New Findings on the Hemetsberger-Knittel Reaction (Synthetic Studies on Indoles and Related Compounds. XLIII[1])

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In the Hemetsberger–Knittel reaction for indole synthesis, the intermediate ethyl 2-azido-3-hydroxy-3-arylpropionate (4) was found to be formed in the reaction of arylaldehyde 1 with ethyl azidoacetate at a lower temperature (−30 °C) as the main product, while only ethyl 2-azidocinnamate (2) is known to be formed at a higher temperature (0 °C). It was also found that fluoride ion was effective for obtaining 4. Compound 4 was converted to 2 in good yield by treatment with $SOCl_2$/pyridine or $SOCl_2/Et_3N$. A trial application of this reaction to ketone is also described.

Key words Hemetsberger–Knittel reaction; indole synthesis; ethyl 2-azidocinnamate; ethyl 2-azido-3-hydroxy-3-arylpropionate; 3-substituted indole

Fischer indolization,[2] Reissert reaction,[3] Batcho–Leimgruber reaction,[4] and Hemetsberger–Knittel reaction[5,6] are representative methods for preparing 3-unsubstituted indoles. The Fischer indolization and Hemetsberger–Knittel reaction have advantages over the other two methods, because they require less substituted benzene derivatives as starting materials. Fischer indolization is well established, while the Hemetsberger–Knittel reaction was first reported relatively recently.

Hemetsberger–Knittel reaction involves formation of an ethyl 2-azidocinnamate (**2**) by condensation of an arylaldehyde (**1**) with ethyl azidoacetate in the presence of sodium ethoxide (NaOEt) at 0 °C as the first step and pyrolysis of **2** in a solvent as the second step to give the corresponding ethyl indole-2-carboxylate (**3**) (Chart 1). Although this reaction is simple and convenient, the yield of the indole (**3**) from **1** is sometimes not high. Another problem is that substrates have been limited to arylaldehydes and thus 3-substituted indoles have not been prepared by this method. We report new findings which extend the scope of the Hemetsberger–Knittel reaction.

The reason for the low yield of the indole (**3**) in this reaction lies mainly in the first step,[5] which produces azidocinnamate (**2**). We have reported[7] that condensation of 2-naphthylaldehyde with ethyl azidoacetate at 0 °C gave the corresponding ethyl 2-azido-3-hydroxy-3-arylpropionate (**4**) as the main product, which is an expected but previously undetected[8] intermediate in this aldol type condensation. Thus, we speculated that the previous inability to detect **4** under the normal reaction conditions caused the low yield of **2**.

Aldol Condensation at Low Temperature We examined in detail the condensation of usual benzaldehyde derivatives with ethyl azidoacetate and found that the reaction temperature holds the key to the yield of products (Table 1).

Reaction at 0 °C generally yielded only azidocinnamate (**2**) as reported,[5] with some exceptions (runs 3, 5, 6, and 9), whereas at −30 °C the intermediate azidoalcohol (**4**) was exclusively or mainly produced. The azidoalcohol (**4**) was an inseparable mixture of two diastereomers (*ca.* 1 : 1) as determined by ^{1}H-NMR (almost all signals were doubled in slightly shifted form) and the mixture was thus characterized as it was. Table 1 shows that reaction at lower temperature (−30 °C) gave more azidoalcohol (**4**) than that at higher temperature (0 °C), and the total yield (**2**+**4**) at a lower temperature was generally much higher than that at the higher temperature. Aldehydes with stronger electron-withdrawing substituents, such as the trifluoromethyl group, tended to give more azidoalcohol (**4**) even at 0 °C (run 9), and the aldehyde with a nitro group afforded the corresponding azidocinnamate (**2**) in low yield (run 10). Worse yields were obtained at much lower temperatures (below −40 °C).

The azidoalcohol (**4**) obtained should be equivalent to

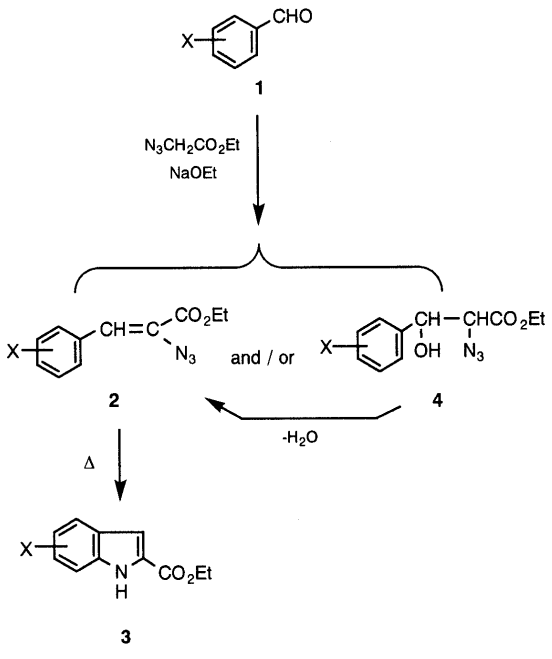

Chart 1

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Table 1. Condensation of Aryl Aldehydes (**1**) and Ethyl Azidoacetate

