) which would allow for the incorporation of a variety of substituents in the six-membered ring. We now wish to report a facile synthesis of **3** which involves a 1,3-dipolar cycloaddition of a mesoionic intermediate, **2**, derived from substituted isatin-*N*-acetic acids (**1**), with dimethyl acetylenedicarboxylate (DMAD). This approach affords some considerable versatility in that the starting isatins are available with a broad range of substituents.

The starting isatin was converted to the sodium salt by treatment with NaH in HMPA; the salt was alkylated, without isolation, with ethyl 2-bromopropionate and the resulting ester was saponified to give the corresponding isatin-*N*-(α-methyl) acetic acids (**1c–g**). The acids **1a** and **1b** were prepared according to previously described procedures.[10-12] The method we used to prepare **1** is both simple and mild, and makes possible N-alkylation of isatins labile to more vigorous conditions.

N-Acyl-α-amino acids, under dehydrating conditions, cyclize to mesoionic oxazolones which react as 1,3 dipoles with acetylenic compounds to give pyrroles.[13-16] Analogously, isatin-*N*-acetic acids (**1**) form mesoionic derivatives, **2**, that undergo 1,3-dipolar cycloaddition reactions in situ with DMAD to give **3**. This reaction (Scheme I) requires more

Scheme I



a, $R_1 = R_2 = R_3 = R_4 = H$
b, $R_1 = R_2 = R_3 = H$; $R_4 = Me$
c, $R_1 = R_3 = H$; $R_2 = Br$; $R_4 = Me$
d, $R_1 = R_3 = H$; $R_2 = R_4 = Me$
e, $R_1 = R_3 = Cl$; $R_2 = H$; $R_4 = Me$
f, $R_1 = H$; $R_2 = R_3 = Cl$; $R_4 = Me$
g, $R_1 = Cl$; $R_2 = H$; $R_3 = OMe$; $R_4 = Me$

vigorous conditions and gives lower yields than the comparable reaction of *N*-phenyl-*N*-acetylalanine with DMAD.[15] The lower reactivity may be due to decreased reactivity of the mesoionic intermediate, due to charge delocalization in **2** through the C-3 carbonyl of isatin, or it may be associated with an increased difficulty to form **2**. The increased strain introduced by the rigid isatin molecule or the development of a positively charged imminium group adjacent to an electron-withdrawing carbonyl could retard the formation of **2**.

The alkyl group α to the carboxylic acid moiety (i.e., R_4) of **1b–g** considerably increased reactivity over that observed for **1a**, where R_4 = H. Thus, **1b** reacts with acetic anhydride–DMAD to give **3b** in 62% yield whereas **1a** reacted to give only 20% yield of **3a**. Ethyl propiolate, a less reactive dipolarophile, gave **4** in 50% yield from **1b**; **1a** failed to react.

A cycloaddition reaction of this type involving an unsymmetrical dipolarophile is complicated by the possibility of two isomeric products, a problem recently discussed by Huisgen.[17] The reaction of **1b** with ethyl propiolate yielded only **4**, with no evidence of the other possible isomer. The direction of the cycloaddition was confirmed by x-ray crystallography.[18]

In summary, the 1,3-dipolar cycloaddition reaction affords a very simple approach to dimethyl 9-oxo-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylates. Each crystallized spontaneously from the cooling reaction mixture and, although no attempt was made to optimize conditions, the yields were good. Substituents R_1, R_2, and R_3 were chosen to illustrate the general applicability of this reaction to the large class of polysubstituted isatins.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer Model 237 infrared spectrophotometer in KBr wafers. NMR spectra were obtained with a Varian Model T-60 spectrometer using $CDCl_3$ as solvent (unless otherwise specified) and Me_4Si as an internal reference. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. All starting materials and reagents were used as received from the manufacturer without additional purification. No attempt was made to optimize yields in these reactions.

