A Convenient Synthesis of Pyridazine-3,4-dicarboxylic Acid by a Hetero Diels-Alder Reaction

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A convenient route to prepare unsubstituted pyridazine-3,4-dicarboxylic acid on a preparative scale is described. The synthesis involves a hetero Diels-Alder reaction between a new 1,2-diaza-1,3-diene and ethyl vinyl ether and oxidation of the intermediate 1,4,5,6-tetrahydropyridazine as the key step.

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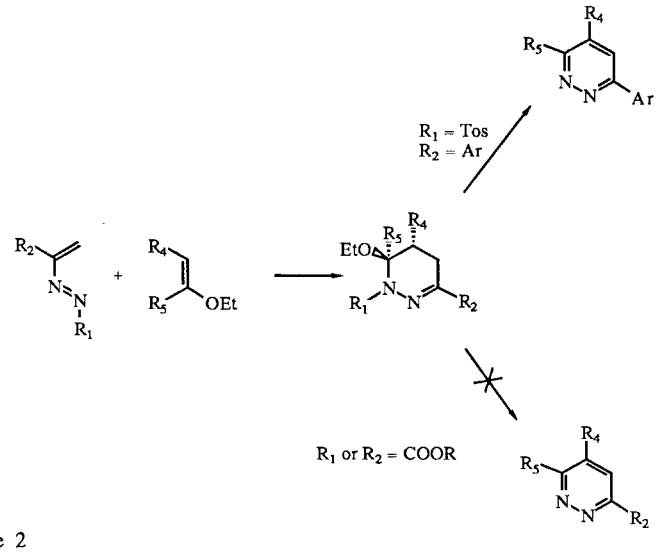
The synthesis of pyridazine-4,5-dicarboxylic acid derivatives *via* oxidation of the easily accessible phthalazines is well documented [1]. The corresponding 3,4-dicarboxylic acid derivatives, however, are considerably more difficult to prepare and thus little described in the literature [2]. Their synthesis involves oxidation of the cinnolines [3], condensation between properly substituted γ-diketones [4] or a γ-ketoester [5] with hydrazine, reaction of an hydrazone with dimethyl acetylenedicarboxylate [6] and rearrangement of 1,2-diazaepin-4-one [7].

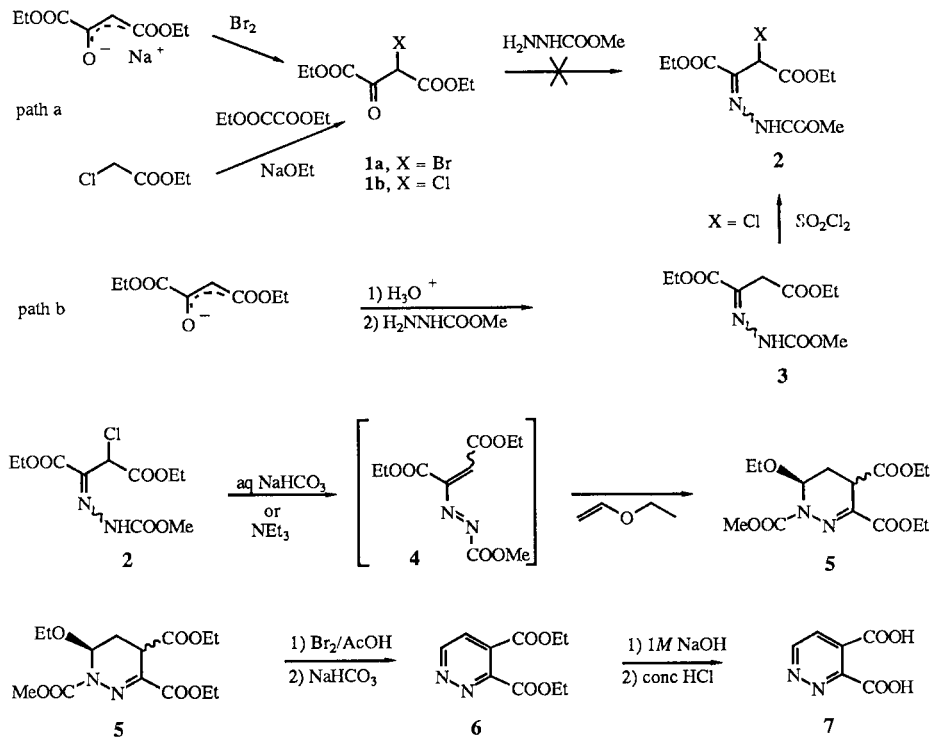
In connection with our synthesis program on biologically active compounds we needed to prepare pyridazine-3,4-dicarboxylic acid. Its diester and diamide had previously been prepared by a tedious route [4b], but the diacid itself was unknown [8].

