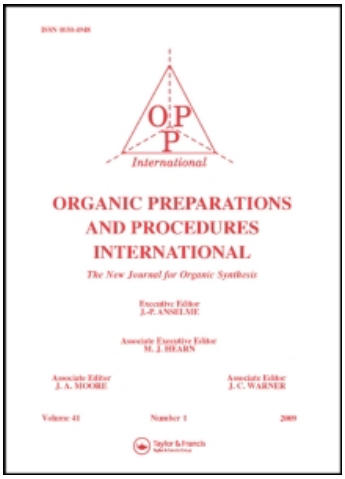

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ALTERNATE PREPARATION OF α-KETO ESTERS FROM ACID CHLORIDES

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ALTERNATE PREPARATION OF α-KETO ESTERS FROM ACID CHLORIDES

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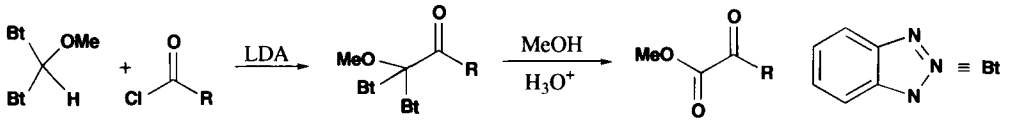
α-Keto esters are of current interest because they are photo-polymerization initiators,[1] are biologically active,[2] and are precursors in the asymmetric synthesis of α-amino- and α-hydroxy-carboxylic acids.[3] The more important synthetic pathways to these compounds include α-oxidation of esters[4] and α-hydroxy esters,[5] Friedel-Crafts acylation using ethyl chloroglyoxylate,[6] the reaction of organometallic species with ethyl chloroglyoxylate,[7] and the homologation of acyl halides *via* the hydrolysis and esterification of acyl cyanides.[1] While the last pathway is general, it suffers from several drawbacks. Acyl cyanides are somewhat labile, suffering hydrolytic loss of cyanide ion in methanol or ethanol[1] and their preparation in good (> 60-70%) yield requires the use of expensive and toxic[8] trimethylsilyl cyanide. While *ortho*-toluoyl cyanide has been hydrolyzed directly to methyl toluoylformate in 82% yield, the conditions were harsh (85% H_2SO_4), and the concentration of sodium bromide catalyst had to be very carefully controlled.[1] We now demonstrate an alternative approach to α-keto esters not bearing β-hydrogens by reaction of acid chlorides with 1,1-di(benzotriazol-1-yl)-1-methoxymethane. This procedure yields intermediate α,α-di(benzotriazol-1-yl)-α-methoxy ketones (54-83%) which, under mild hydrolysis, produce α-keto esters (79-92%), for example methyl toluoylformate in 92% yield (*cf.* ref.[1]).

The key reagent, 1,1-di(benzotriazol-1-yl)-1-methoxymethane (**1**), used to derivatize the acid chlorides **2a-f**, is easily prepared on a large scale from (1,1-dichloromethyl)methyl ether and benzotriazole in 85% yield. Due to the influence of the two benzotriazolyl groups, the α-hydrogen of this molecule is relatively acidic and can be removed with a strong base, such as LDA, to produce a synthetically useful carbanion. When mixtures of **1** and acid chlorides **2a-f** which do not bear α-hydrogens were treated with LDA, the intermediate α,α-di(benzotriazol-1-yl)-α-methoxy ketones **3a-f** were produced in 54-83% isolated yield (Scheme 1, Table 1). These compounds are very



1 2a-f 3a-f 4a-f

Scheme 1

robust, and the yields in Table 1 are for analytically pure samples obtained after purification by column chromatography.

