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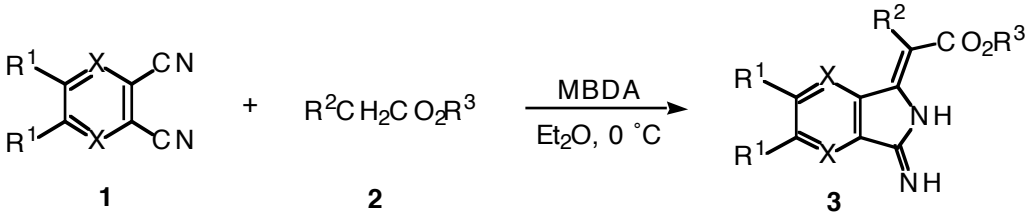
SYNTHESIS OF 2-(3-IMINOISOINDOLIN-1-YLIDENE)CARBOXYLATE DERIVATIVES BY REACTIONS OF ESTER MAGNESIUM ENOLATES WITH PHTHALONITRILE DERIVATIVES

Kazuhiro Kobayashi,* Kiyoto Honma, Shizuka Kondo, Osamu Morikawa, and Hisatoshi Konishi

Department of Materials Science, Faculty of Engineering, Tottori University, Koyama-minami, Tottori 680-8552, Japan

Abstract- Efficient preparation of the title iminoisoindolines and related derivatives can be achieved *via* the coupling between ester magnesium enolates and one of two nitrile moieties of phthalonitriles, followed by the attack of the resulting imino anion to the second nitrile carbon.

We have previously reported that ester magnesium enolates, generated by the treatment of esters with magnesium bis(diisopropylamide) (MBDA), coupled efficiently with a range of nitriles to afford the corresponding vinylogous urethanes.[1,2] The utility of this coupling reaction was demonstrated in the syntheses of useful biologically active natural products, such as amino sugars[3] and naphthalide lignans.[4] We were interested in the investigation of the reaction of ester magnesium enolates with phthalonitrile derivatives, which would be expected to give new iminoisoindoline derivatives. Although iminoisoindoline derivatives are thought to be of potential interest from a biological point of view, there have been few reports on the synthesis of these derivatives in the literature.[5,6] In this report we wish to demonstrate the results of our investigation, which provide a simple and convenient method for the preparation of 2-(3-iminoisoindolin-1-ylidene)carboxylate derivatives (**3**).



Scheme 1.

Initially, the reactions of phthalonitrile (**1a**) with magnesium enolates of four esters (**2a-2d**) were carried out in ether at 0 ˚C, as outlined in Scheme 1. The reaction proceeded smoothly. After the usual aqueous workup, the corresponding products (**3a-3d**) were obtained by purification using

Table. Preparation of 2-(3-iminoisoindolin-1-ylidene)carboxylate derivatives (**3**).

Entry	Phthalonitrile (**1**)	Carboxylic acid ester (**2**)	Product (**3**) (Yield/%)[a]
1	**1a** (R^1 = H, X = CH)	**2a** (R^2 = H, R^3 = *t*-Bu)	**3a** (79)
2	**1a**	**2b** (R^2 = H, R^3 = Et)	**3b** (50)
3	**1a**	**2c** (R^2 = Me, R^3 = *t*-Bu)	**3c** (72)
4	**1a**	**2d** (R^2 = Ph, R^3 = Et)	**3d** (45)
5	**1b** (R^1 = Cl, X = CH)	**2a**	**3e** (70)
6	**1c** (R^1 = F, X = CF)	**2a**	**3f** (81)
7	**1d** [R^1_2 = $(CH=CH)_2$, X = CH]	**2a**	**3g** (79)
8	**1e** (R^1 = H, X = N)	**2a**	**3h** (32)

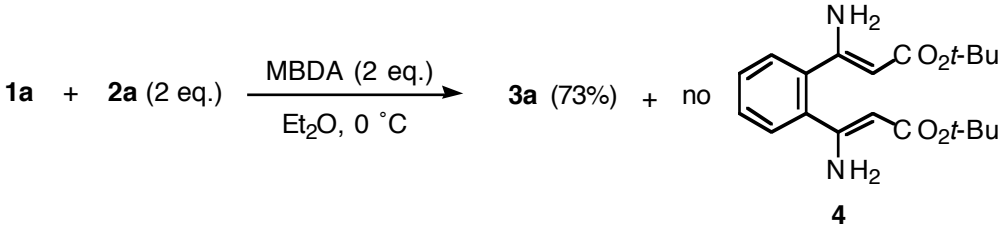
[a]Isolated yields after column chromatography or preparative TLC on silica gel.

