39. Substitution of HMPT by the Cyclic Urea DMPU as a Cosolvent for Highly Reactive Nucleophiles and Bases

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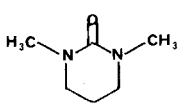
Summary

The cyclic urea DMPU (*N, N'*-dimethyl-*N, N'*-propylene urea = 1,3-dimethyl-2-oxo-hexahydropyrimidine) is shown to exhibit the same effects as HMPT in oxirane-opening with Li-acetylide, in a *Wittig* olefination, in the double deprotonation of a nitroalkane, in the *Michael* addition of Li-dithiane to cyclohexenone, and in selective generations of certain enolates *(Schemes 1–7)*. DMPU might therefore be a safe substitute of the carcinogenic HMPT as a cosolvent with unique properties in diverse types of reactions.

Hexamethylphosphoric triamide (HMPT) is extensively used in research laboratories due to its unique properties as a dipolar aprotic solvent [1] and its superior ability to form cation-ligand complexes [2]. However, in recent years HMPT has been shown to be a carcinogen in animal tests even at low concentrations [3] and 'it was concluded that HMPA ranks in the super league of experimental carcinogens and must be considered as potentially posing a serious risk to man, even at the scale of use in a laboratory' [4]. The need for a safe substitute is thus indispensable. Tetrasubstituted ureas[1])[2]) appeared to us especially attractive since their properties are similar to those of HMPT. We were particularly interested in a cosolvent which *a*) would be compatible with highly nucleophilic and basic reagents[3]), and *b*) could be employed at dry-ice temperature or below. We report



DMPU

[1]) For a review on tetramethylurea, see [5]; for a more recent survey of tetrasubstituted ureas as solvents see [6].

[2]) A few other solvents, cosolvents, and/or complexing agents have also been studied; for example tetraalkylsulfamides [7] and *N, N, N', N'*-tetramethylethylenediamine (TMEDA) [8].

[3]) Other solvents such as dimethyl sulfoxide (acidic) or 1-methyl-2-pyrrolidinone (both acidic and electrophilic) were thus not suitable.

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here about our experiences with the use of *N,N'*-dimethyl-*N,N'*-propylene urea (DMPU)[4][5][6] instead of HMPT in diverse types of reactions.

DMPU is hygroscopic [9] and miscible with water at any ratio. It can be removed from its solution in hydrocarbons or ethers by washing with water. Solvents such as chloroform and methylene chloride, however, retain DMPU in the organic phase; in fact, DMPU can be recovered from water by extraction with these chlorinated hydrocarbons[7]. The boiling points and polarities of DMPU (54°/0.05 Torr, $\varepsilon = 36$, $\mu = 15 \cdot 10^{30}$ Cm) and HMPT (58°/0.08 Torr, $\varepsilon = 30$, $\mu = 18 \cdot 10^{30}$ Cm) are strikingly similar, and both can be dried by distillation from calcium hydride. For DMPU itself, a melting point of *ca.* −20° (m.p. of HMPT: 7°) has been reported [6]; we find that a (1:2)-mixture with THF is clear and homogeneous down to −90°, and during reactions, we have not experienced solvent precipitations at temperatures of −78° or above.

For a carbonyl compound, DMPU is remarkably unreactive: although a vigorous, exothermic reaction takes place[8]), when a hexane solution of butyllithium is added to a (THF/DMPU)-mixture at −78°, only a slow reaction was noticed at −90°. If a more reactive substrate is present in the solution, the DMPU cosolvent does not interfere: thus, at about −35° or below, butyllithium deprotonates diisopropylamine quantitatively in a (2:1) (THF/DMPU)-mixture, and the LDA formed is stable in this medium at temperatures between −78° and −35° for at least two to three hours. Of course, DMPU can also be added to a THF solution of a reagent generated under conventional metallation conditions, just prior to the reaction with an electrophile.

The results of our comparisons of the effects exerted by HMPT and by DMPU are evident from *Schemes 1–7* (for details see the *Experimental Part*). We chose reactions which do not take place or take a different course in the absence of the dipolar aprotic cosolvent. Also, we restrict the discussion to processes which involve the generation of highly reactive C-nucleophiles[9]).

The most simple nucleophile which we studied was the lithium 1-hexyn-1-ide shown in *Scheme 1;* its very inefficient reaction with methyloxirane to give the alcohol **1** could be improved by using 50% DMPU as a cosolvent, albeit not quite as much as with only 17% of HMPT [8]. In the *Wittig* olefination [13] in *Scheme 2*

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[4]) Systematic IUPAC-name of DMPU: 1,3-Dimethyl-2-oxo-hexahydropyrimidine.

[5]) Pharmacological properties of DMPU have been reported [9]; however, we are not aware of carcinogenicity tests.