Among the various syntheses of the pyridazine ring [1], an elegant route involving an inverse electron demand

Scheme 1



Scheme 2



hetero Diels-Alder reaction between 1,2-diazadiene and a dienophile has been described [9]. Only one attempt [9a] has been made to oxidize these 1,4,5,6-tetrahydropyridazines to give pyridazines. Unfortunately, this aromatization reaction is not applicable to the 3-ethoxycarbonyl derivatives nor to an 1-alkoxycarbonyl group [9a] (Scheme 1).

We have found that the aromatization can be conveniently achieved under acidic oxidative conditions when both R_1, R_2 and R_3 are alkoxycarbonyl groups (key step in Scheme 2).

The total synthesis of the pyridazine-3,4-dicarboxylic acid using the same hetero Diels-Alder strategy in summarized in Scheme 2.

The classical synthesis [9b] of the diazadiene precursor **2** (path a) is ineffective in our case; we have never been able to obtain the acylhydrazone from the ketone **1**. However, halogenation of the acylhydrazone **3** gave the expected product **2** (path b) in 76% overall yield.

Following treatment of the hydrazone **2** with base, we were unable to isolate the diazadiene **4**, probably owing to its thermal instability, however, when **2** was generated in 1,2-dichloroethane containing 1.5 equivalents of ethyl vinyl ether, it was readily trapped to give compound **5**. Under our conditions, the reaction is regiospecific but a 70:30 mixture of *cis*/*trans* isomers was obtained with the 6-ethoxy group in a pseudoaxial position [9a]; the presence of *trans* isomer could be due to epimerization of the C_4 ring carbon under the reaction conditions [9b].

Oxidation of the tetrahydropyridazine **5** to pyridazine **6** occurs readily using bromine in acetic acid followed by a basic work-up. We suggest the following mechanism (Scheme 3): bromination α to the double bond well known in the pyridazine series [2] (step a). Elimination of hydrogen bromide (or ethanol) followed by ethanol (or hydrogen bromide) to compound **9** (step b) as it can be deduced from the nmr: when the aromatization was performed in an nmr tube using deuterated acetic acid, we can observe in the 9-11 ppm area, the formation of two sets of two doublets.

The first at 9.33 and 10.40 ppm (J = 4 Hz) corresponds to the heterocyclic protons of the final hydrobromide of **6**. The second at 9.50 ppm and 11.00 ppm (J = 4 Hz) could be due to those of pyridazinium species **9**. This assignment is supported by the fact that the 2nd set of doublets appears faster than the first and disappears in the course of the reaction. Finally (step c), the cleavage of the activated carbamate in **9** which is presumably deacylated with the bromide anion liberated in the medium [10].

The desired pyridazine-3,4-dicarboxylic acid **7** was obtained from its diester **6** by saponification and precipitation in acidic medium. The diacid decomposes on heating at 170° to give, quantitatively, pyridazine-4-carboxylic acid as could be predicted [3a].

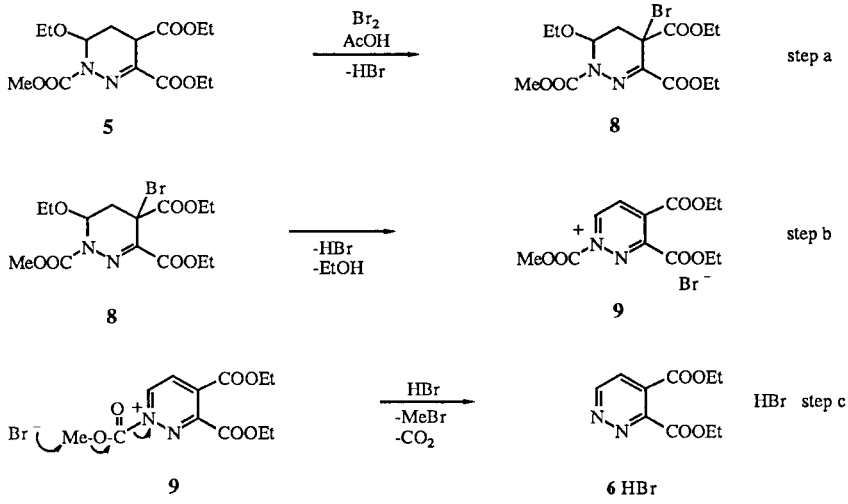
This convenient synthesis has been performed on a molar scale in 52% overall yield and most of the intermediates can be used without purification.