Run	**1** X=	Temp. (°C)	Time (h)	Azidocinnamate (**2**) (%)	Azidoalcohol (**4**) (%)	Total yield (**2**+**4**) (%)
1	H (**1a**)	0	1	42	0	42
		−30	45 min	0	69	69
2	2-CH_3 (**1b**)	0	2.5	50	0	50
		−30	4	6	74	80
3	2-OCH_3 (**1c**)	0	2	58	16	74
		−30	2.5	0	90	90
4	4-OCH_3 (**1d**)	0	2.5	38	0	38
		−30	2.5	28	70	98
5	2,5-diOCH_3 (**1e**)	0	1.5	40[a]	12[a]	52
		−30	1	0	97	97
6	4-Ph (**1f**)	0	1.5	64	12	76
		−30	2.5	4	72	76
7	2-Cl (**1g**)	0	0.5	48	0	48
		−30	2	0	38	38
8	4-Cl (**1h**)	0	2.5	22	0	22
		−30	2.5	12	74	86
9	2-CF_3 (**1i**)	0	1.5	10	89	99
		−30	4	0	11	11[b]
10	4-NO_2 (**1j**)	0	2.5	3	0	3
		−30	2.5	12	39	51

a) In our previous report[17] we obtained the azidocinnamate (**2e**) as a sole product. *b*) Starting material was recovered (83%). Temp. = temperature.

Table 2. Conversion of Ethyl 2-Azido-3-hydroxy-3-arylpropionates (**4**) to Ethyl 2-Azidocinnamates (**2**)

Run	**4** X=	Method[a]	Reaction time (h)	Yield (%)
1	H (**4a**)	B	2	77
2	2-CH_3 (**4b**)	A	Over night	48
3	2-OCH_3 (**4c**)	B	1.5	87
4	4-OCH_3 (**4d**)	B	6	75
5	2-Cl (**4g**)	B	1.5	82
6	2-CF_3 (**4i**)	B	2.5	80

a) Method A: with thionyl chloride in pyridine at room temperature. Method B: with thionyl chloride–triethylamine in dichloromethane at room temperature.

azidocinnamate (**2**), if **4** could be converted to **2** in good yield. Thus, dehydration of **4** was attempted. The azidoalcohol (**4**) (X=H) was treated under the same conditions as those used to convert **1** to **2** (NaOEt/EtOH, 0 °C), but no reaction occurred. Treatment of **4** under acidic conditions did not give the desired result. Finally, the conversion of **4** to **2** was successful with thionyl chloride ($SOCl_2$)/pyridine or $SOCl_2$/triethylamine (Et_3N). This dehydration generally proceeded in good yield as summarized in Table 2. Although we did not examine whether **4** other than those described in Table 2 could be converted into the corresponding azidocinnamates (**2**), they should be convertible in the same way. The yields in the two-step preparation of **2** from **1** were generally better than those in the one-step preparation at 0 °C. Based on the above results, we now believe that the occasional low yield of **2** in the one-step preparation from arylaldehyde (**1**) at 0 °C was not caused by the inability to detect **4**, but rather by consumption of ethyl azidoacetate by self-Claisen condensation or rapid decomposition under basic conditions at a higher temperature (0 °C). Thus, the two-step synthesis of **2** is sometimes more effective than the one-step synthesis.

Most of the azidocinnamates (**2**) thus prepared were already reported[5,6] to convert easily into the corresponding indoles (**3**). The pyrrolysis of the previously unknown 2-azidocinnnamates (**2f** and **2i**) was successful, giving the indoles (**3f** and **3i**) in good yield, regardless of the electronic effect of the substituent.

In addition, the azidoalcohols (**4**) are stable compounds and should be useful for the preparation of β-hydroxyamino acids[9] and related compounds.[10] We are currently examining the potential synthetic applications of **4**.

Aldol Condensation Using Fluoride Ion The above results showed that the total yields of condensation products were better in reactions at lower than at higher temperature, suggesting that milder reaction conditions would result in better product yields. Thus, fluoride ion was used as a base.[11] The results of condensation reactions using potassium fluoride (KF)/crown ether or tetrabutylammonium fluoride (TBAF) are shown in Table 3. Although the reactions were carried out at 0 °C—room temperature, the product was almost exclusively the azidoalcohol (**4**). The yields were moderate, while the reaction required a longer time than that in the case of NaOEt. The reaction using only KF was not successful. Although the reaction using fluoride ion gave a lower yield than that using NaOEt, the former can be applied to base-sensitive substrates.

