triclinic symmetry. Unit cell parameters were determined from 25 computer-centered reflections with 2θ values ranging from 4 to 36° (Mo Kα). Based on the unit cell size there was one molecule per unit cell suggesting space group $P\bar{1}$. Intensity data for the octants were collected on a Nicolet XRD R3 four-circle diffractometer with monochromatized Mo Kα from 4° (2θ) to 60° (2θ) with $2\theta/\theta$ scans. The scan speed varied form 2° (2θ)/min to 6° (2θ)/min depending on the intensity of the reflection. Scan ranges were from 1° < K$\alpha_1(2\theta)$ to 1° > K$\alpha_2(2\theta)$. Backgrounds were measured at the beginning and end of each scan for a total background counting time equivalent to that of the scan time. Two check reflections, ($1\bar{4}\bar{2}$) and ($30\bar{3}$), were collected every 46 reflections. The check reflections were used for scaling and then deleted. The measured reflections were corrected for Lorentz and polarization effects. Reflections with $I < 0.5\sigma(I)$ were reset to $I = 0.25\sigma(I)$. The direct methods part of SHELXTL[19] was used to find four possible phase sets, one of which was correct and indicated the positions of the ring atoms and parts of the isopropyl groups. The rest of the carbon atoms of the isopropyl groups were found on a difference Fourier map. Refinement was done by using the least-squares blocked-matrix-cascading algorithm of SHELXTL.[19] The final model of 91 parameters used in the refinement included hydrogen atoms "riding" on carbon atoms with idealized geometry and with temperature factors fixed at 1.2 (secondary and tertiary H's) of 1.3 (primary H's) times the U_{eq} of the associated carbon atom. Carbon atoms of the isopropyl groups were refined with anisotropic temperature factors. All other C, N, O atoms were refined isotropically. H(1) and H(4), hydrogens at the ring junctures, were allowed to freely refine. Weights for the refinement were taken as $w = 1/[\sigma^2(F) + gF^2]$ with $g = 0.002$ (not refined). For 1653 reflections with $|F_o| > 4\sigma(F_o)$, $R = (\sum |F_o - F_c|/\sum F_o) = 0.080$ after convergence. Final atomic coordinates and temperature factors are given in supplementary material.

Crystal data for **9e**: formula, $C_{20}H_{40}N_4O_2$; M_r 368.57 g/mol. Cell: triclinic, $P\bar{1}$; $a = 5.981$ (1) Å, $b = 9.529$ (1) Å, $c = 10.021$ (2) Å; $\alpha = 97.53$ (1)° $\beta = 101.07$ (1)° $\gamma = 99.66$ (1)°. Density, $d_x = 1.12$ g/cm^3. Crystal size, 0.13 × 0.18 × 0.54 mm^3. Data collection: Mo Kα (monochromated); $\mu = 0.68$ cm^{-1} $F(000) = 203.96$; octants $h\bar{k}\bar{l}$, $hk\bar{l}$, $h\bar{k}l$, hkl; shell 4°(2θ) to 60°(2θ); 3513 data; 2515 unique reflections; 1653 reflections with $F_o > 4\theta(F_o)$. Refinement: over ΔF (blocked cascade); $R = 0.080$; GOF = 1.85.

Registry No. **1b**, 110-70-3; **1c**, 140-28-3; **1d**, 150-61-8; **1e**, 4013-94-9; **1f**, 4062-60-6; **2b**, 61736-90-1; **2c**, 96444-73-4; **3b**, 61736-89-8; **4b**, 96444-72-3; **4c**, 96444-74-5; **4d**, 56018-47-4; **5b**, 7556-57-2; **5c**, 32705-80-9; **5e**, 37791-60-9; **5f**, 96444-75-6; **6f**, 96444-67-6; **8d**, 96444-76-7; **8f**, 96444-68-7; **9b**, 96444-69-8; **9c**, 96444-70-1; **9e**, 96444-71-2; CHOCHO, 107-22-2.

Supplementary Material Available: Table of atom coordinates (2 pages). Ordering information is given on any current masthead page.

(19) SHELXTL, Version 3.0A (Nicolet XRD), July, 1981.

Alkynes from 5-Aminoisoxazoles

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Diazotization of 5-aminoisoxazoles that bear at least one electron-withdrawing group by reaction with sodium nitrite in AcOH–H_2O affords substituted acetylenes. A reaction path is proposed.