This sequence, therefore, constitutes a facile route to derivatives of unsubstituted pyridazine-3,4-dicarboxylic acid.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus or on a Mettler FP 61 and are uncorrected. The nmr spectra were recorded on a Bruker WP 100 and Bruker AC 250 spectrometers. Chemical shifts are expressed in parts per million to TMS

Scheme 3



(^{1}H nmr or using deuteriochloroform or dimethyl sulfoxide-d_6 as the internal reference (^{13}C nmr). The ir spectra were recorded on a Bruker IFS 45 and the mass spectra were recorded on a VG 70E/11250.

Diethyl 3-Chloro-2-(methoxycarbonylhydrazinylidene)butanedioate (**2**).

Path a.

Compounds **1** (chloro or bromo) were prepared according to literature procedures [11]. When these compounds were treated by methyl hydrazonocarboxylate in a similar manner as described below, no traces of **2** were detected.

Diethyl 2-(Methoxycarbonylhydrazinylidene)butanedioate (**3**).

Path b.

To a suspension of 151 g (5.5 moles) of sodium diethyl oxobutanedioate in 2 ℓ of water and 2 ℓ of ether was added 920 ml of 6.2 *N* hydrochloric acid. After two hours, the organic phase was separated, dried over magnesium sulfate, filtered and concentrated *in vacuo* to give 916.2 g (89%) of diethyl oxobutanedioate [12] which was used without further purification; ir (neat): 1736, 1749 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 11.68 (broad s, 0.8H, OH enolic form), 6.02 (broad s, 0.8H, =CH enolic form), 4.40-4.10 (m, 4H, OCH_2), 3.82 (s, 0.2H, CH_2 ketonic form), 1.5-1.2 (m, 3H, CH_2CH_3); ms: (70 eV, electron impact) m/e 188 (molecular ion), 145 (M-OC_2H_5)$^+$, 115 (M-$COOC_2H_5$)$^+$.

Methyl hydrazinocarboxylate (438.5 g, 4.87 moles) was added in one portion to a solution of the above oil in 7 ℓ of diisopropyl ether. After 20 hours at room temperature, the precipitate was filtered, washed with 3 portions of 1 ℓ of diisopropyl ether, dried *in vacuo* to give 1112.1 g (88%) of **3** as a cream-white solid, mp 76-80°; ir (Nujol): 3200 (NH), 1744, 1725, 1713 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 9.80 (broad s, 1H, NH), 4.32 (q, 2H, OCH_2), 4.16 (q, 1H, OCH_2), 3.86 (s, 3H, OCH_3), 3.78 (s, 2H, CH_2CO), 1.35 (t, 3H, CH_2CH_3), 1.25 (t, 3H, CH_2CH_3); ^{13}C nmr (deuteriochloroform): δ 167.5, 163.5, 154.2 (CO), 136.8 (C=N), 61.5, 59.9 (OCH_2), 53.2 (OCH_3), 32.1 (CH_2-CO), 13.7, 13.6 (CH_2CH_3); ms: (70 eV, electron impact) m/e 260 (molecular ion), 215 (M-OC_2H_5)$^+$, 115 (M-$COOC_2H_5$)$^+$.

Anal. Calcd. for $C_{10}H_{16}N_2O_6$: C, 46.15; H, 6.2; N, 10.76. Found: C, 46.12; H, 6.14; N, 10.75.

To 130 g (0.5 mole) of **3** dissolved in 1 ℓ of 1,2-dichloroethane was added during 15 minutes, 68 g (0.5 mole) of sulfonyl chloride. The temperature rises from 20° to 31° with strong gas evolution. After one hour, the light precipitate was filtered and the resulting solution concentrated *in vacuo* to give 144.2 g (98%) of **1** as a yellow oil which can be used without further purification; ir (Nujol): 3250 (NH), 1697, 1661 broad (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 11.92 (broad s, 1H, NH), 5.32 (s, 1H, CH), 4.34 (q, 2H, OCH_2), 4.28 (q, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 1.34 (t, 3H, CH_2CH_3), 1.30 (t, 3H, CH_2CH_3); ^{13}C nmr (deuteriochloroform): δ 166.0, 160.3, 153.1 (C=O), 132.2 (C=N), 62.8, 62.4 (OCH_2), 58.1 (CH), 53.4 (OCH_3), 14.0, 13.7 (CH_2CH_3); ms: (70 eV, electron impact) m/e 294 (molecular ion), 235 (M-$COOCH_3$)$^+$, 221 (M-$COOC_2H_5$)$^+$.

