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An efficient synthesis of 3-cyano-3-benzoyloxyoxindoles via cyanoacylation of isatins in the presence of 4 Å molecular sieves

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ABSTRACT

In the presence of 4 Å molecular sieves in CH_3CN, a process for the cyanobenzoylation and cyanocarbonylation of isatins with benzoycyanides and ethylcyanoformate under mild reaction conditions has been developed. This approach provides easy access to a wide range of 3-cyano-3-benzoyloxyoxindoles and 3-cyano-3-ethoxycarbonyloxyoxindoles in good to excellent yields.

Cyanoacylation of aldehydes and ketones is an important carbon–carbon bond-forming reaction.[1] Cyanohydrin derivatives can be easily converted into a wide variety of compounds, such as α-amino acids, α-hydroxy acids, α-hydroxy aldehydes, α-hydroxy ketones, β-amino alcohols, and vicinal diols.[2] They are also components of commercially significant compounds such as the pyrethroid insecticides, cypermetrin, and fluvaliate.[3] Among various cyanide ion sources, acyl cyanides and alkyl cyanoformates are safe and commercially available reagents.[4–6] Although cyanoacylation reactions are very efficient methods for the preparation of cyanohydrins basic catalysts such as potassium carbonate,[7] 1,4-diazabicyclo[2,2,2]octane (DABCO),[8] DBU,[9] Et_3N,[10] or catalyst-free conditions[11,12] are necessary to promote the reactions.

Isatins have various biological activities. Some derivatives of isatin are key intermediates in the synthesis of natural products.[13] Oxindoles are well known among these compounds,[14] which are utilized as building blocks in the synthesis of alkaloids as well as being potential therapeutic agents.[15] In particular, 3-substituted-3-hydroxyindolin-2-ones, a class of oxindoles, are found in several biologically active alkaloids and pharmacological agents.[16–18] Owing to the significance of this structural motif, numerous methodologies have been developed and continue to be explored for their construction.[19] Recently, Hanefeld and co-workers reported the microbial catalyzed hydrolysis of the indole-2,3-dione derived cyanohydrin acetate.[20]

In recent years, several effective reactions in the presence of 4 Å molecular sieves have been developed. For example, cyanobenzoylation

Table 1
Effect of solvent on the cyanobenzoylation of *N*-benzylisatin[a]

Entry	Solvent	Time (min)	Yield[b] (%)
1	DMSO	20	85
2	DMF	20	Trace
3	CH_2Cl_2	60	85
4	THF	60	Trace
5	CH_3CN	10	95
6	Solvent-free	70	60

[a] Reactions were carried out using *N*-benzylisatin and benzoyl cyanide (1.0 mmol) in solvent in the presence of 4 Å MS (200 mg) at rt for the appropriate times.
[b] Isolated yield.

Table 2
Effect of additives on the cyanobenzoylation of *N*-benzylisatin[a]

Entry	Additive	Amount of additive (mg)	Time (min)	Yield[b] (%)
1	MS 4 Å	—	120	Trace
2	MS 4 Å	200	10	95
3	MS 4 Å	150	15	95
4	MS 4 Å	100	20	85
5	MS 5 Å	500	60	Trace
6	$MgSO_4$	500	60	Trace

[a] All reactions were carried out in CH_3CN using *N*-benzylisatin (1.0 mmol) and benzoyl cyanide (1.0 mmol) at rt.
[b] Yield of isolated product.

