Addition of Grignard Reagents to 1-(*N*-(Alkoxyoxalyl)-*N*-methylamino)-3-methylimidazolium Salts: A General Method for α-Keto Ester Synthesis

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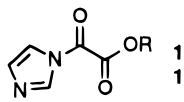
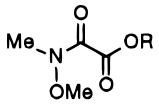
Received July 12, 1996

α-Keto esters are of current interest as precursors of α-keto acids such as pyruvic acid and analogs, oxaloacetic acid, α-ketoglutaric acid, and α-keto acid analogs of protein amino acids, which play essential roles in some biosynthetic and metabolic pathways.[1] In addition, α-keto esters themselves have attracted increasing interest in connection with their activity as potent inhibitors of proteolytic enzymes,[2] inhibitors of leukotriene A4 hydrolase,[3] photopolymerization initiators,[4] and precursors in the asymmetric synthesis of α-hydroxy carboxylic acids.[5]

The more important synthetic methods for these compounds include oxidation of α-hydroxy esters,[6] Friedel−Crafts acylation,[7] hydrolysis and esterification of acyl cyanides,[4] oxidative cleavage of cyano keto phosphoranes,[8] and the reaction of organometallic species with oxalic ester derivatives.[9] Most of these methods suffer from lengthy procedures or lack of generality. While the latter method appears to be one of the simplest and more versatile strategies for the formation of α-keto esters, it suffers from the serious drawbacks associated with the addition of organometallic reagents (typically Grignard or organolithium) to carboxylic acid derivatives, mainly the tendency to overadd to the substrates producing undesirable side reactions.

Although significant progress was made with the introduction of the ethyl and *tert*-butyl α-oxo-1*H*-imidazole-1-acetate (**1**), which on reaction with aryl Grignard reagents[9a] produced the desired α-keto esters in yields up to 54%, these imidazolides failed to give similar yields when alkyl reagents were used, with the corresponding α-keto esters being obtained in such cases in yields lower than 26%. Moreover, it was reported[9b] that the substrate **1a** reacted with lithium phenylacetylide to afford the ethyl 2-oxo-4-phenyl-3-butynoate in only 10% yield, although it was improved (37%) when the lithium reagent was transformed to an organocopper derivative.





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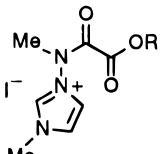
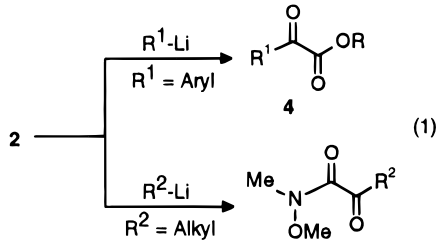


3a: R = Et
3b: R = *t*-Bu

In an attempt to improve the synthesis of 2-oxo-4-phenyl-3-butynoic acid, claimed as a potent irreversible inhibitor of brewers' yeast pyruvate decarboxylase, Jordan and Chiu[9b] introduced the monoethyloxalic acid *N*-methoxy-*N*-methylamide (**2**) as an alternative to substrate **1**. This new oxalic derivative, whose selection was primarily based on the reactivity of *N*-methoxy-*N*-methylamides, can be formally considered as an analog of the "Weinreb amide",[10] whose utility in organic synthesis is well documented.[11] The reaction of **2** with lithium bases derived from phenylacetylene, 4-chlorophenylacetylene, and 1-bromo-2-methoxyphenyl derivatives gave rise to the desired 2-oxo esters **4** in yields between 66 and 78%. However, when the procedure was applied to an aliphatic nucleophile such as *n*-BuLi a 2-oxo amide **5** was obtained in a 52% yield, as the major product (eq 1). With use of 2.0 equiv of base, the 1,2-diketone was isolated as the major component.