Application of Hemetsberger–Knittel Reaction to Ketones Hemetsberger–Knittel reaction has been used for the preparation of 3-unsubstituted indoles starting from arylaldehyde. As many 3-substituted indolic natural products and pharmaceuticals are known, a rapid method of preparation of 3-substituted indoles from aryl alkyl ketones by means of the Hemetsberger–Knittel reaction[12] would be very useful (from **5** to **7** *via* **6**). Thus, we examined the

Table 3. Condensation of Aryl Aldehydes (**1**) and Ethyl Azidoacetate using Fluoride Ion

Run	**1** X=	Fluoride ion source (Solvent)	Catalyst	Temp. (°C)	Time	Azidocinnamate (**2**) (%)	Azidoalcohol (**4**) (%)
1	H (**1a**)	KF (CH_3CN)	Dicyclohexyl-18-crown-6	r.t.	4 d	1.2	25
2	H (**1a**)	TBAF (THF)	—	0	2.5 h	0	37
3	2-OCH_3 (**1c**)	KF (CH_3CN)	Dicyclohexyl-18-crown-6	r.t.	2 d	0	39
4	2-OCH_3 (**1c**)	TBAF (THF)	—	r.t.	3 h	0	58

Temp. = temperature.

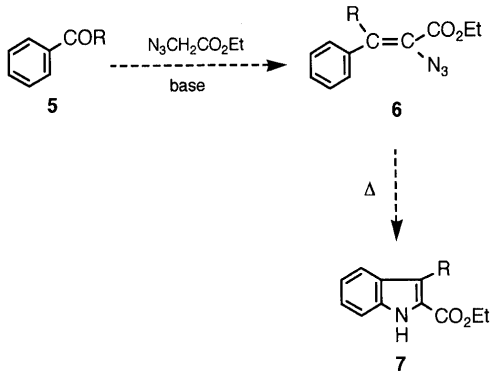

Chart 2

preparation of ethyl 3-methylindole-2-carboxylate using acetophenone (**5**) (R = CH_3) as a substrate.

Firstly, we examined the aldol condensation of acetophenone with ethyl azidoacetate in the presence of a variety of bases, such as NaOEt/EtOH, TBAF/tetrahydrofuran (THF), ammonium acetate-acetic acid/benzene, and zirconium propoxide/benzene. In all cases, however, no reaction occurred and the starting acetophenone was recovered.

Smolinsky and Pryde[12a] reported that pyrolysis of vinyl azide (**9**) prepared from the epoxide (**8**) gave 3-methylindole (**10**). Thus, we next examined this reaction.

Acetophenone was treated with ethyl chloroacetate/potassium *tert*-butoxide (Darzens reaction) to give the epoxide[13] (**11**) as a 1 : 1 mixture of *cis* and *trans* isomers. For conversion into the azidoalcohol (**12**), the epoxide (**11**) was treated with sodium azide (NaN_3) in methanol according to Smolinsky's method to give two kinds of azidoalcohols[14] (**12** and **13**). The ratio of **12** and **13** was 1 : 10 as determined by ^{1}H-NMR, showing that the undesired isomer (**13**) was the main product. Thus, conditions for obtaining the azidoalcohol (**12**) were examined. Treatment of **11** with NaN_3 in dimethyl sulfoxide (DMSO) in the presence of sulfuric acid yielded the azidoalcohol (**12**) as the main product (**12** : **13** = 2 : 1). As these isomers (**12** and **13**) were difficult to isolate, the mixture was treated with $SOCl_2/Et_3N$ in CH_2Cl_2 to give a mixture of *E*- and *Z*-isomers of the vinyl azide (**14**), which were easily separated by column chromatography. The vinyl azide (**14**) thus obtained was heated under reflux in xylene to give the target 3-methylindole[15] (**15**) in good yield. Despite the disadvantage of low yield and low selectivity at the ring-opening stage of **11**, this synthetic route is potentially useful for synthesis of 3-alkylindoles.

Experimental

All melting points were measured on a micro melting point hot stage (Yanaco) and are uncorrected. For spectral data, the following instruments were used: IR, Shimadzu IR-400; ^{1}H-NMR, Hitachi R-24B (60 MHz, unless otherwise stated), JEOL EX-400 (400 MHz); EIMS, JEOL JMS-01-SG-2 spectrometer and FABMS, JEOL JMS-HX110. For column chromatography, silica gel (Kiesel gel 60, 70—230 mesh, Merck) and for TLC, Kiesel gel GF_{254}, Merck, were used.

General Procedure for the Synthesis of Ethyl 2-Azidocinnamates (2) and/or Ethyl 2-Azido-3-hydroxy-3-arylpropionates (4) from Arylaldehydes (1) Reaction with Sodium Ethoxide: A solution of the arylaldehyde (**1**) (1 mmol) and ethyl azidoacetate (4 mmol) in anhydrous EtOH (4 ml) was added to an ethanolic solution of sodium ethoxide prepared from sodium (4 mg atom) in EtOH (5 ml) at the appropriate temperature (0 or −30 °C). The reaction mixture was stirred at the same temperature, poured into ice-water saturated with ammonium chloride, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The residue was chromatographed over silica gel to afford ethyl 2-azidocinnamate (**2**) and/or the ethyl 2-azido-3-hydroxy-3-arylpropionate (**4**). The residue was recrystallized from the solvent indicated in Table 4. Spectroscopic data are listed in Tables 4 and 5.

