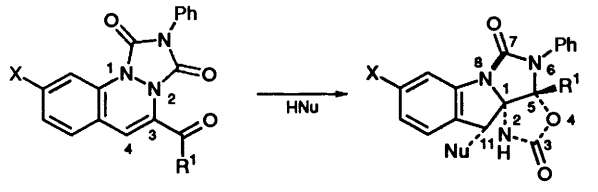
One-pot syntheses of 3-cyanoindoles from 3-acyl- and 3-ethoxycarbonyl-1,2-dihydrocinnoline-1,2-dicarboximides

Satoko Tanaka,[a] Kazuyoshi Seguchi *,[a] and Akira Sera[b]
[a] *Faculty of Life and Environmental Sciences, Mukogawa Women's University, Nishinomiya 663, Japan*
[b] *Department of Chemistry, Faculty of Science, Kobe University, Kobe 657, Japan*

2-Acyl- and 2-ethoxycarbonyl-3-cyanoindoles were prepared from 3-acyl- and 3-ethoxycarbonyl-1,2-dihydrocinnoline-1,2-dicarboximides and potassium cyanide *via* Michael addition, skeletal rearrangement and subsequent elimination of isocyanate.

We have reported that 3-acyl-1,2-dihydrocinnoline-1,2-dicarboximides **1** and related compounds serve as novel precursors for syntheses of heterocyclic compounds.[1–3] In particular, the successful one-pot transformation of compound **1** to a series of hetero analogues **2** of an angular triquinane (tricyclo[6.3.0.0^{1,5}]undecene skeleton)[1] (Scheme 1) and hetero[4.3.3]-propellanes,[3] which proceed *via* a nucleophile-assisted rearrangement of compound **1**, encouraged us to explore the further synthetic potential of compound **1** in organic syntheses. We describe here one-pot syntheses of 2-acyl- and 2-ethoxycarbonyl-3-cyanoindoles based on a cyanide-assisted rearrangement of compound **1** followed by elimination of isocyanates.