(1)

The above considerations encouraged us to search for an efficient new oxalic ester derivative that could selectively provide both aryl and alkyl 2-oxo esters. The 1-(*N*-(ethoxyoxalyl)-*N*-methylamino)-3-methylimidazolium iodide **3a** was initially chosen, on the basis of our previous reports showing the utility of 1-(*N*-acyl-*N*-methylamino)-3-methylimidazolium salts as selective acylating reagents toward organolithium and Grignard reagents.[12]

The salt **3a** was readily accessible by reacting 1-amino-3-methylimidazolium mesitylenesulfonate **6** with ethyl

(1) (a) Cooper, A. J. L.; Ginos, J. Z.; Meister, A. *Chem. Rev.* **1983**, *83*, 321−358. (b) Kovács, L. *Rec. Trav. Chim. Pays-Bas* **1993**, *112*, 471−496.

(2) (a) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Smith, S. A.; Petrillo, E. W., Jr. *J. Med. Chem.* **1993**, *36*, 2431. (b) Ocain, T.; Rich, D. H. *J. Med. Chem.* **1992**, *35*, 451. (c) Iwanowicz, E. J.; Lin, J.; Roberts, D. G.; Michel, I. M.; Seiler, S. M. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1607. (d) Angelastro, M. R.; Mehdi, S.; Burkart, J. P.; Peet, N. P.; Bey, P. *J. Med. Chem.* **1990**, *33*, 11.

(3) (a) Yuan, W.; Wong, C.-H.; Haeggstrom, J. Z.; Wetterholm, A.; Samuelson, B. *J. Am. Chem. Soc.* **1992**, *114*, 6552. (b) Yuan, W.; Muñoz, B.; Wong, C.-H.; Haeggstrom, J. Z.; Wetterholm, A.; Samuelson, B. *J. Med. Chem.* **1993**, *36*, 211.

(4) Photis, J. M. *Tetrahedron Lett.* **1980**, *21*, 3539.

(5) Valentine, D., Jr.; Scott, J. W. *Synthesis* **1978**, 329.

(6) (a) Peet, N. P.; Burkhart, J. P.; Angelastro, M. R.; Giroux, E. L.; Mehdi, S.; Bey, P.; Kolb, M.; Neises, B.; Schirlin, D. *J. Med. Chem.* **1990**, *33*, 394. (b) Burkhart, J. P.; Peet, N. P.; Bey, P. *Tetrahedron Lett.* **1988**, *29*, 3433.

(7) Micetich, R. G. *Org. Prep. Proced. Int.* **1970**, *2*, 249.

(8) Wasserman, H. H.; Ho, W.-B. *J. Org. Chem.* **1994**, *59*, 4364.

(9) (a) Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.* **1981**, *46*, 211. (b) Chiu, C. C.; Jordan, F. *J. Org. Chem.* **1994**, *59*, 5763.

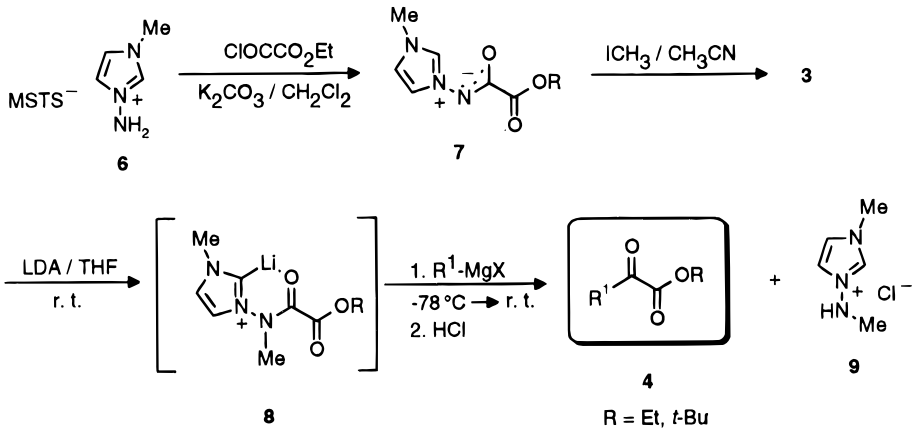
(10) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *56*, 291.