4,7-Dichloroisatin-*N*-(α-methyl)acetic Acid (1e). A stirred solution of 4,7-dichloroisatin (21.6 g, 0.10 mol) in hexamethylphosphoramide (100 ml) (*Caution:* hexamethylphosphoramide is a potent carcinogen; handle with care!) was cooled to 0 °C, treated portionwise with NaH (5.3 g of a 50% oil dispersion, 1.1 equiv), and allowed to warm to room temperature and stirred for 18 h. Ethyl 2-bromopropionate (14.28 ml, 1.1 equiv) was added and the mixture was stirred at room temperature for an additional 18 h. The reaction mixture was poured into Et_2O (500 ml) and extracted with 200-ml portions of H_2O until the aqueous extracts were essentially colorless. The combined aqueous extracts were washed with Et_2O (2 × 200 ml) and the combined ethereal solution was freed of solvent under reduced pressure. The residue was saponified by treatment with a solution of sodium hydroxide (8.0 g, 2 equiv) in 50% aqueous ethanol (400 ml) heated under reflux for 1 h. The mixture was cooled, diluted with H_2O (300 ml), and extracted with Et_2O (2 × 150 ml). The aqueous phase was acidified with concentrated aqueous HCl and extracted with $CHCl_3$ (3 × 150 ml). The combined $CHCl_3$ extracts were dried (Na_2SO_4), concentrated under reduced pressure to 100 ml, and diluted with 100 ml of cyclohexane to yield **1e** (15.57 g, 55%) as an orange powder: mp 180–182 °C dec; IR 3061, 1767, and 1736 (C=O), 1467, 1255, 1110 cm^{-1}; NMR (Me_2SO-d_6–acetone-d_6) δ 1.73 (d, J = 7 Hz, 3 H), 5.42 (q, J = 7 Hz, 1 H), 7.20 (d, $|J_{AB}|$ = 8.8 Hz, 1 H), 7.66 (d, $|J_{AB}|$ = 8.8 Hz, 1 H), 10.33 (br s, 1 H).

Anal. Calcd for $C_{11}H_7NO_4Cl_2$: C, 45.86; H, 2.45; N, 4.86. Found: C, 45.82; H, 2.49; N, 4.93.

5-Bromoisatin-*N*-(α-methyl)acetic Acid (1c). This acid was obtained from 5-bromoisatin as described for **1e**, yield 55% (orange solid), mp 218–220 °C (lit.[12] 219–225 °C).

5-Methylisatin-*N*-(α-methyl)acetic Acid (1d). This acid was obtained from 5-methylisatin as described for **1e**, yield 53% (orange solid), mp 180–183 °C (lit.[12] 180–184 °C).

5,7-Dichloroisatin-*N*-(α-methyl)acetic Acid (1f). This acid was obtained from 5,7-dichloroisatin as described for **1e**, yield 46% (orange solid): mp 217–221 °C dec; IR 3053, 1744, and 1721 (C=O), 1456, 1242, 1118 cm^{-1}; NMR (Me_2SO-d_6–acetone-d_6) δ 1.72 (d, J = 7 Hz, 3 H), 5.5 (q, J = 7 Hz, 1 H), 7.67 (d, $|J_{AB}|$ = 1.55 Hz, 1 H), 7.83 (d, $|J_{AB}|$ = 1.55 Hz, 1 H), 7.67 (br s, 1 H).

Anal. Calcd for $C_{11}H_9NO_4Cl_2$: C, 45.86; H, 2.45; N, 4.86. Found: C, 45.98; H, 2.49; N, 4.78.

4-Chloro-7-methoxyisatin-*N*-(α-methyl)acetic Acid (1g). This acid was obtained from 4-chloro-7-methoxyisatin as described for **1e**, yield 45% (red solid): mp 229–230 °C dec; IR 2938, 1743, and 1720 (C=O), 1497, 1290, 1121 cm^{-1}; NMR (Me_2SO-d_6–acetone-d_6) δ 1.65 (d, J = 7 Hz, 3 H), 3.95 (s, 3 H), 5.42 (q, J = 7 Hz, 1 H), 7.17 (d, $|J_{AB}|$ = 8.5 Hz, 1 H), 7.48 (d, $|J_{AB}|$ = 8.5 Hz, 1 H), 7.83 (br s, 1 H).

Anal. Calcd for $C_{12}H_{10}NO_5Cl$: C, 50.81; H, 3.55; N, 4.94. Found: C, 50.88; H, 3.56; N, 4.94.