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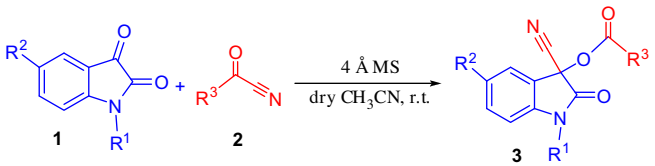
Table 3
Reaction of isatins **1** with cyanides **2** in the presence of 4 Å MS in dry CH_3CN



Product	R^1	R^2	R^3	Time (min)	Yield[a] (%)
3a	Me	H	C_6H_5	10	92
3b	Me	H	4-MeC_6H_4	10	90
3c	Et	H	C_6H_5	10	90
3d	Et	H	4-MeC_6H_4	15	92
3e	Et	Br	4-MeC_6H_4	30	87
3f	$C_6H_5CH_2$	H	C_6H_5	10	95
3g	$C_6H_5CH_2$	H	4-MeC_6H_4	30	90
3h	$C_6H_5CH_2$	Br	4-MeC_6H_4	30	87
3i	$C_6H_5CH_2$	NO_2	C_6H_5	60	90
3j	$C_6H_5CH_2$	NO_2	4-MeC_6H_4	70	75
3k	Me	H	EtO	15	92[b]
3l	Me	Br	EtO	15	85[b]
3m	Et	H	EtO	20	90[b]
3n	$C_6H_5CH_2$	H	EtO	10	95[b]
3o	$C_6H_5CH_2$	Br	EtO	10	78[b]
3p	$C_6H_5CH_2$	NO_2	EtO	15	80[b]

[a] Isolated yield.
[b] Addition 0.01 ml of DMSO.

of aldehydes, cyanocarbonation of aldehydes,[12] trifluoromethylation of carbonyl compounds,[21] and Henry reactions,[22] Knoevenagel reactions,[23] and Michael additions[24] are documented. Due to the fact that the highly reactive β-carbonyl group of isatin is susceptible to nucleophilic attack,[25,26] we envisioned that the cyanoacylation of isatin derivatives might readily proceed under appropriate reaction conditions. As part of our ongoing studies on the development of new reactions of isatins,[27] we report an efficient method for cyanobenzoylation and cyanocarbonation of isatins in the presence of 4 Å molecular sieves in dry CH_3CN, leading to 3-cyano-3-acyloxyoxindoles in high to excellent yields (Table 3). To the best of our knowledge, there is no precedent for the preparation 3-cyano-3-acyloxyoxindoles from isatins.

Initially, we undertook an examination of the solvent effect for the cyanobenzoylation of *N*-benzylisatin (Table 1). The reaction of *N*-benzylisatin with 1.1 equiv of benzoyl cyanide in CH_3CN (2 mL) at room temperature for 10 min afforded the corresponding cyanohydrin product **3f** in 95% yield.[28] When DMF or THF were used as solvent, the yields of the cyanohydrin benzoate **3f** were disappointing (Table 1, entries 2 and 4). With DMSO or CH_2Cl_2, the reactions proceeded smoothly (Table 1, entries 1 and 3). The product was obtained in a lower yield under neat reaction conditions (Table 1, entry 3).

Next, we studied the reaction in the presence of various dehydrating reagents (Table 2). When the reaction was performed without an additive, no reaction occurred (entry 1). On the other hand, the reaction in the presence of 4 Å MS (200 mg) proceeded very smoothly to give the desired product in 95% yield (Table 2, entry 2). Other additives such as 5 Å MS, and $MgSO_4$ were not effective for this transformation (Table 2, entries 5 and 6). A screening of the amount of 4 Å MS showed that the model reaction proceeded smoothly, when 200 mg was used. We suppose that the molecular sieves absorb the small amount of water present in the reaction system preventing hydrolysis of benzoyl cyanide. Accordingly, we used dry CH_3CN (solvent), 4 Å MS (200 mg), (additive) and room temperature as optimal reaction conditions.

To examine the scope of this approach, different isatin derivatives were subjected to the optimized reaction conditions (Table 3).