(11) (a) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15. (b) O'Neill, B. T. *Comprehensive Organic Synthesis*; **1991**; Vol. 1, p 397. (c) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446. (d) Sibi, P. M. Marvin, M.; Sharma., R. *J. Org. Chem.* **1995**, *60*, 5016. (e) Sibi, M. P.; Christensen, J. W.; Kim, S.-G.; Eggen, M. J.; Stessman, C.; Oien, L. *Tetrahedron Lett.* **1995**, *36*, 6209. (f) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, J. J. *Tetrahedron Lett.* **1995**, *36*, 5461. (g) Sawamura, M.; Hamashima, H.; Shinoto, H.; Ito, Y. *Tetrahedron Lett.* **1995**, *36*, 64479. (h) Davies, S. G.; McCarthy, T. D. *Synlett.* **1995**, 700. (i) Braslau, R.; Naik, N.; Olmstead, M. M. *J. Org. Chem.* **1996**, *61*, 368.

(12) Heras, M. A.; Molina, A.; Vaquero, J. J.; García-Navio, J. L.; Alvarez-Builla, J. *J. Org. Chem.* **1993**, *58*, 5862.

S0022-3263(96)01329-1 CCC: $12.00

Scheme 1



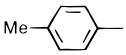
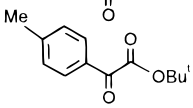
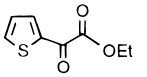
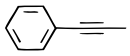
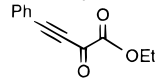
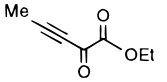
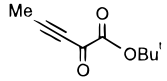
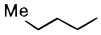
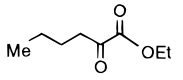
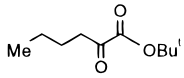
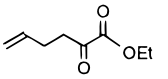
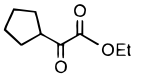
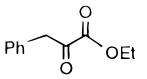
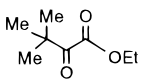
oxalyl chloride to yield the aminide **7a** (63%), which was easily converted into **3a** (97%) by N-methylation with methyl iodide in dry acetonitrile (Scheme 1). After elimination of the solvent the salt was isolated as a slightly hygroscopic yellow oil, stable to storage and able to be used without further purification.

Although both aryl and alkyl α-keto esters can be prepared easily and in high yields (Table 1) by using salt **3a**, several points are noteworthy. The formation of a metalated intermediate **8** plays an essential role in the success of the reaction, since the direct addition of 1.1 equiv of the organometallic reagent gave low conversion, with **3a** being extensively recovered. Alternatively, when **8** was preformed (LDA/THF), the addition of 1.0 equiv of alkyl- or arylorganolithium produced mixtures of the α-keto esters, α-diketones, and α-hydroxy ketones. Only with the addition of 1.0 equiv of aryl Grignard reagents to **8** were the corresponding α-keto esters obtained as the sole reaction products. The procedure was then extended to acetylenic derivatives. Addition of (phenylethynyl)- and propynylmagnesium bromide (Table 1, entries 4 and 5) resulted in the formation of the corresponding α-keto esters in yields up to 70%.[13] Finally, the procedure was tested with alkylmagnesium halides, and it was found to be highly chemoselective, leading to alkyl α-keto esters (Table 1, entries 7 and 9−12) with no signs of 2-oxo amide formation.

To further establish the versatility of the method it was also applied to the salt **3b** with the corresponding *tert*-butyl esters also obtained in good yields (Table 1, entries 2, 6, and 8).

In conclusion, the use of the new oxalic ester derivatives **3**, following the strategy outlined here, provides an easy an efficient method for the preparation of a variety of α-keto esters. Furthermore, the activation of the carbonyl group of the amide moiety via a metalated intermediate and the behavior of the 1-methyl-3-(methylamino)imidazolium moiety as a leaving group suggests considerable generality for the procedure.