Anal. Calcd. for $C_{10}H_{15}ClN_2O_6$: C, 40.76; H, 5.13; Cl, 12.03; N, 9.51. Found: C, 40.65; H, 5.01; N, 9.45; Cl, 12.30.

6-Ethoxy-3,4-diethoxycarbonyl-1-methoxycarbonyl-1,4,5,6-tetrahydropyridazine (**5**).

To 135 g (0.458 mole) of **2** in 1 ℓ of 1,2-dichloroethane and 49.6 g (0.688 mole) of ethyl vinyl ether was added at 15° during 18 minutes, 63.4 ml (0.458 mole) of triethylamine. The temperature rose to 29°. After 19 hours the brown precipitate formed was filtered off and washed with 2 portions of 100 ml of 1,2-dichloroethane. A sample of 160 ml of the filtrate, after concentration *in vacuo*, gave 19.09 g of a brown oil, which was chromatographed on silica gel (dichloromethane/acetone 98/2) to give 15.8 g (82%) of **5** as a yellow viscous oil, *cis*:*trans*, 70.30; ir (neat): 1730, 1715 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 5.76 (dd, 0.3H, H-6 eq *trans*, J = 2.5 Hz, H-6-H-5 eq, J = 2.5 Hz, H-6-H-5 ax), 5.73 (dd, 0.7H, H-6 eq *cis*, J = 2.5 Hz, H-6-H-5 eq, J = 2 Hz, H-6-H-5 ax), 4.37 (m, 1.4H, $COOCH_2$ *cis*), 4.34 (m, 0.6H, $COOCH_2$ *trans*), 4.19 (q, 0.6H, $COOCH_2$ *trans*, J = 7 Hz), 4.09 (m, 1.4H, $COOCH_2$ *cis*), 3.93 (s, 0.9H, $COOCH_3$), 3.92 (s, 2.1H, $COOCH_3$), 3.79 (dd, 0.7H, H-4 eq *cis*, J = 7.6 Hz, H-4-H-5- ax, J = 1 Hz, H-4-H-5 eq), 3.72 (dd, 0.3H, H-4 ax *trans*, J = 13 Hz, H-4-H-5 ax, J = 7 Hz, H-4-H-5 eq), 3.61 (m, 0.6H, OCH_2 *trans*), 3.55 (q, 1.4H, OCH_2 *cis*, J = 7 Hz), 2.84 (ddd, 0.7H, H-5 eq *cis*, J = 13.7 Hz, H-5 eq -H-5 ax, J = 2.5 Hz, H-5 eq -H-6 eq, J = 1 Hz, H-5 eq -H-4 eq), 2.46 (ddd, 0.3H, H-5 eq *trans*, J = 13 Hz, H-5 eq -H-5 ax, J = 7 Hz, H-5 eq -H-4 ax, J = 2.5 Hz, H-5 eq -H-6 eq), 1.88 (ddd, 0.3H, H-5 ax *trans*, J = 13 Hz, H-5 ax -H-5 eq, J = 13 Hz, H-5 ax -H-4 ax, J = 2.5 Hz, H-5 ax -H-6 eq), 1.79 (ddd, 0.7H, H-5 ax *cis*, J = 13.7 Hz, H-5 ax -H-5 eq, J = 7.6 Hz, H-5 ax -H-4 eq, J = 2 Hz, H-5 ax -H-6 eq), 1.38 (t, 2.1H, $COOCH_2CH_3$ *cis*, J = 7 Hz), 1.36 (t, 0.9H, $COOCH_2CH_3$ *trans*, J = 7 Hz), 1.25 (t, 0.9H, $COOCH_2CH_3$ *trans*, J = 7 Hz), 1.20 (t, 2.1H, $COOCH_2CH_3$ *cis*, J = 7 Hz), 1.13 (t, 0.9H, OCH_2CH_3 *trans*, J = 7 Hz), 1.06 (t, 2.1H, OCH_2CH_3 *cis*, J = 7 Hz); ms: (70 eV, electron impact) m/e 330 (molecular ion), 285 (M-OC_2H_5)$^+$, 257 (M-$COOC_2H_5$)$^+$.