Reaction with Potassium Fluoride: Ethyl azidoacetate (4 mmol) was added to a solution of arylaldehyde (**1**) (1 mmol), potassium fluoride (2 mmol), and dicyclohexyl-18-crown-6 (0.1 mmol) in acetonitrile (1 ml) at room temperature. The reaction mixture was stirred at the same temperature, poured into ice-water, and extracted with ether. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The residue was chromatographed over silica gel to afford ethyl 2-azidocinnamate (**2**) and/or the ethyl 2-azido-3-hydroxy-3-arylpropionate (**4**) (see Table 3).

Reaction with Tetrabutylammonium Fluoride (TBAF): Ethyl azidoacetate (2 mmol) was added to a solution of arylaldehyde (**1**) (1 mmol) and TBAF (1 M solution in THF) (1 mmol) in THF (5 ml) at room temperature under an argon atmosphere. The reaction and work-up were carried out in the same manner as described above (see Table 3).

Analytical and High-resolution Mass Spectroscopic Data for Previously Unknown Ethyl 2-Azidocinnamates (2) and Ethyl 2-Azido-3-hydroxy-3-arylpropionates (4) Ethyl 2-Azido-3-(4-biphenyl)propenoate (**2f**): Yellow prisms, mp 99—103 °C (hexane). *Anal.* Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.70; H, 5.17; N, 14.38.

Ethyl 2-Azido-3-[2-(trifluoromethyl)phenyl]propenoate (**2i**): Yellow prisms, mp 35—36.5 °C (pentane). *Anal.* Calcd for $C_{12}H_{10}F_3N_3O_2$: C, 50.53; H, 3.53; N, 14.73. Found: C, 50.37; H, 3.54; N, 14.38.

Ethyl 2-Azido-3-(4-nitrophenyl)propenoate (**2j**): Yellow amorphous solid (unstable). FABMS *m/z*: 233 ($M^+ + H - NO$), no molecular ion peak.

Ethyl 2-Azido-3-hydroxy-3-phenylpropionate (**4a**)[8]: Colorless oil. HR-FABMS *m/z* : Calcd for $C_{11}H_{14}N_3O_3$: 236.1035 ($M^+ + H$). Found: 236.1050.

Ethyl 2-Azido-3-hydroxy-3-(2-methylphenyl)propionate (**4b**): Yellow oil. *Anal.* Calcd for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.95; H, 6.16; N, 16.60.

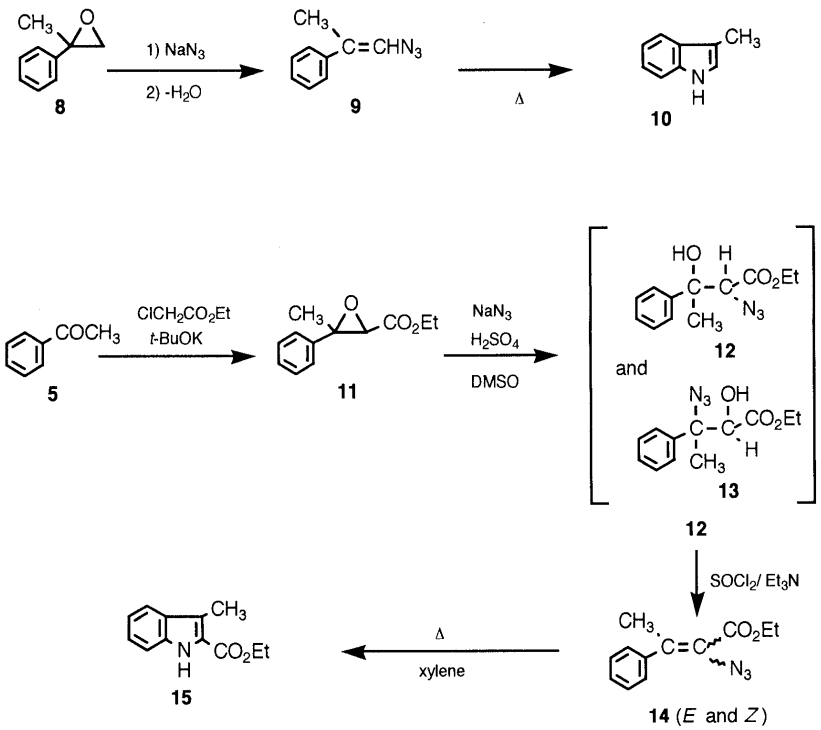

Chart 3

Ethyl 2-Azido-3-hydroxy-3-(2-methoxyphenyl)propionate (**4c**): Pale yellow oil. HR-FABMS *m/z*: Calcd for $C_{12}H_{16}N_3O_4$: 266.1119 ($M^+ + H$). Found: 266.1149.