Table 1. α-Keto Esters 4 Prepared by Reaction of Grignard Reagents with 3

Entry	R^1-MgX	α-Keto Ester	Yield (%)
1			76
2			72
3			82
4			77
5			72
6			68
7			81
8			66
9			80
10			77
11			68
12			56

Experimental Section

General experimental techniques and analytical measurements were applied as previously described.[14] Chromatography was performed on silica gel 60 (230−400 mesh). All reagents were obtained from commercial sources. THF was distilled from sodium−benzophenone. CH_3CN was dried from calcium hydride. All solutions of organometallic reagents were titrated before use. Reactions involving organometallics were carried out under an argon atmosphere in glassware that had been dried at 100 °C for at least 3 h. LDA was used as a commercial 2 M solution in THF, and Grignard reagents were used as commercial solutions in THF (Table 1, entries 1, 2, 4−8, and 12), Et_2O (Table 1, entry 10) or prepared according to standard

(13) The ethyl 2-oxo-4-phenyl-3-butynoate has recently been prepared by benzotriazole methodology in good yield. Katritzky, A. R.; Lang, H. *J. Org. Chem.* **1995**, *60*, 7612.

(14) Santiesteban, I.; Siro, J.; Vaquero, J. J.; García-Navio, J. L.; Alvarez-Builla, J.; Castaño, O.; Andrés, J. L. *J. Org. Chem.* **1995**, *60*, 5667.

procedures (Table 1, entries 3, 9 and 11). 1-Amino-3-methylimidazolium mesitylenesulfonate **(6)** was prepared as previously described.[12]

1-((Alkoxyoxalyl)amino)-3-methylimidazolium Hydroxide Inner Salts 7. General Procedure. To a mixture of 1-amino-3-methylimidazolium mesitylenesulfonate (3.36 mmol, 1 g) and K_2CO_3 (13.44 mmol, 1.85 g) in methylene chloride (30 mL) was slowly added a solution of the corresponding alkoxyoxalyl chloride (4 mmol) in methylene chloride (15 mL), and the mixture was stirred at room temperature for 18 h. The reaction mixture was then filtered through Celite, and the solid was washed with methylene chloride (50 mL). The filtrate and the washes were combined and concentrated under reduced pressure. The residue was triturated with ethyl acetate. The title compounds were isolated by filtration and recrystallized from ethyl acetate.

7a: white powder, 63%; mp 129−130 °C; IR (KBr) 3158, 3093, 3056, 1719, 1622, 1557, 1505, 1454, 1320, 1216, 1109, 1095 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.63 (s, 1H), 7.50 (s, 1H), 4.09 (q, J = 7.3 Hz, 2H), 3.79 (s, 1H), 1.20 (t, J = 7.3 Hz, 1H) ppm; MS (EI, 70 eV) m/z (rel int) 197 (M^+, 3), 124 (100), 82 (33), 56 (14). Anal. Calcd for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 48.37; H, 5.40; N 21.00.

7b: white powder, 60%; mp 160−161 °C; IR (KBr) 3150, 2980, 1719, 1606, 1564, 1512, 1366, 1327, 1243, 1157, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.888(s, 1H), 7.51 (s, 1H), 6.92 (s, 1H), 3.84 (s, 1H), 1.57 (s, 9H) ppm. Anal. Calcd for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.66. Found: C, 53.08; H, 6.69; N 18.42.

1-(*N*-(Alkoxyoxalyl)-*N*-methylamino)-3-methylimidazolium Iodides 3. General Procedure. To a suspension of the corresponding aminide **7** (1 mmol) in dry CH_3CN (5 mL) was added methyl iodide (4 mmol, 0.44 mL), and the mixture was stirred at reflux for 6 h. The reaction mixture was concentrated under reduced pressure to give the salts as yellow oils.

3a: 97%; IR (neat) 3141, 3085, 1744, 1704, 1585, 1468, 1377, 1253, 1211, 1091 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.75 (d, J = 2.2 Hz, 1H), 7.54 (d, J = 2.2 Hz, 1H), 3.91 (s, 3H), 3.62 (q, J = 6.9 Hz, 2H), 2.94 (s, 3H), 1.17 (t, J = 6.9 Hz, 3H) ppm; Anal. Calcd for $C_9H_{14}N_3O_3$ 212.1031, found 212.1035.