The nature of the products formed in the diazotization of 5-aminoisoxazoles is controversial,[1] and such reactions carried out at the same acidity have been reported to give different products.[2] Diazotization in dilute acid or under aprotic conditions leads to either triazene derivatives or 4-isoxazolyl-3,4-dialkylisoxazol-5-ones.[3] Thermal or photochemical reactions of 5-amino-3,4-dimethylisoxazole with an excess of an alkyl nitrite are reported to generate the corresponding isoxazol-5-yl radical.[4]

We wish to report that 5-aminoisoxazoles bearing at least one electron-withdrawing group react with sodium nitrite in AcOH–H_2O solution to give substituted acetylenes (Scheme I).

Good yields are obtained when the electron-withdrawing group is in the 4-position of the isoxazole (Table I). The effect of the group at the 4-position is illustrated by comparison of the yields of ethyl phenylpropiolate from **1b** and **1n**.

Isoxazoles **1h,i**, unsubstituted at the 3-position, gave acetylenes in very low yields (10%), and (arylsulfonyl)-

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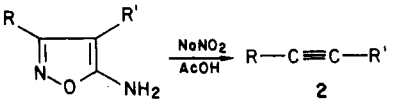
0022-3263/85/1950-2372$01.50/0

Table I. Diazotization Products from 5-Aminoisoxazoles 1

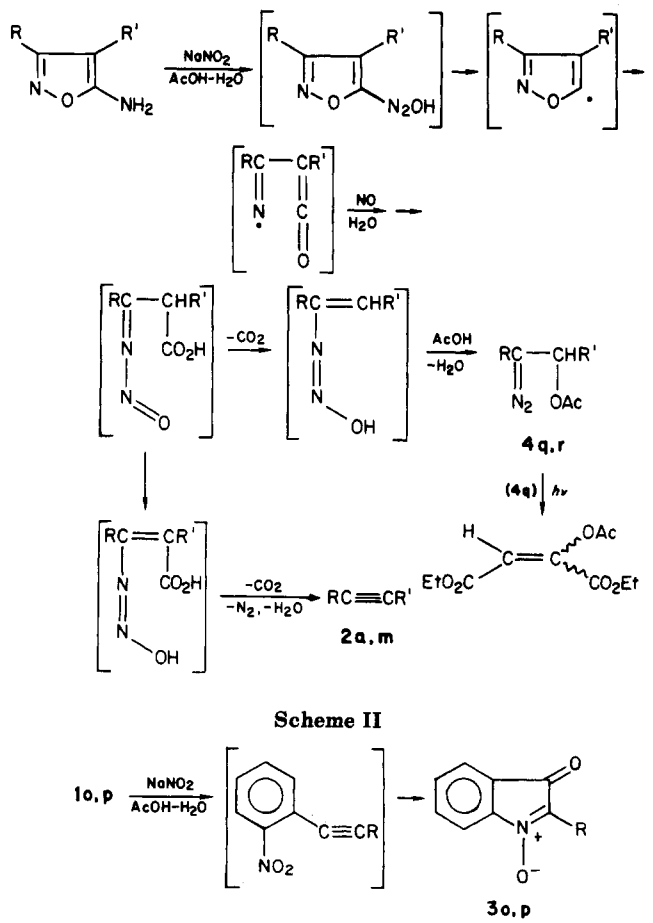


1 2

starting material	R	R′	product (yield %)	eluant	mp, °C (lit. mp, °C)
1a[5]	Ph	$CONH_2$	**2a** (52)		102[a] (99–100[23,24])
1b[5]	Ph	CO_2Et	**2b** (82)	CH_2Cl_2–hexane 1:2	95–100 (8) (149 (15)[24])[b]
1c[6,7]	Ph	CN	**2c** (46)		90–95 (10)[b] (38.5–39[24,25])
1d[7]	Ph	$C_6H_4NO_2$-*p*	**2d** (37)	CH_2Cl_2–hexane 1:4	118–119[a] (119–120[26])
1e[8]	Ph	$PO(OEt)_2$	**2e** (64)		130–135 (0.1) (132 (0.1)[27])[b]
1f[7]	Ph	$SO_2C_6H_5$	**2f** (56)	CH_2Cl_2–hexane 1:1	72–73[a] (72–75[28])
1g[7]	Ph	$SO_2C_6H_4Me$-*p*	**2g** (71)	CH_2Cl_2–hexane 1:1	79–80[a] (80–81[29])
1h[9]	H	$SO_2C_6H_5$	**2h** (10)	CH_2Cl_2–hexane 1:4	110–115 (0.1) (103–105 (0.1)[30])[b]
1i[9]	H	$SO_2C_6H_4Me$-*p*	**2i** (10)	CH_2Cl_2–hexane 1:4	73–74[c] (74–75[30,31])
1k[7]	Ph	4-Pyridyl	**2k** (55)	Et_2O–MeOH 20:1	92–93[d] (104.5–105.5[22])
1l[7]	Ph	Pyrazinyl	**2l** (80)	Et_2O–hexane 1:5	48[a]
