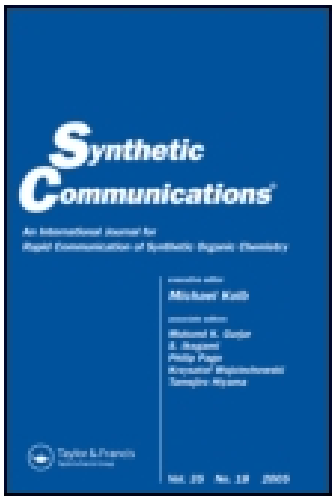

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THE CHEMISTRY OF 2H-3,1-BENZOXAZINE-2,4(1H)-DIONE (ISATOIC ANHYDRIDE). XXIV. *N*-BENZYLATION OF ISATOIC ANHYDRIDE UNDER MITSUNOBU CONDITIONS

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ABSTRACT

Isatoic anhydride is readily alkylated on nitrogen with benzylic alcohols in the presence of triphenylphosphine and diethyl azodicarboxylate. Both electron donating and electron withdrawing groups are tolerated.

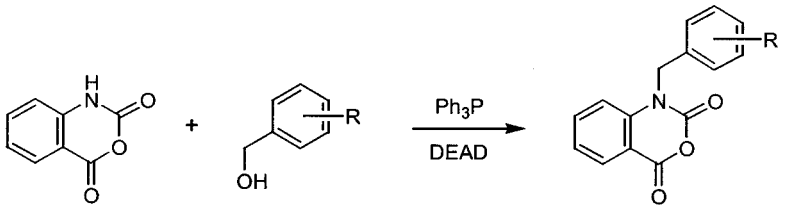
Isatoic anhydride (**1**) and its *N*-alkyl analogs can be considered an internally protected and activated form of anthranilic acid. The susceptibility of the C-4 carbonyl to nucleophilic attack has shown this class of compounds to be extremely versatile intermediates for the preparation of a wide variety of heterocycles and natural products.[1–7]

Even though isatoic anhydrides have been known for more than a century, relatively few methods are known to prepare *N*-alkyl derivatives. Simple methylation can be performed with diazomethane,[8] however, higher

alkyl groups need to be introduced by deprotonation of the N-H of **1** with bases such as sodium carbonate[9] or sodium hydride[10] and subsequent alkylation with an appropriate alkyl halide or tosylate. Alternatively, the alkyl group can be incorporated during the construction of the heterocycle by cyclization of *N*-alkyl anthranilic acids with phosgene.[10,11]

In a search for an alternate and mild method for the *N*-alkylation of **1** which does not involve the use of strong bases, the Mitsunobu reaction was considered. It is essentially a dehydrative alkylation of an acidic nucleophile (Nu-H) with an alcohol.[12] Classically, the reaction utilizes the adduct formed between diethyl azodicarboxylate (DEAD) and triphenylphosphine to activate the alcohol via an oxyphosphonium ion intermediate which then reacts with the nucleophile in an S_N2 process to furnish the alkylated product. A requirement of this method is that the acidic hydrogen in Nu-H should have a pK_a less than 11 for the reaction to proceed satisfactorily.[13]

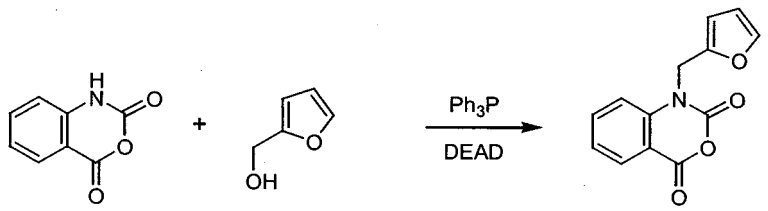
The pK_a value for isatoic anhydride[14] is 8.25 which falls within the acceptable limits of reactivity of the Mitsunobu reaction. Consequently, when **1** is allowed to react with benzyl alcohol in the presence of triphenylphosphine and DEAD, *N*-alkylation occurs smoothly and *N*-benzylisatoic anhydride (**3a**) is produced in 75% yield. The aromatic ring of the benzyl alcohol can accommodate either electron donating or electron withdrawing groups (e.g., F, Cl, OMe, NO_2) to furnish the corresponding substituted derivatives **3b–e** in good yields. In general, the reactions are usually complete within 1 h, however, the 2-nitro derivative **3c** requires 18–24 h. In most cases the products are purified simply by filtration through a pad of silica gel in order to remove the relatively polar triphenylphosphine oxide by-product.



1 **2** **3**

An added advantage of this type of alkylation is that it is not necessary to prepare an alkyl halide in instances when they are either not commercially available or have limited stability. For example, furfuryl chloride or bromide is not commercially available, although furfuryl alcohol (**4**) is

inexpensive. Alkylation of **1** with **4** under Mitsunobu conditions affords *N*-furfurylisatoic anhydride (**5**) in 79% yield.