3b: 96%; IR (neat) 3140, 3070, 3070,1739, 1704, 1585, 1468, 1377, 1253, 1211, 1091 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 9.43 (s, 1H), 8.12 (s, 1H), 7.93 (s, 1H), 4.01 (s, 3H), 3.54 (s, 3H), 1.53 (s, 9H) ppm; MS (70 eV, CI) m/z (rel int) 240 (100, M^+), 165 (30), 112 (16), 83 (3). Anal. Calcd for $C_{11}H_{18}IN_3O_3$: C, 35.92; H, 4.94; N, 11.44. Found: C, 36.18; H, 5.02; N, 11.34.

General Method for the Synthesis of α-Keto Esters 4. LDA (0.55 mmol, 0.27 mL, 2 M solution in THF) was added dropwise to a solution of **3** (0.5 mmol, 0.17 g) in 5 mL of dry THF at room temperature, and the mixture was ultrasonically irradiated for 30 min. The corresponding Grignard reagent (0.55 mmol) was then added dropwise to at −78 °C. The reaction mixture was allowed to warm to room temperature and then quenched with hydrochloric acid (5%, 5 mL) and extracted with ethyl ether (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel. Elution with hexane/EtOAc (9:1) gave pure α-keto esters.

Ethyl 2-oxo-2-(2-thienyl)acetate (Table 1, entry 3):[15] pale yellow oil; IR (neat) 2930, 2858, 1764, 1740, 1452, 1309, 1187, 1099, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.23−7.28 (m, 2H), 7.02 (dd, J = 1.2, 4.9 Hz, 1H), 4.36 (q, J = 7.3 Hz, 2H), 1.38 (t, J = 7.3 Hz, 3H) ppm. Anal. Calcd for $C_8H_8O_3S$: C, 52.16; H, 4.38; S, 17.40. Found: C, 51.80; H, 4.15; S, 17.56.

Ethyl 2-oxo-3-pentynoate (Table 1, entry 5): pale yellow oil; IR (neat) 2927, 2856, 2221, 1740, 1683, 1451, 1174, 1019 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.33 (q, J = 7.3 Hz, 2H), 2.13 (s, 3H), 1.36 (t, J = 7.3 Hz, 3H) ppm. Anal. Calcd for $C_7H_8O_3$: C, 60.00; H, 5.75. Found: C, 59.86; H, 5.56.

***tert*-Butyl 2-oxo-3-pentynoate (Table 1, entry 6)**: pale yellow oil; IR (neat) 3074, 2931, 2221, 1732, 1684, 1454, 1372, 1151, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.13 (s, 3H), 1.55 (s, 9H) ppm. Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.13; H, 7.18.

The structure of the following compounds was confirmed by comparison of their spectral and/or analytical data with those of authentic samples or previously reported data.

Ethyl 2-oxo-2-phenylacetate (Table 1, entry 1):[16] IR (neat) 2926, 1730, 1695, 1451, 1247, 1200, 1158, 1023 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.03−8.00 (m, 2H), 7.67−7.63 (m, 1H), 7.54−7.49 (m, 1H), 4.46 (q, J = 6.9 Hz, 2H), 1.43 (t, J = 6.9 Hz, 3H) ppm.

***tert*-Butyl 2-(4-methylphenyl)-2-oxoacetate (Table 1, entry 2)**:[17] IR (neat) 3075, 2929, 1734, 1701, 1439, 1375, 1113, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.87 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 2.44 (s, 3H), 1.54 (s, 9H) ppm.

Ethyl 2-oxo-4-phenyl-3-butynoate (Table 1, entry 4):[9b,13] IR (neat) 2963, 2930, 2174, 1739, 1677, 1446, 1260, 1187, 1153, 1078, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.74−7.71 (m, 2H), 7.54−7.51 (m, 1H), 7.36−7.29 (m, 2H), 4.37 (q, J = 6.9 Hz, 2H), 1.37 (t, J = 6.9 Hz, 3H) ppm.