preparative TLC on silica gel. The Table summarizes these results. It shows that fair to good yields were obtained with use of *t*-butyl esters (**2a** and **2c**) (Entries 1 and 3) and that ethyl esters (**2b** and **2d**) gave somewhat lower yields (Entries 2 and 4), probably due to some liability of self-condensation of these esters compared to *t*-butyl esters. It should be noted that lithium enolates derived from these esters did not undergo the reaction sequence with **1a**, in which **1a** was recovered almost quantitatively in each case. In place of **1a**, 4,5-dichlorophthalonitrile (**1b**; Entry 5), 3,4,5,6-tetrafluorophthalonitrile (**1c**; Entry 6), and naphthalene-2,3-dicarbonitrile (**1d**; Entry 7) were then allowed to react with magnesium enolate of **2a**. It was found that these reactions also proceeded smoothly to lead to the formation of the corresponding desired iminoisoindoline derivatives (**3e-3g**) in good yields. While pyrazine-2,3-dicarbonitrile (**1e**) was also found to be usable, a rather disappointing yield of the desired product (**3h**) was found (Entry 8), probably due to the lability of pyrazine structure toward nucleophiles in the reaction mixture.

The stereochemistry of isoindolin-1-ylidene part of the products (**3**) was assigned to be *Z*. The *Z*-preference is ascribed to intramolecular hydrogen bonding between the 2-H of isoindoline ring and ester carbonyl. NOE experiments were carried out to confirm the stereochemistry of **3a** unambiguously. Thus, irradiation of the signal at δ 5.53, assignable to the vinyl proton, resulted in a 10% enhancement of the signal at δ 7.63 assignable to the 4-H of isoindoline ring. The stereochemistry of **3c** was also unambiguously determined; an 18% enhancement of the signal at δ 7.90 of 4-H of isoindoline ring was observed upon irradiation of the signal at δ 2.30 assignable to 3-protons. Although one of the possible stereoisomers was obtained as a sole product in each reaction, the stereochemistry of 3-imino moiety was not yet clarified.

It is noteworthy that the reaction of phthalonitrile (**1a**) with 2 equivalents of magnesium enolate derived from *t*-butyl acetate (**2a**) under similar reaction conditions gave nothing but a trace amount of the 1:2 adduct (**4**). This reaction gave only **3a** in a yield nearly equal to that in the Table, as depicted in Scheme 2.

In conclusion, we have shown that the reaction of ester magnesium enolates with phthalonitrile derivatives provides a simple method for the preparation of 2-(3-iminoisoindolin-1-ylidene)carboxylates and related compounds. We now can therefore construct a new type of iminoisoindoline system from readily available starting materials and under mild conditions.



Scheme 2.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were measured with a Perkin-Elmer 1600 Series FT IR spectrophotometer as KBr disk. The ^{1}H NMR spectra were observed in CD_3OD (unless otherwise stated) using TMS as an internal reference with a JEOL JNM-GX270 FT NMR spectrometer (270 MHz); *J* values are given in Hz. TLC was carried out on a Merck Kieselgel 60 PF_{254}. Low-resolution MS analyses were performed on a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, our University). All organic solvents used in this study were dried over appropriate agents and distilled prior to use.

Starting Materials. All chemicals used in this study were commercially available.

General Procedure for the Reactions of Phthalonitrile Derivatives (1) with Magnesium Enolates of Carboxylic Esters (2), Yielding 2-(3-Iminoisoindolin-1-ylidene)carboxylate Derivatives (3). To a stirred (0 ˚C) turbid solution of MBDA, prepared by a treatment of diisopropylamine (2.0 mmol, 0.20 g) with ethylmagnesium bromide (2.0 mmol) in Et_2O (6 mL) at reflux temperature for 1 h, was added one of the carboxylates (**2**) (1.0 mmol) under argon. After 5 min stirring, one of the phthalonitriles (**1**) (1.0 mmol) in THF (9 mL) was added. The reaction mixture was stirred for 40 min at the same temperature and then quenched by the addition of saturated aqueous NH_4Cl (20 mL). The Organic layer was separated and aqueous layer was extracted with Et_2O (20 mL□2). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and then evaporated. The residue was purified by column chromatography or preparative TLC on silica gel (EtOAc–hexane) to give **3**.

***t*-Butyl (3-Iminoisoindolin-(*Z*)-1-ylidene)acetate (3a):** mp 110–113 ˚C (Et_2O–hexane); □$_{max}$/cm^{-1} 3384, 3297, 1679, 1652, 1634 (sh); □$_H$ ($CDCl_3$) 1.55 (9H, s), 2.55–4.8 (1H, br), 5.53 (1H, s), 7.3–7.8 (4H, m), 8.4–10.95 (1H, br); MS *m/z* 244 (M^+, 11), 188 (100). Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.59; H, 6.89; N, 11.45.