1m[7]	CO_2Et	$C_6H_4NO_2$-*p*	**2m** (38)	Et_2O–hexane 1:7	120–121[a] (123–123.8[33])
1n[10]	CO_2Et	Ph	**2b** (34)		
1o[7]	Ph	$C_6H_4NO_2$-*o*	**3o** (41)	CH_2Cl_2–hexane 1:2	183[e] (186[34])
1p[7]	CO_2Et	$C_6H_4NO_2$-*o*	**3p** (45)	CH_2Cl_2–hexane 1:2	105–106[e] (111[35])
1q[11]	CO_2Et	CO_2Et	**4q** (30)	Et_2O–hexane 1:3	100–103 (0.5)[b]
1r[7]	CO_2Et	CN	**4r** (25)	Et_2O–hexane 1:3	97–99 (0.5)[b]
1s[12]	Me	NO_2			
1t[13]	Ph	NO_2			
1u[7]	CO_2Et	$SO_2C_6H_4Me$-*p*			

[a] From Et_2O–hexane. [b] Boiling range. [c] From hexane. [d] From EtOH–H_2O. [e] From CH_2Cl_2–hexane.

Scheme I



Scheme II

Scheme III

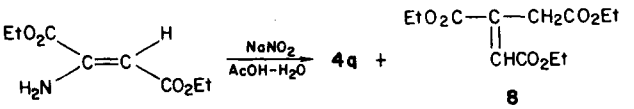
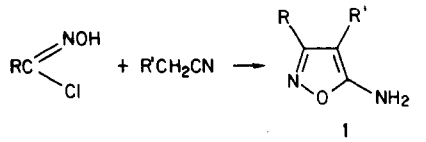


Table II. Synthesis of 5-Aminoisoxazoles



1

product[a]	eluant	mp,°C (solvent)	yield, %
1c		190–191[b] (Et_2O–hexane)	73
1d		165–166 (CH_2Cl_2–Et_2O)	62
1f[20]		120–121 (Et_2O)	46
1g[21]		108 (Et_2O)	45
1k		189–190 (CH_2Cl_2)	41
1l[22]	CH_2Cl_2–pentane 2:1	192–193 (CH_2Cl_2–pentane)	46
1m	CH_2Cl_2–pentane 3:1	179–180 (CH_2Cl_2–pentane)	25
1o	CH_2Cl_2–hexane 1:1	156–157 (CH_2Cl_2–Et_2O)	38
1p		185–186 (CH_2Cl_2)	20
1r	CH_2Cl_2–Et_2O 6:1	173–174 (CH_2Cl_2–Et_2O)	48
1u[21]	CH_2Cl_2	107–108 (Et_2O–pentane)	39

[a] Reference to $R'CH_2CN$. [b] Reference 6 gives mp 193 °C.

acetonitriles were also formed. The *o*-nitrophenyl-substituted isoxazoles **1o,p** underwent ring closure to give the isatogenes **3o,p**, which are probably derived from initially formed (*o*-nitroaryl)acetylenes (Scheme II).

Diazotization of **1q,r** gave the diazo derivatives **4q,r**, identified by analytical and spectroscopic data as well as by chemical behavior and synthesis. Thus, irradiation of **4q** (EtOH, Pyrex, high-pressure Hg lamp) afforded a mixture of diethyl acetoxyfumarate and diethyl acetoxymaleate, identified by comparison with authentic samples (Scheme I).[16]

Compound **4q** was also prepared in low yield by an independent synthesis that yielded a comparable quantity of 8, which was identified by analytical and spectroscopic

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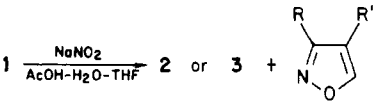
Table III. Diazotization of 5-Aminoisoxazoles in the Presence of THF