Dimethyl 9-Oxo-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylate (3a). A solution of isatin-*N*-acetic acid (**1a**,[10] 2.05 g, 0.01 mol) in *n*-butyric anhydride (20 ml) was treated with DMAD (10 ml, 8 equiv) and heated under reflux (200 °C bath) for 6 h. Volatile reaction components were removed under reduced pressure (1 Torr, 130 °C bath) leaving a black tar which was dissolved in hot methanol (40 ml); on extended standing at −20 °C. **3a** (0.56 g, 20%) precipitated as dark red crystals. One recrystallization from $CHCl_3$–cyclohexane afforded the analytical sample as a pale orange wool: mp 178–179 °C; IR 3100, 1739, 1719, and 1706 (C=O), 1498, 1208, 1091 cm^{-1}; NMR δ 3.89 (s, 3 H), 4.03 (s, 3 H), 7.18–7.85 (m, 4 H), 7.72 (s, 1 H).

Anal. Calcd for $C_{15}H_{11}NO_5$: C, 63.16; H, 3.89; N, 4.91. Found: C, 63.20; H, 3.92; N, 4.93.

Dimethyl 9-Oxo-3-methyl-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylate (3b). A solution of isatin-*N*-(α-methyl)acetic acid (**1b**,[12] 10.56 g, 0.05 mol) in *n*-butyric anhydride (50 ml) was treated with DMAD (25 ml, 4 equiv) and heated under reflux (200 °C bath) for 6 h. Volatile reaction components were removed under reduced pressure (1 Torr, 150 °C bath) leaving a brown tar which was dissolved in 125 ml of hot methanol; **3b** (9.21 g, 62%) precipitated on cooling. One recrystallization from methanol afforded the analytical sample as orange needles: mp 201.5–202.5 °C; IR 2962, 1744, and 1706 (C=O), 1481, 1206, 1114 cm^{-1}; NMR δ 2.79 (s, 3 H), 3.84 (s, 3 H), 3.97 (s, 3 H), 7.03–7.73 (m, 4 H).

Anal. Calcd for $C_{16}H_{13}NO_5$: C, 64.21; H, 4.38; N, 4.68. Found: C, 64.02; H, 4.38; N, 4.70.

Dimethyl 9-Oxo-7-bromo-3-methyl-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylate (3c). A solution of 5-bromoisatin-*N*-(α-methyl)acetic acid (**1c**, 11.92 g, 0.04 mol) in acetic anhydride (40 ml) was treated with DMAD (20 ml, 4.1 equiv) and heated under reflux (155 °C bath) for 6 h. On cooling crystals of **3c** (9.623 g, 64%) spontaneously precipitated. One recrystallization from 1,2-dichloroethane–cyclohexane (1:1) afforded the analytical sample as orange whiskers: mp 235.5–236.5 °C; IR 2935, 1739, 1721, and 1706 (C=O), 1478, 1211, 1121 cm^{-1}; NMR δ 2.84 (s, 3 H), 3.92 (s, 3 H), 4.03 (s, 3 H), 7.33–8.00 (m, 3 H).

Anal. Calcd for $C_{16}H_{12}NO_5Br$: C, 50.82; H, 3.20; N, 3.70. Found: C, 50.94; H, 3.23; N, 3.72.

Dimethyl 9-Oxo-3,7-dimethyl-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylate (3d). This pyrrolo[1,2-*a*]indole was obtained from 5-methylisatin-*N*-(α-methyl)acetic acid (**1d**) as described for **3c**, but with a 36-h reflux period, yield 70% (orange needles from 1,2-dichloroethane): mp 132.5–133.5 °C; IR 2960, 1747, and 1732 (C=O), 1489, 1214, 1123 cm^{-1}; NMR δ 2.36 (s, 3 H), 2.75 (s, 3 H), 3.83 (s, 3 H), 3.96 (s, 3 H), 7.17–7.43 (m, 3 H).

Anal. Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.14; H, 4.84; N, 4.44.

Dimethyl 9-Oxo-5,8-dichloro-3-methyl-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylate (3e). This pyrrolo[1,2-*a*]indole was obtained from 4,7-dichloroisatin-*N*-(α-methyl)acetic acid (**1e**) as described for **3c**, but with a 33-h reflux period, yield 51% [yellow-orange, chunky prisms from 1,2-dichloroethane–cyclohexane (1:1)]: mp 199.5–200.5 °C; IR 3066, 1739, 1710, and 1717 (C=O), 1456, 1221, 1112 cm^{-1}; NMR δ 3.02 (s, 3 H), 3.83 (s, 3 H), 3.95 (s, 3 H), 7.11 (d, $|J_{AB}|$ = 8.25 Hz, 1 H), 7.36 (d, $|J_{AB}|$ = 8.25 Hz, 1 H).