Anal. Calcd. for $C_{14}H_{22}N_2O_7$: C, 49.36; H, 6.37; N, 8.86. Found: C, 49.36; H, 6.38; N, 8.88.

The rest of the filtrate (1100 ml) was used without purification in the next step.

Diethyl Pyridazine-3,4-dicarboxylate (**6**).

To the preceeding solution (0.4 mole) in 500 ml of acetic acid was added during 4 minutes 68.5 g (0.428 mole) of bromine. The temperature rose from 23° to 31°, the colour changed from red to brown and there was evolution of gas. After 23 hours, the reaction mixture was concentrated *in vacuo* to give 153.6 g (>100%) of a brown oil which was washed by two portions of 250 ml of diisopropyl ether to give 125.7 g (100%) of **6** hydrobromide hemihydrate as a brown oil; ir (Nujol): 2325 (H-Br, broad), 1747 (C=O), 1600 and 1580 (ν ring) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 10.68 (d, 1H, H-6, J = 5 Hz), 9.12 (d, 1H, H-5, J = 5 Hz), 4.46 (q, 4H, CH_2, J = 7.5 Hz), 1.38 (t, 6H, CH_3, J = 7.5 Hz); ^{13}C nmr (deuteriochloroform): δ 160.8, 160.7 (C=O), 153.2 (C-6), 150.4 (C-3), 136.9 (C-5), 136.1 (C-4), 64.6, 64.3 (CH_2), 46.4 (CH_3); ms: (70 eV, electron impact) m/e 224 (base peak), 180 (M-CO_2)$^{+\cdot}$, 151 (M-$COOC_2H_5$)$^{+\cdot}$.

Anal. Calcd. for $C_{10}H_{12}N_2O_4 \cdot HBr \cdot \frac{1}{2}H_2O$: C, 38.28; H, 4.49; N, 8.92; Br, 25.44. Found: C, 38.55; H, 4.42; N, 8.91; Br, 25.75.

This oil was diluted with 250 ml of dichloromethane and the resulting solution was treated with 59 g of sodium hydrogen carbonate in 250 ml of water. After separation, the aqueous phase was extracted with 100 ml of dichloromethane. The combined organic extracts were dried over magnesium sulfate and filtered to give 89.6 g (100%) of **6** as a brown-black oil which was used

without further purification; 71.6 g of the oil obtained was distilled to give 29.8 g (33%) of **6** as a yellow oil, bp 165-166° at 0.2-0.4 mm, (lit 117-119° at 0.05 mm [4b]), whose ir and ^{1}H nmr spectra are in accordance with those previously reported [4b]; ^{13}C nmr (deuteriochloroform): δ 163.2, 163.1 (C=O), 152.3 (C-6), 151.7 (C-3), 128.3 (C-4), 125.6 (C-5), 62.6 (CH_2), 13.5 (CH_3); ms: (70 eV, electron impact) m/e 224 (molecular ion), 151 $(M-COOC_2H_5)^+$.

Pyridazine-3,4-dicarboxylic Acid (**7**).

To 14.7 g (65 mmoles) of **6** was added, in one portion, 144 ml of 1*N* sodium hydroxide. The temperature rose from 23° to 33°. After 15 minutes, 60 ml of concentrated hydrochloric acid was added to the resulting solution. After cooling for 1 hour at 3°, the precipitate was filtered off and dried, to give 7.4 g (68%) of **7** as a pale yellow solid. An analytical sample was obtained by passing the disodium salt through a short column filled with Dowex 50 W8 (H^+ form), mp 170° dec; ir (Nujol): 3100, 2500-1900 (OH), 1740 (C=O), 1590 and 1560 (ν ring) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 14 (broad s, 2H, COOH) 9.51 (d, H-6, J = 5 Hz), 8.06 (d, H-5, J = 5 Hz); ^{13}C nmr (DMSO-d_6): δ 166.1, 165.1 (COOH), 153.0 (C-6), 152.7 (C-3), 128.7 (C-4), 126.4 (C-5); ms: (70 eV, electron impact) m/e 124 ($(M-CO_2)^{+\cdot}$, base peak), 44 $CO_2^{+\cdot}$.