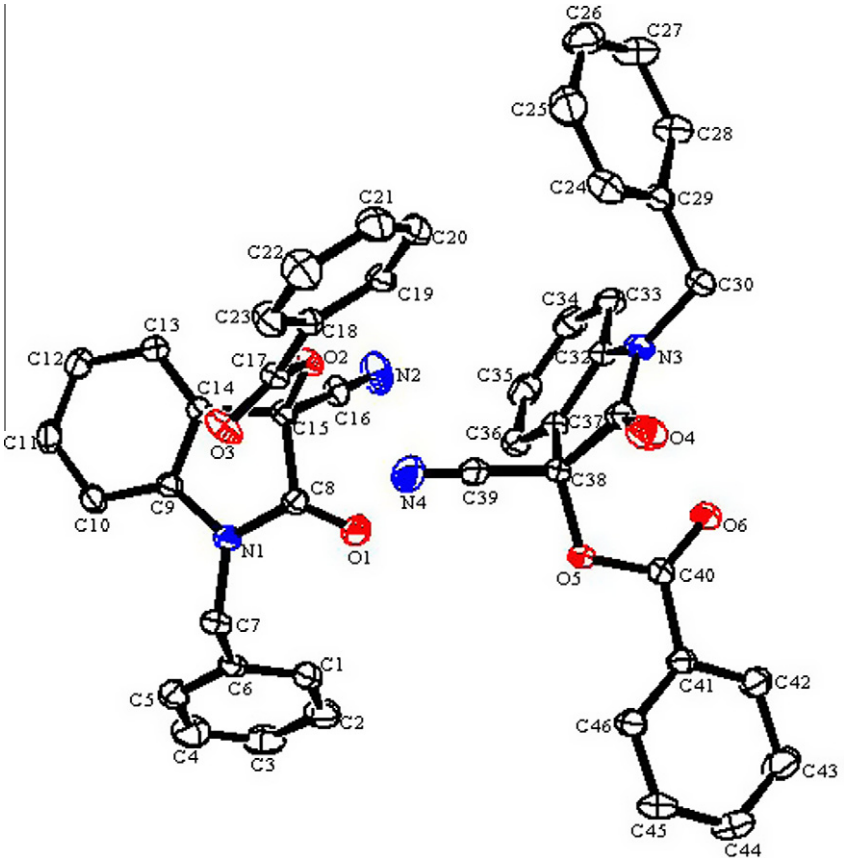


Figure 1. ORTEP diagrams of compound **3f**.

Various isatin derivatives bearing either electron-donating or electron-withdrawing substituents on the ring were excellent substrates for this reaction leading to the corresponding products in high to excellent yields (75–95%), (Table 3). The reaction also proceeded well with substrates bearing methyl, ethyl, and benzyl substituents at the *N* position in high to excellent yields. When, using ethyl cyanoformate as the cyanoacylating component in the presence of 4 Å MS, the addition of a trace amount of DMSO was necessary (Table 3, products **3k**–**p**). The exact reason for this is not clear, but we think that the DMSO acts as an acyl transfer agent activating the ethyl cyanoformate, under the reaction conditions. Accordingly, we use one drop of dry DMSO, 4 Å MS (200 mg), and room temperature as optimal reaction conditions for the synthesis of products **3k**–**p**.

The structures of products **3a**–**p** (Table 3) were deduced from their elemental analyses, IR, mass, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m*/*z* (%) values (see Supplementary data).

For example, the IR spectrum of **3a** showed two carbonyl groups at 1730 and 1745 cm^{-1}. The vibration band for the CN triple bond stretching did not appear in the IR spectrum of **3** due to the electron-accepting oxygen and carbonyl groups.[29] Nevertheless, the appearance of a strong band at 2258 cm^{-1} in the FT-Raman spectrum of **3n**, clearly confirmed the presence of a nitrile group in the product (see Supplementary data). The ^{1}H NMR spectrum of **3a** exhibited a singlet readily recognized as arising from methyl protons (3.35 ppm) and a characteristic multiplet (6.94–7.19 ppm) due to one of the aromatic protons, along with three multiplets for the other aromatic protons (7.43–7.51, 7.60–7.65 and 7.97–8.05 ppm).