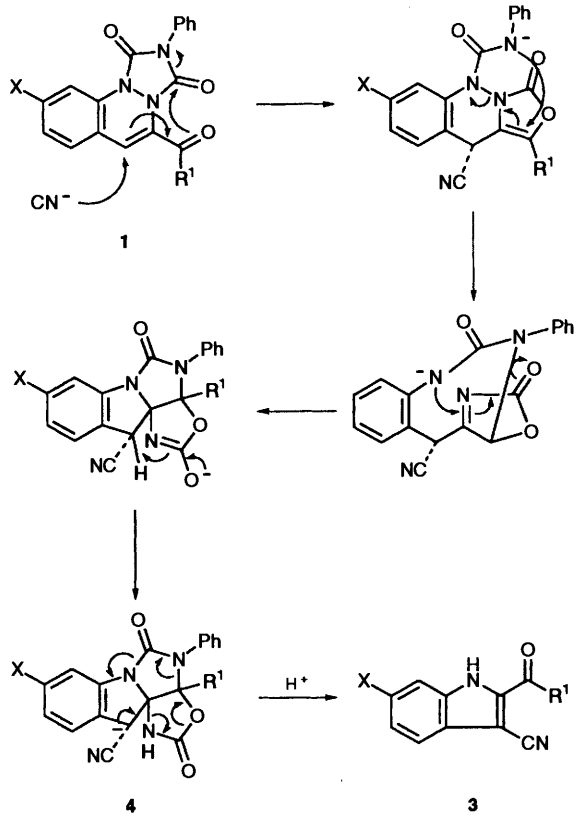


Scheme 1

3-Acyl- and 3-ethoxycarbonyl-1,2-dihydrocinnoline-*N*-phenyl-1,2-dicarboximides **1a–j** were prepared by addition–elimination reactions of 4-phenyl-4,5-dihydro-3*H*-1,2,4-triazole-3,5-dione (PTAD) with benzylidene ketones.[4] The reaction of **1a** with an excess of powdered potassium cyanide in aqueous DMF gave fluorescent colourless crystals of compound **3a** in 54% yield. The structure of **3a** was determined by spectral data and elemental analyses. Its IR spectrum showed the presence of an amino and a cyano group (3200 and 2200 cm^{-1}). The ^{1}H NMR showed an amino proton signal at δ 9.80, which disappeared on addition of D_2O. The ^{13}C NMR spectrum showed the presence of a 3-cyanoindole skeleton[5] and a carbonyl group. Furthermore, methylation of **3a** with methyl iodide under phase-transfer catalysed conditions[6] gave the corresponding 1-methylindole. These results and other spectral data indicate that the product **3a** is 2-acetyl-3-cyanoindole.

Other substituted dicarboximides **1b–j** also afforded the corresponding 2-acyl- and 2-ethoxycarbonyl-3-cyanoindoles **3b–j** in moderate yields.† Some characteristic spectral data are given in Table 1. These reactions did not take place under buffered acidic or neutral conditions.

The mechanism of indole formation is assumed to be as depicted in Scheme 2. The initial reaction involves the Michael addition of a cyanide ion to the polar enone substructure of **1**. Opening of the dicarboximide ring by participation of the resulting enolate, and subsequent skeletal rearrangement with cooperative cleavage of the nitrogen–nitrogen bond, gives **4** (a carbanion of **2b**), which spontaneously eliminates isocyanate (NH=C=O) and phenyl isocyanate in basic conditions to afford an indole derivative. Although the oxazolidinone **2a** incorporating ethanol, prepared by ethanol-assisted rearangement of **1a**,[1] was extremely stable under basic conditions and hence could be isolated, the tricyclic oxazolidinone **2b** incorporating hydrogen cyanide seemed to be quite unstable. All attempts to isolate **2b** failed. This is responsible for the difference of stability of carbanions at C-11 of compounds **2a** and **2b**.



Scheme 2

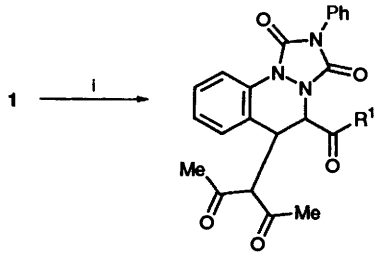
However, isolation of the initial Michael adduct, which should act as a precursor in the present reaction, was difficult. High reversibility of the nucleophile addition process associated with rapid participation of the resuting enolate ion with the dicarboximide group probably makes the isolation difficult. However, when compound **1a** was treated with a weak

† All new compounds showed satisfactory spectral data and elemental analyses.

Table 1 Preparation of 2-acyl- and 2-ethoxycarbonyl-3-cyanoindoles **3** from compounds **1**

Starting compound						
	X	R^1	Product	Yield (%)	δ_C[a] (C-3)	ν_{CN}/cm^{-1}[b]
1a	H	Me	**3a**	54	90.3[c]	2200
1b	H	Ph	**3b**	74	92.1	2215
1c	H	PhCH=CH	**3c**	49	87.0[d]	2215
1d	OMe	Me	**3d**	69	93.1	2220
1e	OMe	Pr^i	**3e**	74	94.2	2210
1f	OMe	Ph	**3f**	69	92.3	2220
1g	OMe	2-Furyl	**3g**	88	89.9[d]	2225
1h	OMe	*p*-OMePhCH=CH	**3h**	50	92.3[d]	2210
1i	H	OEt	**3i**	22	91.1	2220
1j	OMe	OEt	**3j**	28	92.7	2230

[a] In $CDCl_3$. [b] KBr disk. [c] In [$^2H_6$]acetone. [d] In [$^2H_6$]DMSO.