TABLE 1. Preparation of α,α-Di(benzotriazol-1-yl)-α-methoxyketones (**3**)

Cmpd No.	R	Yield[a] (%)	mp (°C)	Elemental Analysis (Found) C		H		N	
3a	*t*-butyl	83	142-144	62.62	(62.98)	5.53	(5.59)	23.07	(23.36)
3b	phenyl	76	149-151	65.60	(65.24)	4.20	(4.20)	21.87	(22.26)
3c	*o*-methylphenyl	54	160-162	66.31	(66.59)	4.56	(4.62)	21.10	(21.47)
3d	*p*-methoxyphenyl	82	138-141	63.76	(64.00)	4.38	(4.39)	20.28	(20.55)
3e	*p*-chlorophenyl	77	55-57			419.1023	(419.1042)		
3f	β-naphthyl	61	68-70	69.12	(69.44)	4.18	(4.26)	19.34	(19.26)

a) Isolated yield of analytically pure material. b) HRMS M+1 ion obtained by FAB-MS.

When compounds **3a-f** were refluxed in aqueous methanol with an acid catalyst, the corresponding α-keto esters **4a-f** were produced in excellent yield (Scheme 1, Table 2).

TABLE 2. Preparation of α-Keto Esters (**4**)

Cmpd No.	R	Yield[a] (%)	mp (°C)	Elemental Analysis (Found) C		H		Ref.
4a	*t*-butyl[b]	88	207-209	48.13	(48.05)	4.98	(4.92)	9
4b	phenyl	87	oil	[c]		–	–	10
4c	*o*-methylphenyl	92	oil	67.39	(67.33)	5.66	(5.68)	11
4d	*p*-methoxyphenyl	81	42-43	61.85	(61.86)	5.19	(5.23)	10
4e	*p*-chlorophenyl	79	58-60	54.43	(54.43)	3.55	(3.50)	10
4f	β-naphthyl	81	oil	72.88	(72.71)	4.71	(4.75)	new

a) Isolated yield of analytically pure material. b) Compound **4a** was isolated and characterized as the 2,4-dinitrophenylhydrazone adduct. c) Compound **4b** was identified by comparison of its ^{13}C NMR data with that of the authentic compound found in the Sadtler Library of NMR Data, spectrum 2700C.

Attempts to react **1** with acid chlorides bearing α-hydrogens gave only complex mixtures, presumably due to deprotonation of the acid chloride by LDA. When the anion was generated prior to the addition of the acid chloride, the only products isolated were *cis*- and *trans*-1,2-di(benzotriazol-1-yl)-1,2-dimethoxyethene. The structures of both isomers were confirmed by X-ray crystallography. Figure 1 shows perspective views and atom labelling of the structures. The *cis* isomer crystallizes with

a whole molecule in the asymmetric unit and has approximate C_2 symmetry which is destroyed by small torsion angle differences. The *trans* isomer crystallizes with half a molecule in the asymmetric unit, the other half being related by a crystallographic center of inversion.

These unsaturated compounds could have been formed by an S_N2 type attack of the initially formed anion upon unreacted **1**, with benzotriazole anion acting as the leaving group. Loss of benzotriazole from this intermediate would then produce the observed mixture of isomeric alkenes.

While this method is limited to the preparation of α-keto esters without β-hydrogens, it has distinct advantages over comparable approaches for the preparation of such compounds.