Anal. Calcd. for $C_6H_4N_2O_4$: C, 42.87; H, 2.40; N, 16.66; O, 38.07. Found: C, 42.62; H, 2.44; N, 16.49; O, 37.94.

Pyridazine-4-carboxylic Acid (**5**).

The diacid **7** (15 g, 0.15 mole) in 150 ml of 1-methyl-2-pyrrolidinone was heated at 170° until the evolution of gas ceased. After cooling and evaporation of the solvent *in vacuo*, the resulting solid was washed thoroughly with diethyl ether to give 18.6 g (100%) of a brown solid, mp 235-237° dec, (lit 230-240° dec [13]), identical with an authentic sample prepared from the permanganate oxidation of 4-methylpyridazine [14,1].

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REFERENCES AND NOTES

[1] J. W. Mason, "Heterocyclic Compounds", Vol **28**, R. N. Castle, ed, John Wiley and Sons, Inc., New York, NY, 1973, p 407.

[2] M. Tišler and B. Stanovnik, "Advances in Heterocyclic Chemistry", Vol **24**, A. R. Katritzky and A. J. Boulton, eds, Academic Press, New York, 1979, p 363.

[3a] M. Hieda, K. Omura and S. Yurugi, *Yakugaku Zasshi*, **92**, 1327 (1972); [b] C. M. Atkinson and R. E. Rodway, *J. Chem. Soc.*, 1 (1959); [c] R. Stoermer and O. Gaus, *Ber.*, **45**, 3104 (1912); [d] R. Stoermer and H. Fincke, *Ber.*, **42**, 3115 (1909).

[4a] A. Turck, G. Queguiner and P. Pastour, *J. Heterocyclic Chem.*, **10**, 1081 (1973); [b] G. M. Singerman and R. N. Castle, *J. Heterocyclic Chem.*, **4**, 393 (1967); [c] R. G. Jones, *J. Org. Chem.*, **25**, 956 (1960).

[5a] F. H. McMillan and J. A. King, *J. Am. Chem. Soc.*, **77**, 3376 (1955); [b] H. Gault, G. Kalopissis, N. Rist and F. Grumbach, *Bull. Soc. Chim. France*, **21**, 916 (1954).

[6] R. K. Gupta and M. V. George, *Indian J. Chem.*, **10**, 875 (1972).

[7] R. K. Bly, E. C. Zoll and J. A. Moore, *J. Org. Chem.*, **29**, 2128 (1964).

[8] The diacid has been cited once, without description by F. De Sio, S, Chimichi and R. Nesi, *Heterocycles*, **19**, 1427 (1982).

[9a] S. J. Clarke and T. L. Gilchrist, *J. Chem. Res.* (S), 310 (1985); *J. Chem. Res.* (M), 3371 (1985); [b] S. J. Clarke, D. E. Davies and T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. I*, 1803 (1983); [c] T. L. Gilchrist and P. Richards, *Synthesis*, 153 (1983); [d] R. Faragher and T. L. Gilchrist, *J. Chem. Soc., Perkin Trans I*, 249 (1979); [e] S. Sommer, *Tetrahedron Letters*, 117 (1977); [f] S. Sommer, *Chem. Letters*, 583 (1977); [g] S. Sommer, *Angew Chem., Int. Ed. Engl.*, **16**, 58 (1977); [h] R. Faragher and T. L. Gilchrist, *J. Chem. Soc., Chem. Commun.*, 581 (1976).

[10] M. C. Wani, H. F. Campbell, G. A. Brine, J. A. Kepler and M. E. Wall, *J. Am. Chem. Soc.*, **94**, 3631 (1972).

[11a] L. H. Conover and D. S. Tarbell, *J. Am. Chem. Soc.*, **72**, 5221 (1950) using carbon tetrachloride instead of chloroform; [b] G. W. Holton, G. Parker and A. Robertson, *J. Chem. Soc.*, 2049 (1949).

[12] J. C. Lewis and R. M. Seifert, *Org. Prep. Proced. Int.*, **3**, 243 (1971).

[13] W. J. Leanza, H. J. Becker and E. F. Rogers, *J. Am. Chem. Soc.*, **75**, 4086 (1953).

[14] R. H. Mizzoni and P. E. Spoerri, *J. Am. Chem. Soc.*, **76**, 2201 (1954).