Ethyl 2-Azido-3-hydroxy-3-(4-methoxyphenyl)propionate (**4d**): Colorless prisms, mp 98—102 °C. HR-FABMS *m/z*: Calcd for $C_{12}H_{15}KN_3O_4$: 304.0700 ($M^+ + K$). Found: 304.0689.

Ethyl 2-Azido-3-hydroxy-3-(2,5-dimethoxyphenyl)propionate (**4e**): Colorless prisms, mp 76—119 °C (ethyl acetate–hexane). *Anal.* Calcd for $C_{13}H_{17}N_3O_5$: C, 52.88; H, 5.80; N, 14.23. Found: C, 52.79; H, 5.84; N, 14.20.

Ethyl 2-Azido-3-hydroxy-3-(4-biphenyl)propionate (**4f**): Pale yellow prisms, mp 69—72 °C (hexane). *Anal.* Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.72; H, 5.53; N, 13.38.

Ethyl 2-Azido-3-hydroxy-3-(2-chlorophenyl)propionate (**4g**): Pale yellow oil. HR-FABMS *m/z*: Calcd for $C_{11}H_{13}ClN_3O_3$: 270.0646 ($M^+ + H$). Found: 270.0645.

Ethyl 2-Azido-3-hydroxy-3-(4-chlorophenyl)propionate (**4h**): Yellow oil . HR-FABMS *m/z*: Calcd for $C_{11}H_{13}ClN_3O_3$: 270.0646 ($M^+ + H$). Found: 270.0652.

Ethyl 2-Azido-3-hydroxy-3-[2-(trifluoromethyl)phenyl]propionate (**4i**): Pale yellow prisms, mp 64.5—66 °C (hexane–ether). *Anal.* Calcd for $C_{12}H_{12}F_3N_3O_3$: C, 47.53; H, 3.99; N, 13.86. Found: C, 47.67; H, 3.96; N, 13.80.

Ethyl 2-Azido-3-hydroxy-3-(4-nitrophenyl)propionate (**4j**): Yellow prisms, mp 88—96 °C (hexane–ether). *Anal.* Calcd for $C_{11}H_{12}N_4O_5$: C, 47.15; H, 4.32; N, 19.99. Found: C, 47.32; H, 4.26; N, 19.90.

General Procedure for Conversion of Ethyl 2-Azido-3-hydroxy-3-arylpropionates (4) to Ethyl 2-Azidocinnamates (2) Method A: Thionyl chloride (2.8 mmol) was added to a solution of an ethyl 2-azido-3-hydroxy-3-arylpropionate (**4**) (1 mmol) in pyridine (5 ml) under ice-cooling, and the mixture was stirred at room temperature. The reaction mixture was poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with 5% copper sulfate and brine, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The residue was chromatographed over silica gel to afford the desired ethyl 2-azidocinnamate (**2**).

Method B: Thionyl chloride (2 mmol) and triethylamine (7 mmol) were added to a solution of ethyl 2-azido-3-hydroxy-3-arylpropionate (**4**) (1 mmol) in dichloromethane (5 ml) under ice-cooling, and the mixture was stirred at room temperature. It was poured into ice-water, and extracted with dichloromethane. The organic layer was washed with 5% hydrochloric acid, saturated sodium bicarbonate, and brine, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The residue was chromatographed over silica gel to afford the desired ethyl 2-azidocinnamate (**2**).

Pyrolysis of 2-Azidocinnnamate (2) Ethyl 4-(Trifluoromethyl)indole-2-carboxylate (**3i**): Typical Procedure: A solution of ethyl 2-azido-3-[2-(trifluoromethyl)phenyl]propenoate (**2i**) (86 mg, 0.30 mmol) in *p*-xylene (4.3 ml) was heated with stirring at 160 °C for 50 min. After the reaction was over, the solvent was removed *in vacuo*. The resulting residue (77 mg) was column-chromatographed over silica gel with hexane–ethyl acetate (5 : 1) to give the title compound (55 mg, 71%). Recrystallization from ethyl acetate–hexane gave colorless needles, mp 149—150 °C (lit.[16] mp 148—149 °C). *Anal.* Calcd for $C_{12}H_{10}F_3NO_2$: C, 56.04; H, 3.92; N, 5.45. Found: C, 56.22; H, 3.69; N, 5.53. IR ν_{max}^{KBr} cm^{-1}: 3311, 1695. ^{1}H-NMR ($CDCl_3$) (400 MHz) δ: 1.44 (3H, t, J=7.1 Hz, CH_2Me), 4.45 (2H, q, J=7.1 Hz, OCH_2), 7.38 (1H, br t, J=7.8 Hz, 6-H), 7.39 (1H, br s, 3-H), 7.47 (1H, br d, J=7.8 Hz, 5- or 7-H), 7.61 (1H, br d, J=7.8 Hz, 7- or 5-H), 9.26 (1H, br s, NH). FABMS *m/z*: 258 ($M^+ + H$).