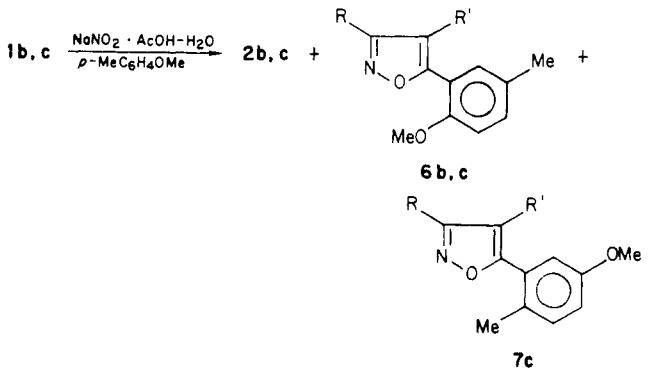


5

				5	
starting material	eluant	2 yield, %	3 yield, %	mp, °C (solvent)	yield, %
1d	Et_2O–hexane 1:7	31	0	120–121 (Et_2O–pentane)	23
1m	CH_2Cl_2–hexane 1:2	7	0	118–119 (Et_2O)	31
1n	CH_2Cl_2–hexane 1:4	12	0	105–107 (0.01)[a]	70
1o	CH_2Cl_2–hexane 1:4	0	12	117–118 (Et_2O)	38
1p	CH_2Cl_2–hexane 1:2	0	9	79–80 (Et_2O)	47

[a] Boiling range.

Scheme IV



data (Scheme III). The double bond stereochemistry was not investigated.

The formation of diazo derivatives **4q,r** evidently depends on the ester function stabilizing the diazotate formed by decarboxylation. However, no analogous diazo derivatives were detected (IR) from diazotizations of **1m,n,p**.

Isoxazoles **1s–u** (Table I) failed to react with sodium nitrite under our conditions.

Some of the isoxazoles used in this study were prepared by reaction of the appropriate hydroxamic acid chloride with a substituted acetonitrile in the presence of a base (Table II). The reaction path shown in Scheme I is proposed for the formation of alkynes from the 5-aminoisoxazoles, based on the following experimental evidence.

A GLC analysis[14] of the gas evolution during the reaction shows the presence of N_2 and CO_2, but no N_2O. Accordingly, the corresponding isoxazol-5-ones are not intermediates in the reaction; indeed with $NaNO_2$ in AcOH–H_2O they are converted into dimeric products.[15] When the diazotization of **1d,m–p** was carried out in the presence of THF, the principal products were 5-unsubstituted isoxazoles **5** accompanied by minor amounts of acetylenes (Table III), whereas **1a,b,f–i** gave only acetylenes under these conditions. These results indicate the presence of an intermediate isoxazol-5-yl radical.

When the diazotization of **1b** was carried out in the presence of 4-methylanisole, a small amount of 5-arylisoxazole **6b** was formed in addition to acetylene **2b**. A similar result was obtained with **1c**, except that two arylation products, **6c** and **7c**, were isolated in the ratio 7:1 (see Experimental Section) (Scheme IV).

The formation of α-diazo esters and α-diazo ketones from substituted isoxazoles and aminoethylenes via nucleophilic addition is under investigation.

Experimental Section

Melting and boiling points are uncorrected. IR spectra were determined with a Perkin-Elmer 377 instrument. NMR spectra were recorded on a Varian EM-390 spectrometer with tetramethylsilane as the internal standard. IR and NMR spectra are given in Table IV.

Column chromatography was performed on Merck Kieselgel 60, 0.063–0.2 mm. Magnesium sulfate was used as the drying agent. Evaporation was carried out under vacuum in a rotary evaporator. Irradiation was carried out with a 125-W HPK Philips high-pressure Hg lamp and a Pyrex filter. Satisfactory combustion analysis (±0.3%) for C, H, and N were obtained.

Preparation of 5-Aminoisoxazoles 1. A solution of the substituted acetonitrile (0.05 mol, commercial source unless otherwise indicated in Table II) in dry THF (80 mL) was added, at room temperature with stirring and under nitrogen, to a solution of EtONa (0.05 mol) in dry EtOH (80 mL). The mixture was cooled to 5 °C and a solution of the appropriate hydroxamic acid chloride[18,19] (0.05 mol) in EtOH (70 mL) was added dropwise at 5–10 °C. After 1 h at room temperature, the mixture was heated to 45 °C for 1 h and then evaporated. The residue was taken up in water (150 mL), extracted with CH_2Cl_2 (3 × 100 mL) and dried, and the solvent evaporated. The crude product was purified by column chromatography on silica gel and/or by crystallization.