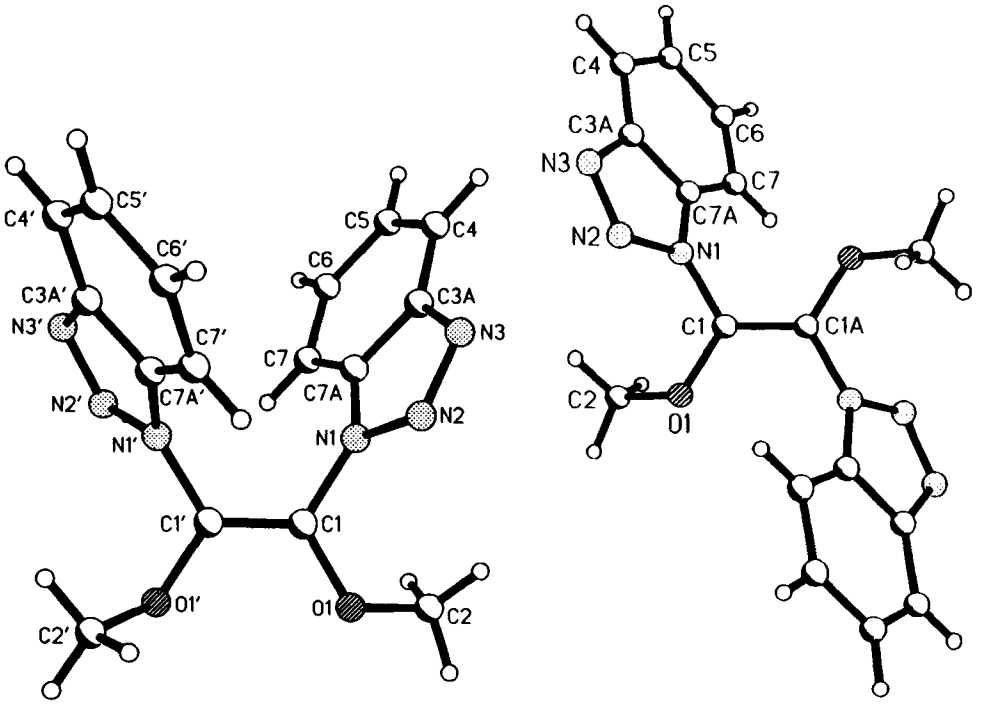


Fig. 1 Perspective Views and Atom Labelling of Crystal Structures

EXPERIMENTAL SECTION

NMR spectra were recorded in deuteriochloroform on a Varian Gemini 300 spectrometer. Low resolution mass spectra were recorded on a Hewlett Packard 5972A GC / mass spectrometer. High resolution mass measurements were made on a Finnigan MAT 95Q mass spectrometer. Melting points are uncorrected. Column chromatography was carried out using 230-400 mesh silica.

1,1-Di(benzotriazol-1-yl)-1-methoxymethane (1).- A stirred suspension of benzotriazole (60 g, 500 mmol) in toluene (500 mL) was warmed to 80°, and 1,1-(dichloromethyl)methyl ether (27 mL, 300 mmol) was added dropwise over 1 hr. Triethylamine (76 mL, 550 mmol) was added dropwise to the mixture, which was stirred for a further 5 hrs before being poured onto ice water (700 mL). The

aqueous mixture was extracted with toluene, and the organic layer was washed with water, dried over magnesium sulfate, and evaporated to dryness to give a white solid (56 g, 85%). Recrystallization from methanol provided colorless prisms, mp 112-113°; ^{1}H NMR: 3.73 (s, 3H), 7.40 (t, J = 7.3 Hz, 2H), 7.51 (t, J = 7.3 Hz, 2H), 7.82 (d, J = 7.3 Hz, 2H), 8.08 (d, J = 7.3 Hz, 2H), 8.38 (s, 1H); ^{13}C NMR: 57.2, 94.7, 111.1, 120.2, 124.9, 128.8, 131.4, 146.3.

Anal. Calcd. for $C_{14}H_{12}N_6O$: C, 59.98; H, 4.32; N, 30.00. Found: C, 59.76; H, 4.28; N, 30.32

α,α-Di(benzotriazol-1-yl)-α-methoxy Ketones 3a-f. General Procedure.- All of these reactions were carried out under a nitrogen atmosphere. A solution of **1** (1.4 g, 5 mmol) in THF (60 mL) was cooled to -78° and to this was added the appropriate acid chloride (**2a-f**) (5 mmol) dissolved in THF (4 mL). To this mixture was added LDA (3.67 mL of a 1.5 M solution in THF), and the reaction was allowed to slowly warm to room temperature overnight. The reaction mixture was quenched with water (40 mL), and then extracted with ether, which was dried over magnesium sulfate and evaporated to dryness. The crude mixture was triturated with hexane (5 mL) and ether (5 mL), which provided the desired product in > 95% purity. This material can be used in the hydrolysis without further purification, however, the yields reported in Table 1 are for analytically pure samples obtained after column chromatography using ethyl acetate/hexane (1:2) as eluent. The yield and analytical data for **3a-f** are shown in Table 1, with ^{1}H and ^{13}C NMR data in Tables 3 and 4.