1 **4** **5**

Efforts are currently underway to investigate the scope of this alkylation using a variety of primary and secondary alcohols in addition to the use of polymer-supported reagents.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Uni-melt apparatus and were uncorrected. IR spectra were obtained on a Nicolet Magna-550 spectrometer. ^{1}H-NMR spectra were recorded on a Bruker ARX-300 or Bruker DPX-300 instrument, and chemical shifts were relative to internal Me_4Si. ^{13}C-NMR spectra were recorded at 75.48 MHz. The described reactions were not optimized.

General Procedure for *N*-Alkylation of Isatoic Anhydride

To a stirred solution of 326 mg (2 mmol) of **1**, 524 mg (2 mmol) of triphenylphosphine and 2 mmol of the benzylic alcohol **2** in 15 ml of tetrahydrofuran were added dropwise a solution of 348 mg (2 mmol) of diethyl azodicarboxylate in 0.5 ml of tetrahydrofuran. The mixture was stirred at room temperature for 1 h, then the solvent was removed under reduced pressure. The residue was filtered through a pad of silica gel using methylene chloride to elute the product **3** which was then crystallized from methylene chloride/MTBE.

3a: (R=H), 75% yield, m.p. 138–140°C (lit.[10] m.p. 140–142°C). IR (CH_2Cl_2): 1784, 1730, 1608 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.16 (d, $J=8$ Hz,

1H), 7.63 (m, 1H), 7.40–7.20 (m, 5H), 7.06 (d, $J = 8.5$ Hz, 1H), 5.30 (s, 2H); ^{13}C-NMR ($CDCl_3$): δ 158.37, 148.47, 141.36, 137.26, 134.38, 130.78, 129.12 (2 carbons), 128.10, 126.58 (2 carbons), 124.17, 114.77, 111.76, 48.48.

3b: (R=2-Cl), 57% yield, m.p. 165–167°C (lit.[10] m.p. 165–167°C). IR (CH_2Cl_2): 1786, 1733, 1609 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.20 (d, $J = 8$ Hz, 1H), 7.65 (t, 1H), 7.47 (d, $J = 8$ Hz, 1H), 7.35–7.15 (m, 3H), 7.04 (d, $J = 8.5$ Hz, 1H), 6.93 (d, $J = 8.5$ Hz, 1H), 5.41 (s, 2H); ^{13}C-NMR ($CDCl_3$): δ 158.18, 148.37, 141.08, 137.45, 132.50, 131.47, 130.93, 130.04, 129.79, 127.54, 126.68, 124.42, 114.60, 111.78, 46.14.

3c: (R=2-NO_2), 54% yield, m.p. 208–211°C (lit.[10] m.p. 211–213°C). IR (CH_2Cl_2): 1787, 1734, 1608 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.25 (t, 2H), 7.71–7.50 (m, 3H), 7.34 (t, 1H), 7.18 (d, $J = 8$ Hz, 1H), 6.91 (d, $J = 8$ Hz, 1H), 5.74 (s, 2H); ^{13}C-NMR ($CDCl_3$): δ 157.95, 148.12, 147.59, 141.07, 137.58, 134.52, 131.23, 130.19, 129.02, 126.70, 126.15, 124.70, 114.25, 111.82, 46.66.

3d: (R=3-F), 83% yield, m.p. 133–136°C (lit.[10] m.p. 133–136°C). IR (CH_2Cl_2): 1785, 1732, 1608 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.19 (d, $J = 8$ Hz, 1H), 7.66 (t, 1H), 7.39–7.25 (m, 5H), 7.12–6.90 (m, 4H), 5.30 (s, 2H).

3e: (R=4-OCH_3), 28% yield, m.p. 134–137°C (lit.[10] m.p. 138–139°C). IR (CH_2Cl_2): 1783, 1730, 1609 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.16 (d, $J = 8$ Hz, 1H), 7.65 (t, 1H), 7.30–7.24 (m, 3H), 7.17 (d, $J = 8.5$ Hz, 1H), 6.88 (d, $J = 8.5$ Hz, 2H), 5.24 (s, 2H), 3.78 (s, 3H); ^{13}C-NMR ($CDCl_3$): δ 159.40, 158.40, 148.49, 141.41, 137.16, 130.84, 128.18 (2 carbons), 126.35, 124.10, 114.73, 114.50 (2 carbons), 111.85, 55.31, 48.04.

5: 79% yield, m.p. 139–140°C (lit.[10] m.p. 141–143°C). IR (CH_2Cl_2): 1784, 1735, 1609 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 8.16 (d, $J = 8$ Hz, 1H), 7.77 (t, 1H), 7.49 (d, $J = 8$ Hz, 1H), 7.38–7.25 (m, 2H), 6.47 (m, 1H), 6.36 (m, 1H), 5.25 (s, 2H); ^{13}C-NMR ($CDCl_3$): δ 158.23, 148.09, 147.83, 142.81, 141.22, 137.21, 130.84, 124.22, 114.47, 111.73, 110.82, 109.97, 41.43.

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