Ethyl 6-Phenyindole-2-carboxylate (**3f**): Yield, 87%. Colorless needles (ethyl acetate–hexane), mp 130—133 °C. *Anal.* Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.11; H, 5.57; N, 5.35. IR ν_{max}^{KBr} cm^{-1}: 3260, 1690. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz, CH_2Me), 4.38 (2H, q, J=7 Hz, OCH_2), 7.07—7.82 (8H, m, aromatic H), 7.15 (1H, d, J=2 Hz, 3-H), 9.05 (1H, br s, NH). MS *m/z* : 265 (M^+, 100%).

Ethyl 2-Azido-3-methylcinnamate (14) Ring Opening of Ethyl 2,3-Epoxy-3-methyl-3-phenylpropionate (**11**) with Sodium Azide and Sulfuric Acid: Sodium azide (1.947 g, 30.0 mmol) and concentrated sulfuric acid (d=1.84, 0.111 ml, 2.08 mmol) were added to a solution of ethyl 2,3-epoxy-3-methyl-3-phenylpropionate (**11**) (prepared from acetophenone by means of the Darzens reaction)[13] (0.615 g, 2.98 mmol) in DMSO (15 ml). The mixture was stirred at 90 °C for 2 h, poured into ice-water, and extracted with ether. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The residue (0.625 g) was a yellow oil, consisting of an inseparable mixture of the desired ethyl 2-azido-3-hydroxy-3-phenylbutyrate (**12**) and its isomer (**13**) (the product ratio was determined by ^{1}H-NMR, **12** : **13** = 2 : 1). **12**: ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7.0 Hz CH_2Me), 1.64 (3H, s, CMe), 3.63 and 3.94 (each 1H, s, OH or β-H), 4.01 (2H, q, J=7.0 Hz, OCH_2), 7.09—7.51 (5H, m, aromatic H). **13**: ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.0 Hz, CH_2Me), 1.86 (3H, s, CMe), 3.28 and 4.29 (each 1H, s, OH or α-H), 4.18 (2H, q, J=7.0 Hz, OCH_2), 7.12—7.65 (5H, m, aromatic H).

Dehydration of Ethyl 2-Azido-3-hydroxy-3-phenylbutyrate (**12**) to Ethyl 2-Azido-3-methylcinnamate (**14**): Thionyl chloride (0.362 ml, 4.96

Table 4. Spectral Data for Ethyl 2-Azidocinnamates (**2**)

Compound (Formula)	mp (°C) (lit. mp) (Solvent)	IR ν cm^{-1} (N_3, C=O)	^{1}H-NMR (δ, J in Hz) ($CDCl_3$)
2a $C_{11}H_{11}N_3O_2$	38.5—41 (42—43)[5]	2120, 1700	1.39 (3H, t, J=7.0, CMe), 4.35 (2H, q, J=7.0, OCH_2), 6.83 (1H, s, vinylic H), 7.20—7.91 (5H, m, ArH)
2b $C_{12}H_{13}N_3O_2$	56.5—57 (55—56)[5] (Hexane)	2090, 1690	1.40 (3H, t, J=7.0, CMe), 2.35 (3H, s, ArMe), 4.37 (2H, q, J=7.0, OCH_2), 7.05—7.35 (4H, m, vinylic H and ArH), 7.90 (1H, br, ArH)
2c $C_{12}H_{13}N_3O_3$	62.5—64.5 (63—64)[5]	2120, 1700	1.37 (3H, t, J=7.0, CMe), 3.78 (3H, s, OMe), 4.30 (2H, q, J=7.0, OCH_2), 7.27 (1H, s, vinylic H), 8.05 (4H, m, ArH)
2d $C_{12}H_{13}N_3O_3$	54—55 (61—62)[5]	2117, 1702	1.39 (3H, t, J=7.0, CMe), 3.34 (3H, s, OMe), 4.35 (2H, q, J=7.0, OCH_2), 6.88 (1H, s, vinylic H), 6.90 (2H, d, J= 8.5, ArH), 7.79 (2H, d, J=8.5, ArH)
2e $C_{13}H_{15}N_3O_4$	84—86.5 (84—86.5)[17] (Benzene–hexane)	*a)*	*a)*
2f $C_{17}H_{15}N_3O_2$	99—103 (Hexane)	2130, 1710	1.39 (3H, t, J=7.0, CMe), 4.35 (2H, q, J=7.0, OCH_2), 6.99 (1H, s, vinylic H), 7.17—7.99 (9H, m, ArH)
2g $C_{11}H_{10}ClN_3O_2$	39—45.5 (46—47)[5]	2120, 1710	1.41 (3H, t, J=7.3, CMe), 4.40 (2H, q, J=7.3, OCH_2), 7.23—7.32 (2H, m, ArH), 7.30 (1H, s, vinylic H), 7.41 (1H, dd, J=7.8, 1.5, ArH), 8.17 (1H, dd, J=7.3, 1.5, ArH)
2h $C_{11}H_{10}ClN_3O_2$	Oil (33-34)[5]	2122, 1712	1.40 (3H, t, J=7.0, CMe), 4.36 (2H, q, J=7.0, OCH_2), 6.82 (1H, s, vinylic H), 7.33 (2H, d, J=8.5, ArH), 7.73 (2H, d, J=8.5, ArH)
2i $C_{12}H_{10}F_3N_3O_2$	35—36.5 (Pentane)	2120, 1720	1.38 (3H, t, J=7.0, CMe), 4.36 (2H, q, J=7.0, OCH_2), 7.13—8.17 (5H, m, vinylic H and ArH)
2j $C_{11}H_{10}N_4O_4$	Oil	2122, 1717	1.43 (3H, t, J=7.0, CMe), 4.44 (2H, q, J=7.0, OCH_2), 7.26 (1H, s, vinylic H), 8.22 (2H, d, J=8.5, ArH), 8.28 (2H, d, J=8.5, ArH)