Ethyl 2-oxohexanoate (Table 1, entry 7):[16] IR (neat) 2962, 2873, 1728, 1462, 1259, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.31 (q, J = 7.3 Hz, 2H), 2.83 (t, J = 7.3 Hz, 2H), 1.67−1.54 (m, 4H), 1.37 (t, J = 7.3 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H) ppm.

***tert*-Butyl 2-oxohexanoate (Table 1, entry 8)**:[18] IR (neat) 2959, 2930, 2861, 1723, 1459, 1359, 1258, 1136, 1086, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.76 (t, J = 7.3 Hz, 2H), 1.46−1.66 (m, 4H), 1.48 (s, 9H), 0.91 (t, J = 7.3 Hz, 3H) ppm.

Ethyl 2-oxo-5-hexenoate (Table 1, entry 9):[19] IR (neat) 2964, 1725, 1445, 1259, 1092, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.75−5.86 (m, 1H), 4.94−5.10 (m, 2H), 4.33 (q, J = 7.2 Hz, 2H), 2.95 (t, J = 6.9 Hz, 2H), 2.36−2.43 (m, 2H), 1.37 (t, J = 7.2 Hz, 3H) ppm.

Ethyl 2-cyclopentyl-2-oxoacetate (Table 1, entry 10):[20] IR (neat) 2959, 2871, 1727, 1450, 1261, 1093, 1023 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.33 (q, J = 7.3 Hz, 2H), 3.49 (m, 1H), 1.87−1.95 (m, 2H), 1.78−1.85 (m, 2H), 1.58−1.67 (m, 4H), 1.37 (t, J = 7.3 Hz, 3H) ppm.

Ethyl 2-oxo-3-phenylpropanoate (Table 1, entry 11):[21] IR (neat) 2985, 2937, 1742, 1451, 1315, 1191, 1012 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36−7.41 (m, 5H), 5.31 (s, 2H), 4.35 (q, J = 6.9 Hz, 2H), 1.37 (t, J = 6.9 Hz, 3H) ppm.

Ethyl 3,3-dimethyl-2-oxobutanoate (Table 1, entry 12):[22] IR (neat) 2961, 2928, 1709, 1400, 1256, 1197, 1087, 1019 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.34 (q, J = 7.3 Hz, 2H), 1.35 (t, J = 7.3 Hz, 3H), 1.11 (s, 9H) ppm.

Acknowledgment. The authors acknowledge support of this work from the the Comisió Interdepartamental de Recerça i Innovació Técnologica (CIRIT, project QFN94-4619) for financial support and the Ministerio de Educación y Ciencia for a studentship (M.A.H.). We also thank to Professor A. R. Katritzky for helpful suggestions.

JO961329Z

(15) Karavanov, N. A. *Uch. Zap. Permisk. Gos. Univ. Im. A. M. Gor'kogo* **1963**, *25*, 123.; *Chem. Abstr.* **1963**, *61*, 3055a.

(16) Wasserman, H. H.; Ives, J. L. *J. Org. Chem.* **1985**, *50*, 3573.
(17) Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.* **1981**, *46*, 211.
(18) Nokami, J.; Sonoda, T.; Wakabayashi, S. *Synth. Commun.* **1983**, 763.
(19) Van Leeuwen, P. W.; Roobek, C. F.; Wife, R. L.; Frijns, J. H. G. *J. Chem. Soc., Chem. Commun.* **1986**, *1*, 30.
(20) Rabjohn, N.; Harbert, C. A. *J. Org. Chem.* **1970**, *10*, 3240.
(21) Poisel, H. *Chem. Ber.* **1978**, *111*, 3136.
(22) Jaeger, D. A.; Broadhurst, M. D.; Cram, D. J. *J. Am. Chem. Soc.* **1975**, 717.