Anal. Calcd for $C_{16}H_{11}NO_5Cl_2$: C, 52.20; H, 3.01; N, 3.80. Found: C, 52.14; H, 3.04; N, 3.78.

Dimethyl 9-Oxo-5,7-dichloro-3-methyl-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylate (3f). This pyrrol[1,2-*a*]indole was obtained from 5,7-dichloroisatin-*N*-(α-methyl)acetic acid (**1f**) as described for **3c**, but with a 13.5-h reflux period, yield 47% [red-orange, chunky prisms from 1,2-dichloroethane–cyclohexane (1:1)]: mp 200.5–201.5 °C; IR 3064, 1750, and 1712 (C=O), 1447, 1233, 1110 cm^{-1}; NMR δ 3.01 (s, 3 H), 3.84 (s, 3 H), 3.94 (s, 3 H), 7.50 (s, 2 H).

Anal. Calcd for $C_{16}H_{11}NO_5Cl_2$: C, 52.20; H, 3.01; N, 3.80. Found: C, 52.04; H, 3.01; N, 3.76.

Dimethyl 9-Oxo-8-chloro-5-methoxy-3-methyl-9*H*-pyrrolo[1,2-*a*]indole-1,2-dicarboxylate (3g). This pyrrolo[1,2-*a*]indole was obtained from 4-chloro-7-methoxyisatin-*N*-(α-methyl)acetic acid (**1g**) as described for **3c**, but with a 35-h reflux period, yield 29% [bright yellow wool from 1,2-dichloroethane–cyclohexane (1:1)]: mp 209–210 °C; IR 2949, 1736, and 1711 (C=O), 1458, 1226, 1129 cm^{-1}; NMR δ 2.72 (s, 3 H), 3.83 (s, 3 H), 3.89 (s, 3 H), 3.93 (s, 3 H), 6.95 (s, 2 H).

Anal. Calcd for $C_{17}H_{14}NO_6Cl$: C, 56.13; H, 3.88; N, 3.85. Found: C, 56.01; H, 3.87; N, 3.85.

Ethyl 9-Oxo-3-methyl-9*H*-pyrrolo[1,2-*a*]indole-2-carboxylate (4). A solution of isatin-*N*-(α-methyl)acetic acid (**1b**,[12] 12.0 g, 0.055 mol) in *n*-butyric anhydride (60 ml) was treated with ethyl propiolate (25.0 g, 4.66 equiv) heated under reflux (170 °C bath) for 6.5 h. Volatile reaction components were removed under reduced pressure (1 Torr, 130 °C bath). The maroon-colored syrup residue was dissolved in $CHCl_3$ and eluted through a 150-g alumina (neutral, Brockman III) dry column with the same solvent. The mobile band was collected, freed of solvent under reduced pressure, and crystallized from $CHCl_3$–petroleum ether (1:2) to give **4** (6.94 g, 49%). One recrystallization from methanol afforded the analytical sample as yellow needles: mp 168–169 °C; IR 3984, 1691 (C=O), 1477, 1227, 1097 cm^{-1}; NMR δ 1.35 (t, J = 7 Hz, 3 H), 2.76 (s, 3 H), 4.28 (q, J = 7 Hz, 2 H), 7.02 (s, 1 H), 7.08–7.62 (m, 4 H). The attachment of the carboxylate ester to C-2 was determined by x-ray crystallography.[18]

Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.56; H, 5.17; N, 5.51.

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Registry No.—**1a**, 60705-96-6; **1b**, 19612-69-2; **1c**, 19612-71-6; **1d**, 19612-73-8; **1e**, 60705-97-7; **1f**, 60705-98-8; **1g**, 60705-99-9; **3a**,

60706-00-5; **3b**, 60706-01-6; **3c**, 60706-02-7; **3d**, 60706-03-8; **3e**, 60706-04-9; **3f**, 60734-17-0; **3g**, 60706-05-0; **4**, 60706-06-1; 4,7-dichloroisatin, 18711-13-2; ethyl 2-bromopropionate, 535-11-5; 5-bromoisatin, 87-48-9; 5-methylisatin, 608-05-9; 5,7-dichloroisatin, 6374-92-1; 4-chloro-7-methoxyisatin, 60706-07-2; DMAD, 23055-10-9; ethyl propiolate, 105-37-3.