a) Reported in reference 17.

Table 5. Spectral Data for Ethyl 2-Azido-3-hydroxy-3-arylpropionates (**4**)[a)]

Compound (Formula)	mp (°C) (Solvent)	IR ν cm^{-1} (OH, N_3, C=O)	^{1}H-NMR (δ, J in Hz) ($CDCl_3$)
4a $C_{11}H_{13}N_3O_3$	Oil	3440, 2120, 1730	1.20, 1.23 (total 3H, each t, J=7.0, CMe), 2.95, 3.15 (total 1H, each d, J=6.0, OH), 3.87—4.40 (3H, m, OCH_2, CHN_3), 4.85—5.30 (1H, m, CHOH), 7.27 (5H, s, ArH)
4b $C_{12}H_{15}N_3O_3$	Oil	3470, 2120, 1740	1.20, 1.23 (total 3H, each t, J=7.0, CMe), 2.30, 2.35 (total 3H, each s, ArMe), 2.76, 3.01 (total 1H, each d, J=5.0, 4.0, OH), 4.18, 4.20 (total 2H, each q, J=7.0, OCH_2), 3.96, 4.04 (total 1H, each d, J=4.0, 7.0, CHN_3), [5.20 (dd, J=7.0, 5.0), 5.38 (t, J=4), total 1H, CHOH], 6.95—7.65 (4H, m, ArH)
4c $C_{12}H_{15}N_3O_4$	Oil	3470, 2120, 1735	1.22, 1.25 (total 3H, each t, J=7.0, CMe), 3.05, 3.37 (total 1H, each d, J=7.0, OH), 3.82 (3H, s, OMe), 3.95—4.45 (3H, m, OCH_2, CHN_3), 5.00—5.65 (1H, m, CHOH), 6.70—7.55 (4H, m, ArH)
4d $C_{12}H_{15}N_3O_4$	98—102	3435, 2116, 1727	0.85, 0.88 (total 3H, each t, J=7.0 , CMe), 2.20, 2.39 (total 1H, each s, OH), 3.31, 3.32 (total 3H, each s, OMe), 3.70 (1H, d, J=7.0, CHN_3), 3.87, 3.90 (total 2H, each q, J=7.0, OCH_2), 4.88—5.04 (1H, m, CHOH), 6.77 (2H, d, J=8.5, ArH), 7.18 (2H, d, J=8.5, ArH)
4e $C_{13}H_{17}N_3O_5$	76—119 (AcOEt–hexane)	3515 and 3410, 2105, 1735 and 1720	1.22, 1.29 (total 3H, each t, J=7.0, CMe), 2.98, 3.38 (total 1H, each d, J=7.0, OH), 3.77, 3.79, 3.83, 3.85 (total 6H, each s, OMe), 4.18—4.30 (3H, m, OCH_2, CHN_3), [5.12 (dd, J=7.8, 6.8), 5.41 (dd, J=6.5, 3.5), total 1H, CHOH], 6.80—6.85 (2H, m, ArH), 6.92, 7.03 (total 1H, each m, ArH)
4f $C_{17}H_{17}N_3O_3$	69—72 (Hexane)	3470, 2110, 1705	1.22 (3H, t, J=7.0, CMe), 2.72—3.10 (1H, br, OH), 3.90—4.45 (3H, m, OCH_2, CHN_3), 4.92—5.40 (1H, br, CHOH), 7.40—7.78 (9H, m, ArH)
4g $C_{11}H_{12}ClN_3O_3$	Oil	3450, 2110, 1730	1.15, 1.32 (total 3H, each t, J=7.0, CMe), 2.98, 3.25 (total 1H, each d, J=7.0, OH), 3.85—4.55 (3H, m, OCH_2, CHN_3), 5.25—5.85 (1H, m, CHOH), 7.00—7.80 (4H, m, ArH)
4h $C_{11}H_{12}ClN_3O_3$	Oil	3444, 2115, 1736	0.73—0.80 (total 3H, m, CMe), 2.11, 2.33 (total 1H, each m, OH), 3.45, 3.63 (total 1H, each d, J=7.0, CHN_3), 3.73—3.81 (2H, m, OCH_2), 4.61—4.80 (1H, m, CHOH), 6.85 (2H, d, J=8.5, ArH), 6.98 (2H, d, J=8.5, ArH)
4i $C_{12}H_{12}F_3N_3O_3$	64.5—66 (Hexane–ether)	3450, 2110, 1710	1.30 (3H, t, J=7.0, CMe), 2.84 (1H, d, J=5.0, OH), 3.98 (1H, d, J=3.0, CHN_3), 4.29 (2H, q, J=7.0, OCH_2), 5.70 (1H, m, CHOH), 7.30—8.00 (4H, m, ArH)
4j $C_{11}H_{12}N_4O_5$	84—86	3468, 2117, 1734	0.80, 0.88 (total 3H, each t, J=7.0, CMe), 2.03, 2.28 (total 1H, each s, OH), 3.41, 3.59 (total 1H, each d, J=7.0, CHN_3), 3.78—3.91 (2H, m, OCH_2), 6.91 (2H, d, J=8.5, ArH), 7.86 (2H, d, J=8.5, ArH)