Diazotization of 5-Aminoisoxazoles. The 5-aminoisoxazole 1 (4 mmol) was dissolved in a mixture of AcOH (20 mL) and H_2O (7 mL). $NaNO_2$ (40 mmol) was added under stirring at room temperature over a period of 1 h. The mixture was diluted with water (150 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with $NaHCO_3$ solution and with water. Drying and evaporation of the solvent afforded the crude product, which was purified by silica gel column chromatography and/or distillation or crystallization.

Diazotizations in the presence of THF were carried out by the same procedure by using the isoxazole (4 mmol), AcOH (20 mL), H_2O (7 mL), THF (10 mL), and $NaNO_2$ (40 mmol).

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The same procedure was used for diazotization in the presence of 4-methylanisole, replacing the THF with 2 mL of 4-methylanisole. From **1b** (eluant CH_2Cl_2–hexane 1:4): **2b**, 385 mg (55%), and **6b**, 81 mg (6%), mp 84–85 °C (Et_2O–hexane). From **1c** (eluant CH_2Cl_2–hexane 1:4): **2c**, 82 mg (16%), **6c**, 141 mg (12%), mp 105–106 °C (Et_2O–pentane), and **7c**, 20 mg (2%), mp 103–104 °C (Et_2O–pentane).

Irradiation of 4q. Compound **4q** (350 mg, 1.36 mmol) was dissolved in EtOH (80 mL), N_2 was bubbled through the solution for 5 min, and irradiation was carried out for 3 h. Evaporation of the solvent afforded a mixture of diethyl acetoxyfumarate and diethyl acetoxymaleate (285 mg 91%): bp 90–95 °C (0.4 mm); IR 1767, 1725, 1650, 1620 cm^{-1}; NMR δ 6.7 (s, 0.23), 6.17 (s, 0.77), 4.38 (m, 4), 2.38 (s, 0.69), 2.32 (s, 2.31), 1.36 (m, 6). The same mixture with a different E/Z ratio was synthesized following a literature procedure.[16]

Preparation of 4q from Diethyl Aminofumarate. Diethyl aminofumarate[17] (2 g, 10.7 mmol) was dissolved in AcOH (40 mL) and a solution of $NaNO_2$ (7.4 g) in H_2O (15 mL) was added with stirring at room temperature over a period of 1 h. After workup as described for the diazotizations, the products were isolated by silica gel column chromatography (eluant hexane–Et_2O, 8:1): **4q**, 161 mg (6%); **8**, 240 mg (9%), bp 98–100 °C (0.2 mm).

Registry No. **1a**, 15783-70-7; **1b**, 29278-09-9; **1c**, 14246-77-6; **1d**, 96129-31-6; **1e**, 49750-31-4; **1f**, 96129-32-7; **1g**, 96129-33-8; **1h**, 67960-26-3; **1i**, 67960-27-4; **1k**, 96129-34-9; **1l**, 96129-35-0; **1m**, 96129-36-1; **1n**, 53983-15-6; **1o**, 96129-37-2; **1p**, 96129-38-3; **1q**, 15911-21-4; **1r**, 96129-39-4; **1s**, 41230-51-7; **1t**, 19747-21-8; **1u**, 96129-40-7; **2a**, 7223-30-5; **2b**, 2216-94-6; **2c**, 935-02-4; **2d**, 1942-30-9; **2e**, 3450-67-7; **2f**, 5324-64-1; **2g**, 28995-88-2; **2h**, 32501-94-3; **2i**, 13894-21-8; **2k**, 13295-94-8; **2l**, 96129-41-8; **2m**, 35283-08-0; **3o**, 1969-74-0; **3p**, 28048-30-8; **4q**, 96129-42-9; **4r**, 96129-43-0; **5d**, 96129-44-1; **5m**, 96129-45-2; **5n**, 96129-46-3; **5o**, 91477-03-1; **5p**, 96129-47-4; **6b**, 96129-48-5; **6c**, 96129-49-6; **7c**, 96129-50-9; **8**, 5349-99-5; PhC(Cl)=NOH, 698-16-8; $R'CH_2CN$ (R^1 = CN), 109-77-3; $R'CH_2CN$ (R^1 = $C_6H_4NO_2$-*p*), 555-21-5; $R'CH_2CN$ (R^1 = SO_2Ph), 7605-28-9; $R'CH_2CN$ (R^1 = $SO_2C_6H_4Me$-*p*), 5697-44-9; $R'CH_2CN$ (R^1 = 4-pyridyl), 13121-99-8; $R'CH_2CN$ (R^1 = pyrazinyl), 5117-44-2; EtOCOC(Cl)=NOH, 14337-43-0; $R'CH_2CN$ (R^1 = $C_6H_4NO_2$-*o*), 610-66-2; diethyl acetoxyfumarate, 56715-92-5; diethyl acetoxymaleate, 56715-93-6; diethyl aminofumarate, 36016-13-4.