Ethyl (3-Iminoisoindolin-(*Z*)-1-ylidene)acetate (3b): mp 105–108 ˚C (Et_2O–hexane); □$_{max}$/cm^{-1} 3378, 3288, 1682, 1659, 1644 (sh); □$_H$ 1.34 (3H, t, *J* 7.3), 1.35–2.05 (1H, br), 4.26 (2H, q, *J* 7.3), 5.59 (1H, s),

7.3–7.8 (4H, m), 8.8–9.9 (1H, br); MS *m/z* 216 (M^+, 71), 171 (56), 144 (100). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.66; H, 5.56; N, 13.03.

***t*-Butyl 2-(3-Iminoisoindolin-(*Z*)-1-ylidene)propanoate (3c):** mp 116-119 ˚C (Et_2O–hexane); ν_{max}/cm^{-1} 3331, 3268, 1651, 1607; δ_H 1.56 (9H, s), 2.30 (3H, s), 2.7–4.2 (1H, br), 7.5–7.65 (2H, m), 7.8–7.95 (2H, m), 8.8–12.0 (1H, br); MS *m/z* 258 (M^+, 10), 202 (100). Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.59; H, 7.28; N, 10.84.

Ethyl 2-(3-Iminoisoindolin-(*Z*)-1-ylidene)-2-phenylacetate (3d): mp 117–119 ˚C (Et_2O–hexane); ν_{max}/cm^{-1} 3305, 3298, 1678, 1649; δ_H 1.20 (3H, t, *J* 7.3), 2.3-4.3 [3H in total, br and q (*J* 7.3) at □ 4.21], 7.16 (1H, td, *J* 8.2, 1.3), 7.25–7.5 (7H, m), 7.74 (1H, d, *J* 7.3), 8.7–11.8 (1H, br); MS *m/z* 292 (M^+, 98), 218 (100). Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.90; H, 5.68; N, 9.39.

***t*-Butyl (5,6-Dichloro-3-iminoisoindolin-(*Z*)-1-ylidene)acetate (3e):** mp 194–196 ˚C (Et_2O-hexane); ν_{max}/cm^{-1} 3488, 3370, 1693, 1663, 1632; δ_H 1.53 (9H, s), 2.6–4.6 (1H, br), 5.48 (1H, s), 7.71 (1H, s), 7.92 (1H, s), 8.5–10.5 (1H, br); MS *m/z* 312 (M^+, 15), 256 (100). Anal. Calcd for $C_{14}H_{14}N_2O_2Cl_2$: C, 53.69; H, 4.51; N, 8.94. Found: C, 53.65; H, 4.53; N, 8.85.

***t*-Butyl (4,5,6,7-Tetrafluoro-3-iminoisoindolin-(*Z*)-1-ylidene)acetate (3f):** mp 240–243 ˚C (hexane–CH_2Cl_2); ν_{max}/cm^{-1} 3491, 1714, 1664, 1630; δ_H 1.53 (9H, s), 2.6–4.2 (1H, br), 5.76 (1H, s), 9.2–10.0 (1H, br); MS *m/z* 316 (M^+, 14), 260 (100). Anal. Calcd for $C_{14}H_{12}N_2O_2F_4$: C, 53.17; H, 3.82; N, 8.86. Found: C, 53.14; H, 4.00; N, 8.82.

***t*-Butyl (3-Iminobenz[*f*]isoindolin-(*Z*)-1-ylidene)acetate (3g):** mp 120–123 ˚C (Et_2O–hexane); ν_{max}/cm^{-1} 3380, 3294, 1682, 1659, 1633; δ_H 1.56 (9H, s), 3.3–4.5 (1H, br), 5.67 (1H, s), 7.55–7.65 (2H, m), 7.9–8.05 (2H, m), 8.12 (1H, s), 8.28 (1H, s), 9.0–10.5 (1H, br); MS *m/z* 294 (M^+, 36), 238 (100). Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.35; H, 6.19; N, 9.46.

***t*-Butyl (3-Imino-2,3-dihydropyrrolo[3,4-*b*]pyrazin-(*Z*)-1-ylidene)acetate (3h):** mp 123–126 ˚C (Et_2O–hexane); ν_{max}/cm^{-1} 3477, 1711, 1677, 1628; δ_H 1.55 (9H, s), 2.3–4.6 (1H, br), 6.00 (1H, s), 8.3–8.9 and 8.72 (3H in total, br and s); MS *m/z* 246 (M^+, 33), 190 (100). Anal. Calcd for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.43; H, 5.83; N, 22.64.

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