5

a R^1 = Me
b R^1 = Ph

Scheme 3 *Reagents:* i, $MeCOCH_2COMe$, DMF–H_2O–KOH

nucleophile, acetylacetone in aqueous DMF in the presence of potassium hydroxide (Scheme 3), no indole derivative was detected but the Michael adduct **5a** was isolated in 62% yield (adduct **5a** was unstable under basic conditions and a retrograde reaction to compound **1a** occurred). The reaction of compound **1b** with acetylacetone afforded the adduct **5b** in 52% yield. The enolate anion which resulted from Michael addition may be transformed to a more stabilized β-diketone carbanion, which could not lead to the participated rearrangement. Hence the successful isolation of the Michael adduct **5** was achieved. These results suggest that a stabilized enolate ion generated from the addition of cyanide ion is an essential requisite in the indole formation.

This novel indole synthesis is useful in that it introduces two useful functional groups at 2- and 3-positions of an indole skeleton in a one-pot reaction.

Experimental

2-Acetyl-3-cyanoindole 3a

To a DMF solution (10 cm^3) of **1a** (0.50 mmol) were added an excess of powdered potassium cyanide (1.0 mmol) and water (0.5 cm^3). The suspended solution was stirred overnight at 25 °C, and then diluted with water. The resulting faint yellow precipitate was filtered off, washed with chilled ethanol and recrystallized from dichloromethane to give the indole **3a** as colourless needles in 54% yield, mp 221–222 °C; $\delta_H(CDCl_3$; 90 MHz) 2.87 (3 H, s, Me), 7.35–7.60 (3 H, m, Ph), 7.88 (1 H, d, Ph) and 9.65 (brs, 1 H, NH); δ_C[$(CD_3)_2CO$; 22.5 MHz] 28.4 (q), 90.3 (s, C-3), 115.0 (d), 116.2 (s, CN), 121.6 (d), 124.5 (d), 128.3 (d), 129.5 (s), 137.1 (s, C-2), 140.8 (s) and 197.8 (s, CO); *m/z* 184 (M^+, 79%), 169 (100), 142 (39) and 114 (47) (Found: M^+, 184.0636. $C_{11}H_8N_2O$ requires *M*, 184.0640).

3-Acetyl-4-(diacetylmethyl)-1,2,3,4-tetrahydrocinnoline-*N*-phenyl-1,2-dicarboximide 5a

To a DMF solution of **1a** (1.00 mmol) and acetylacetone (5.00 mmol) were added powdered potassium hydroxide (5.00 mmol) and water (0.5 cm^3). After being stirred overnight at 25 °C, the mixture was diluted with water, neutralized immediately with dilute hydrochloric acid and extracted with dichloromethane (10 cm^3 × 2). The combined extracts were dried over sodium sulfate and concentrated using a rotary evaporator and then a vacuum pump. The residual solid was recrystallized from ethanol to give the title compound **5a** as colourless needles in 62% yield, mp 120–122 °C; $\delta_H(CDCl_3$; 90 MHz) 1.88 (3 H, s, Me), 2.20 (3 H, s, Me), 2.27 (3 H, s, Me), 4.27 (2 H, s, CH), 4.93 (1 H, s, CH), 6.93–7.73 (8 H, m, Ph) and 8.43 (1 H, d, Ph); $\delta_C(CDCl_3$; 50 MHz) 25.8 (q), 31.0 (q), 33.0 (q), 38.1 (d), 62.5 (d), 70.0 (d), 116.3 (d), 116.8 (s), 124.1 (d), 126.1 (d), 128.2 (d), 128.5 (d), 129.2 (d), 129.9 (d), 130.8 (s), 132.1 (s), 146.3 (s), 152.3 (s), 200.1 (s), 200.4 (s) and 202.3 (s); ν_{max}(KBr)/cm^{-1} 1775, 1704, 1488, 1417, 1165, 752 and 690; *m/z* 419 (M^+, 18%), 376 (59), 334 (100), 317 (27), 277 (42), 215 (34) and 130 (79) (Found: M^+, 419.1456. $C_{23}H_{21}N_3O_5$ requires *M*, 419.1480).

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