TABLE 3. ^{1}H NMR Data for α,α-Di(benzotriazol-1-yl)-α-methoxyketones (**3**)

	Benzotriazolyl Hydrogens				OCH_3	R Group Hydrogens				
	H-4	H-5	H-6	H-7						
3a	8.15 (m, 2H)	7.43 (m, 2H)	7.43 (m, 2H)	7.12 (m, 2H)	3.69 (s, 3H)	1.21 (s, 9H)				
3b	8.06 (m, 2H)	7.39 (m, 2H)	7.39 (m, 2H)	7.39 (m, 2H)	3.85 (s, 3H)	7.39 (m, 2H)	7.52 (t, J = 7.2 Hz, 1H)		8.06 (m, 2H)	
3c	8.07 (m, 2H)	7.37 (m, 2H)	7.37 (m, 2H)	7.37 (m, 2H)	3.82 (s, 3H)	2.52 (s, 3H)	7.07 (t, J = 7.3 Hz, 1H)	7.24 (d, J = 7.3 Hz, 1H)	7.37 (m, 1H)	7.79 (d, J = 7.3 Hz, 1H)
3d	8.07 (m, 2H)	7.41 (m, 2H)	7.41 (m, 2H)	7.41 (m, 2H)	3.85 (s, 3H)	3.78 (s, 3H)	6.82 (d, J = 9.0 Hz, 2H)		8.07 (m, 2H)	
3e	8.08 (d, J = 8.1 Hz, 2H)	7.40 (m, 2H)	7.40 (m, 2H)	7.40 (m, 2H)	3.84 (s, 3H)	8.03 (d, J = 8.1 Hz, 2H)			7.40 (m, 2H)	
	3f	8.07 (m, 2H)	7.48 (m, 2H)	7.48 (m, 2H)	7.78 (s, 3H)	3.91 (m, 4H)	7.48 (d, J = 7.8 Hz, 1H)	7.86 (m, 1H)	8.07 (s, 1H)	8.72

α-Keto Esters 4a-f. General Procedure.- A mixture of the α,α-di(benzotriazol-1-yl)-α-methoxy ketone (**3a-f**) (2.6 mmol) and Amberlite H^+ ion exchange resin IR-120 HCP (250 mg) in aqueous methanol (15% w/w, 45 mL) was refluxed overnight. The mixture was cooled, and the resin was filtered off. The methanol was removed under reduced pressure, and benzene was added to remove the water by azeotropic distillation, also under reduced pressure. The crude mixture, which consisted of the product and benzotriazole, was easily purified using a short column of silica with chloroform/hexane (95:5) as eluent. The yield, physical properties, and analytical data for the products (**4a-f**) are presented in Table

2, while the corresponding ^{13}C and ^{1}H NMR data are found in Tables 5 and 6.

TABLE 4. ^{13}C NMR Data for α,α-Di(benzotriazol-1-yl)-α-methoxyketones (**3**)

	Benzotriazolyl Carbons						OMe	C=O	α	R Group Carbons					
	C-4	C-5	C-6	C-7	C-3a	C-7a									
3a	120.3	124.8	128.8	112.1	146.4	132.4	55.7	200.5	102.0	27.5	45.2				
3b	120.2	125.0	128.7	112.4	146.5	132.4	56.5	185.6	101.2	128.8	130.5	132.5	134.4		
3c	120.2	124.9	128.8	112.4	146.5	132.7	56.1	188.7	101.4	21.6	125.5	130.0	130.1	132.1	132.6
140.9															
3d	119.9	124.8	128.6	112.4	146.3	132.3	56.4	183.6	101.3	55.4	113.9	124.9	133.1	164.5	
3e	120.2	125.0	128.9	112.2	146.4	132.2	56.3	184.5	100.9	129.0	130.7	131.9	141.2		
3f	120.1	124.9	128.8	112.3	146.4	132.3	56.5	185.4	101.3	125.0	126.9	127.5	128.4	129.4	129.6
130.1															
										132.1	133.2	135.9			