Supplementary Material Available: Table IV containing principal infrared bands and NMR data for **1d,f,g,1e–o,p,r,u**, **2l**, **4q,r**, **5d,m–p**, **6b,c,7c**, and **8** (1 page). Ordering information is given on any current masthead page.

Notes

Facile Synthesis of Acyl-Substituted Lactone Derivatives from Acyclic Keto Esters

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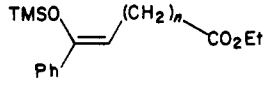
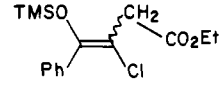
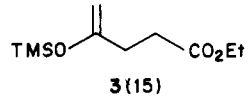
We have recently described the selective formation of trimethylsilyl enol ethers from the corresponding keto esters using trimethylsilyl iodide in the presence of hexamethyldisilazane.[1] In this fashion, the trimethylsilyl enol esters **1** and **2** were generated in high yield. In the case



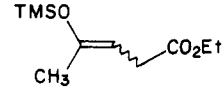
1a *n* = 1
1b *n* = 2



2



3 (15)



4 (85)

of ethyl levulinate, which yields a mixture of both **3** and **4**, the chemoselectivity is maintained, but the reaction is less regioselective. In spite of this, the internal olefin **4** is still the major component of the product mixture.[1]

Since trimethylsilyl enol ethers are extremely useful synthetic reagents,[2] we felt that derivatives such as **1–4** which contain multiple but differentiated chemical functionality offered considerable synthetic potential. In this regard, if the Lewis acid catalyzed condensation of carbonyl derivatives such as aldehydes and ketones[3] could be directed selectively to the silyl enol ether site, the resulting β-hydroxy ketones would be potential lactone precursors due to the presence of the proximate ester functionality.[4] We report here the realization of this goal and describe the production of synthetically useful acyl-substituted γ-butyro- and δ-valerolactone derivatives.[6]

The condensation of **1a** with trioxane in the presence of titanium tetrachloride leads to the formation of the corresponding aldol **6** (R_1 = R_2 = H) in excellent crude yield. The aldol is, however, extremely prone to cyclization and produces the lactone **5** (Table I) in the presence of traces of acid. This cyclization occurs even upon prolonged standing over $MgSO_4$ drying agent. Similarly, the condensation of **1a** with benzaldehyde proceeds as shown above. Although both diasterioisomers **6a** and **6b** are initially generated, most of **6a** undergoes spontaneous intramolecular cyclization under the workup conditions to yield **7a**. The stability of **6b** is much greater, and it is easily isolated from the reaction mixture. Attempts to cyclize **6b** using Lewis acids (BF_3·Et_2O, $TiCl_4$, $SnCl_4$, etc.) resulted primarily in a retroaldol reaction to regenerate methyl β-benzoylpropionate and benzaldehyde. However, the use of protic acid catalysts such as p-toluenesulfonic acid caused rapid cyclization to the lactone **7b**. The structure and configuration of **7b** were indicated by the spectral data and were confirmed by X-ray analysis.[7] The reaction

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(4) The synthesis of β-benzoyl and β-acetyl butyrolactone in low yield by the base-catalyzed condensation of the respective β-keto acids with formaldehyde has been reported.[5]
(5) Rothe, J.; Zimmer, H. *J. Org. Chem.* **1959**, *24*, 586.
(6) (a) Mukiayama, T.; Hanna, T.; Inoue, T.; Sato, T. *Chem. Lett.* **1974**, 381. (b) Mukiayama, T.; Wada, M.; Hanna, T. *Chem. Lett.* **1974**, 1181. (c) Sato, T.; Junichi, H.; Nakamura, H.; Mukiayama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1055.

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