The ^{13}C NMR spectrum of **3a** showed 15 distinct resonances in agreement with the suggested structure (see Supplementary data). Additionally, the structure of **3f** was determined by single-crystal X-ray analysis; two ORTEP diagrams of **3f**, from different viewpoints are shown in Figure 1, confirming unambiguously the structures and the presence of CN in the products.[30]

In conclusion, we have developed a convenient cyanoacylation of isatins in CH_3CN in the presence of 4 Å MS to give 3-cyano-3-acyloxyindolin-2-ones in good to excellent yields. Further investigations to broaden the scope and synthetic applications of this efficient and convenient cyanation are underway in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.014.

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28. *Typical procedure for the synthesis of products* ***3f***: A mixture of an N-substituted isatin (0.237 g, 1.0 mmol), benzoyl cyanide (0.145 g, 1.1 mmol), and 4 Å MS (200 mg) in dry CH_3CN (2 mL) was stirred at room temperature for the indicated time (Table 3). The progress of the reaction was monitored by TLC. After completion of the reaction, the MS were recovered by filtration, and washed with CH_3CN. The filtrate was evaporated to dryness on a rotary evaporator under reduced pressure and the residue was crystallized from a mixture of CH_2Cl_2 and petroleum ether, which yielded the pure product 1-benzyl-3-cyano-2-oxoindon-3-yl-benzoate (**3f**): White solid, Mp: 137–139 °C. Yield: 0.35 g (95%); IR (KBr) (ν_{max}/cm^{-1}): 1736 and 1720 (C=O), 1608 (Ar); Anal. Calcd for $C_{23}H_{16}N_2O_3$ (368.38): C, 74.99; H, 4.38; N, 7.60. Found: C, 75.1; H, 4.3; N, 7.7.; ^{1}H NMR (299.8 MHz, $CDCl_3$): δ_H (ppm) 4.88–5.07 (2H, AB quartet, $^2J_{HH}$ = 7.9 Hz), 6.73 (2H$_{arom}$, d, $^3J_{HH}$ = 3.9 Hz), 7.55–7.02 (8H$_{arom}$, m), 7.59 (2H$_{arom}$, d, $^3J_{HH}$ = 3.5 Hz), 8.03 (2H$_{arom}$, d, $^3J_{HH}$ = 4 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ_C (ppm) 44.98 (NCH_2), 70.91 (C3), 110.70 (CH_{arom}), 113.63 (CN), 121.96 (C_{ipso}), 124.16 (CH_{arom}), 125.39 (CH_{arom}), 127.30 (CH_{arom}), 127.42 (C_{ipso}), 128.12 (CH_{arom}), 128.73 (CH_{arom}), 129.06 (CH_{arom}), 130.35 (CH_{arom}), 132.40 (CH_{arom}), 134.29 (C_{ipso}), 134.47 (CH_{arom}), 143.20 (C_{ipso}), 163.48 (O–C=O), 166.51 (N–C=O); MS: *m*/*z* (%) 368 (M+, 28.1), 263 (1.3), 246 (7.2), 105 (100), 91 (55.6).
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30. *Crystal data for* ***3f***: $C_{23}H_{16}N_2O_3$ (CCDC 760175): MW = 368.38, monoclinic, space group P21/c, a = 10.944(2) Å, b = 12.153(2) Å, c = 28.799(6) Å, α = 90 β = 91.53(3), γ = 90°, V = 3828.8(13) Å3, Z = 8, Dc = 1.278 mg/m3, F (000) = 1536, crystal dimension 0.41 × 0.33 × 0.25 mm, radiation, MoKα (λ = 0.71073 Å), 1.82⩽2θ⩽29.36, intensity data were collected at 298(2) K, and employing ω/2θ scanning technique, in the range of −15⩽h⩽15, −16⩽k⩽14, −30⩽l⩽39; the structure was solved by a direct method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 6552 observed reflections with R (into) = 0.1129 by a full-matrix least-squares technique converged to R = 0.0698 and Raw = 0.1533 [I > 2sigma(I)].