TABLE 5. ^{13}C NMR Data for α-Keto Esters (**4**)

	MeO	CO_2	C=O	R Group Carbons					
4a[a]	52.2	162.4		28.3	38.1	116.5	122.9	129.6	130.6
				138.9	144.8	149.0			
4b	52.4	163.8	185.9	128.6	129.7	132.1	134.7		
4c	52.4	164.7	188.3	125.7	130.9	132.0	132.1	133.5	140.9
4d	52.2	164.1	184.2	55.2	113.9	125.0	132.1	164.8	
4e	52.9	163.4	184.4	129.3	130.9	131.5	141.7		
4f	52.6	164.0	185.8	123.7	127.0	127.7	128.7	129.4	129.5
				129.8	132.0	133.3	136.1		

a) Data for the corresponding 2,4-dinitrophenylhydrazone adduct.

TABLE 6. ^{1}H NMR Data for α-Keto Esters (**4**)

	OCH_3	R Group Hydrogens				
4a[a]	4.02 (s, 3H)	1.36 (s, 9H)	2.18 (s, 1H)	8.06 (d, *J* = 9.3 Hz, 1H)	8.38 (m, 1H)	9.13 (s, 1H)
4b	3.96 (s, 3H)	7.49 (m, 2H)	7.64 (m, 1H)	8.01 (m, 2H)		
4c	3.93 (s, 3H)	2.58 (s, 3H)	7.29 (m, 2H)	7.46 (m, 1H)	7.68 (m, 1H)	
4d	3.92 (s, 3H)	3.82 (s, 3H)	6.91 (d, *J* = 9.0 Hz, 2H)	7.94 (d, *J* = 9.0 Hz, 2H)		
4e	3.99 (s, 3H)	7.50 (d, *J* = 8.6 Hz, 2H)	8.00 (d, *J* = 8.6 Hz, 2H)			
4f	4.01 (s, 3H)	7.55 (m, 2H)	7.85 (m, 3H)	8.00 (d, *J* = 8.5 Hz 1H)	8.51 (s, 1H)	

a) Data for the corresponding 2,4-dinitrophenylhydrazone adduct.

X-Ray Crystallography

Crystal Data for the *cis* Isomer.- $C_{16}H_{14}N_6O_2$, Mr = 322.3, colorless block, 0.82 × 0.52 × 0.47 mm; monoclinic, $P2_1/n$; a = 8.837(1), b = 11.677(2), c = 14.930(1)Å, β = 99.87(1)°, V = 1517.8(3) Å^3; T = -143°, D_c = 1.41 g cm^{-3}; Z = 4, F(000) = 672, $2\theta_{max}$ = 52°; 219 parameters, wR2 = 0.084 for all 2986

data, R1 = 0.036 for 2180 data with $F_o > 4\sigma(F_o)$.

Crystal Data for the *trans* Isomer.- $C_{16}H_{14}N_6O_2$, Mr = 322.3, colorless block, 0.65 × 0.36 × 0.33 mm; monoclinic, $P2_1/n$; a = 6.030(1), b = 7.535(1), c = 16.435(2)Å, β = 100.18(1)°, V = 735.0(2) Å^3; T = -143°, D_c = 1.46 g cm^{-3}; Z = 2, F(000) = 336, $2\theta_{max}$ = 52°; 111 parameters, wR2 = 0.082 for all 1441 data, R1 = 0.032 for 1214 data with $F_o > 4\sigma(F_o)$. Full tables of atom coordinates, thermal parameters, bond lengths, bond angles and structure factors are available from the author P. J. S. and have been deposited with the Cambridge Crystallographic Data Base.

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