a) A mixture of diastereoisomers.

mmol) and triethylamine (2.42 ml, 17.4 mmol) were added to a solution of the above mixture (**12** and **13**) (0.618 g, 2.48 mmol) in dichloromethane (15 ml) under ice-cooling. The whole was stirred for 4 h at room temperature. The above procedure was repeated with additional thionyl chloride (0.181 ml, 2.48 mmol) and triethylamine (1.04 ml, 7.44 mmol). Then, the reaction mixture was stirred at room temperature for a further 21 h, poured into ice-water, and extracted with dichloromethane. The organic layer was washed with 5% hydrochloric acid, saturated sodium bicarbonate, and brine, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The residue (0.862 g) was chromatographed over silica gel using benzene–hexane (1 : 2) as an eluent to afford two fractions. The first fraction gave a yellow oil (*E*-**14**) (39.9 mg, 6%), and the second fraction also gave a yellow oil (*Z*-**14**) (72.5 mg, 11%) (totally 112.4 mg, 17% from **11**).

E-**14**: IR ν_{max}^{neat} cm^{-1}: 2110, 1705. ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, J=7 Hz, CH_2Me), 2.12 (3H, s, CMe), 3.94 (2H, q, J=7 Hz, OCH_2), 6.93—7.53 (5H, m, aromatic H). MS *m/z*: 231 (M^+), 203, 103 (100%). HR-FABMS *m/z*: Calcd for $C_{12}H_{13}NO_2$: 203.0964 ($M^+ - N_2$). Found: 203.0963.

Z-**14**: IR ν_{max}^{neat} cm^{-1}: 2110, 1705. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7 Hz, CH_2Me), 2.33 (3H, s, CMe), 4.38 (2H, q, J=7 Hz, OCH_2), 6.97—7.62 (5H, m, aromatic H). MS *m/z*: 203, 103 (100%) (no molecular ion peak). HR-FABMS *m/z*: Calcd for $C_{12}H_{13}NO_2$: 203.0964 ($M^+ - N_2$). Found: 203.0954.

Ethyl 3-Methylindole-2-carboxylate (15) A solution of the azidocinnamate (*E*-**14**) (23.3 mg) in xylene (3 ml) was refluxed for 50 min under an argon atmosphere. The solvent was removed *in vacuo* to afford a yellow solid (18.6 mg). The crude solid was purified with silica gel chromatography with cyclohexane–ether (2 : 1) to give colorless needles (**15**), mp 136—140 °C (lit.[15] mp 133—134 °C), 15.1 mg (74%), which were recrystallized from benzene–hexane. IR ν_{max}^{nujol} cm^{-1} 3315, 1670. ^{1}H-NMR ($CDCl_3$) (400 MHz) δ: 1.43 (3H, t, J=7.1 Hz, CH_2Me), 2.61 (3H, s, ArMe), 4.42 (2H, q, J=7.1 Hz, OCH_2), 7.14, 7.32 (each 1H, dt, J=7.5, 0.98 Hz, 5- and 6-H), 7.36 (1H, d, J=8.3 Hz, 7-H), 7.67 (1H, dd, J=7.8, 0.98 Hz, 4-H), 8.65 (1H, br s, NH).

The same result was obtained using *Z*-**14** as a starting material.

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