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Ion Radicals. 37. Preparation and Isolation of Cation Radical Tetrafluoroborates by the Use of Nitrosonium Tetrafluoroborate[1,2]

B. K. Bandlish and H. J. Shine*

Department of Chemistry, Texas Tech University, Lubbock, Texas 79409

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During the last several years we have reported the preparation of a number of heteroaromatic and aromatic cation radical perchlorates. Methods of oxidation of the organic substrates have varied, e.g., by using $I_2/AgClO_4$, perchloric acid itself, and anodic oxidation in the presence of a perchlorate salt electrolyte. In the case of phenothiazine and 10-methylphenothiazine we have also used disproportionation of the parent heterocycle and its 5-oxide in perchloric acid solution.[3] The preparation of perchlorate salts has been useful not only because of the relative ease of isolating them, but also because the perchlorate ion is an innocuous nucleophile, a desirable feature for our interest in mapping out the reactions of these cation radicals with nucleophilic agents. A hazard that is always present with the cation radical perchlorates (and some of the perchlorate salt products of reaction) is their potential explosiveness,[4] so that their use has always been limited to small amounts. The isolation of solid salts other than perchlorates is attractive, but we have not until now been successful in easily preparing usable ones. Cation radical hexachloroantimonates are very easily obtained,[5] but, in our admittedly limited use of them, they have been troublesome both in interference by chloride ion in nucleophilic reactions and inclusion of antimony in products of reaction.[6] Tetrafluoroborates appear to be attractive alternates to perchlorates. Thianthrene cation radical tetrafluoroborate was prepared by Rundel and Scheffler from the disproportionation reaction in fluoroboric acid,[7] but this preparation requires the use of dry $HF{\cdot}BF_3$. Oxidation by $I_2/AgBF_4$ is suitable in principle, but we have not had encouraging success with this method ourselves.

We have found recently that commercially available nitrosonium tetrafluoroborate ($NOBF_4$)[8] is very useful in cleanly oxidizing a number of aromatics and heteroaromatics to the cation radicals (eq 1), and we have isolated a number of crystalline tetrafluoroborates of high purity. Our practice is to carry out the oxidation in, e.g., acetonitrile solution after purging with N_2 and keeping a stream of N_2 bubbling through the solution to carry out the NO that is formed. Unless this is done, complications can arise from the formation of, and subsequent reactions with, NO_2.

$$Ar + NO^+BF_4^- \rightarrow Ar^+{\cdot}BF_4^- + NO \qquad (1)$$

Nitrosonium salts have been used recently by others. Connelly and co-workers, for example, have pointed out that among the several reactions that are known to occur between $NOPF_6$ and transition-metal complexes are nitrosation and one-electron oxidation.[9] Musker and Wolford have used $NOBF_4$ in making solutions of the cation radical tetrafluoroborates of 1,5-dithiacyclooctane and thianthrene; the salts were not isolated.[10] In our own work, use of $NOBF_4$ has given the solid tetrafluoroborates of phenothiazine (**1**), 10-methylphenothiazine (**2**), 10-phenylphenothiazine (**3**), 10-phenylphenoxazine (**4**), and 5,10-dimethyl-5,10-dihydrophenazine (**5**). The yields varied from 45% (**2**) to 69% (**3** and **5**), while the cation-radical content determined iodimetrically (except with **5**) was 95–99%. No attempts were made to optimize yields. Carbazole (**6**) and *N*-ethylcarbazole (**7**) gave the cation radicals of their dimers, namely 3,3′-dicarbazolyl- and 9,9′-diethyl-3,3′-dicarbazolyl tetrafluoroborates, in 97–98% yield. In contrast, the latter's perchlorate was obtained in 48% yield in solution with $I_2/AgClO_4$.[11] Oxidation of **5** was controlled by the use of less than the stoichiometrically required amount of $NOBF_4$ (i.e., 0.85 equiv), because **5** is easily oxidized also to the dication. Since $5^+{\cdot}$ is not reduced by iodide, the purity of $5^+{\cdot}BF_4^-$ was not assayed; the cation radical was identified by its visible spectrum. Use of an appropriate amount of $NOBF_4$ gave $5^{2+}{\cdot}2BF_4^-$.

Several compounds were easily oxidized to their cation radicals but we could not isolate the solid tetrafluoroborates

Chart of Compounds