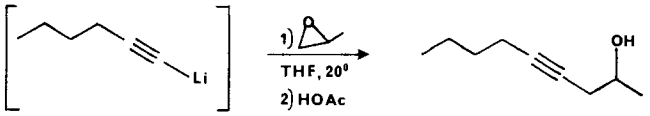
[6]) *N,N'*-Dimethyl-*N,N'*-ethylene urea (DMEU) [systematic IUPAC-name: 1,3-dimethyl-2-imidazolidinone], the corresponding five-membered analogue, has been used successfully in organometallic reactions [10]. However, its low solubility prevents its use at low temperatures: below −30° DMEU crystallizes from a (1:2)-mixture with tetrahydrofuran (THF).

[7]) 80–90% recovery of DMPU after three extractions with CH_2Cl_2 or $CHCl_3$ from a 15% aq. solution.

[8]) Subsequent addition of benzaldehyde and aq. workup did not lead to the isolation of 1-phenyl-1-pentanol, but only to aldehyde recovery.

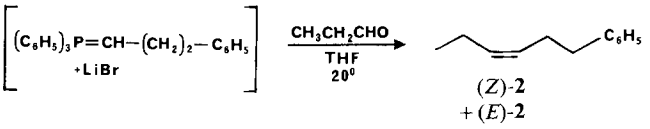
[9]) In other reactions the HMPT effects may also be reproduced by employing DMPU. For example, the *esterification* of 2,4,6-trimethylbenzoic acid with $NaOH/CH_3I$ in neat DMPU proceeded just as reported for HMPT [11]. However, our attempts to prepare a solution of CrO_3 in DMPU for oxidizing alcohols always met with explosive decomposition and a short-lived fire – an event reported for HMPT only if CrO_3 was previously crushed [12].

Scheme 1



Cosolvent (% vol.)	Yield (%)
–	5
HMPT (17)	70
DMPU (29)	26
(50)	59

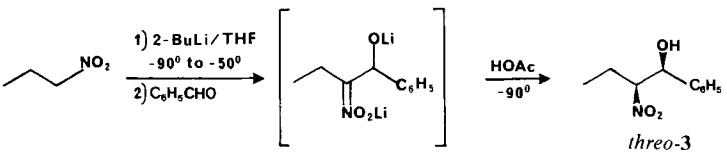
Scheme 2



(*Z*)-**2**
+ (*E*)-**2**

Cosolvent (% vol.)	Yield (%)	(*Z*)-**2**/(*E*)-**2**
–	46	83:17
HMPT (35)	44	92:8
DMPU (35)	39	93:7

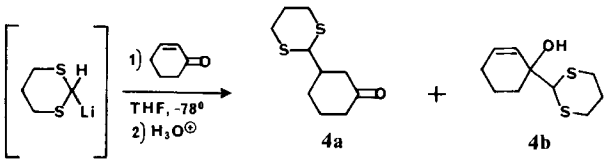
Scheme 3



threo-**3**
+ *erythro*-**3**

Cosolvent (% vol.)	Yield (%)	*threo*-**3**/*erythro*-**3**
–	60	1:1
HMPT (17)	78	9:1 [15]
DMPU (25)	65	9:1

Scheme 4



4a **4b**

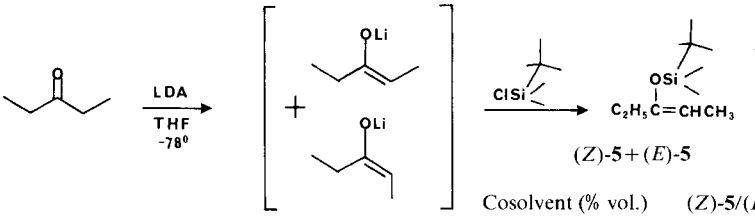
Additive (equiv.)	Yield (%) (**4a** + **4b**)	**4a**/**4b**
–	90	2:98
2 HMPT	50–80	95:5 [16]
2 DMPU	70	82:18
4 DMPU	70	92:8

the (*Z*)-content of the product **2** can be significantly increased by admixture of this dipolar cosolvent.

The two reactions outlined in *Schemes 3* and *4* involve the d^1-reagents [14] α-lithio lithiumnitronate and lithiodithiane, respectively. While DMPU brings about only a slight improvement in the chemical yield of the nitroaldol **3**, it renders the protonation of the originally formed alkoxide-nitronate as *threo*-selective as does HMPT [15]. The suppression of the 1,2-(→**4b**) in favor of the 1,4-addition of the lithiodithiane (→**4a**) to cyclohexenone occurs almost as effectively with DMPU as with HMPT [16] (see *Scheme 4*).

Finally, we have also looked at three different effects of an aprotic dipolar cosolvent in the field of lithium enolate chemistry. The results are shown in *Schemes 5*, *6* and *7*. The (*Z*)-selectivity [17] of enolate generation as judged from

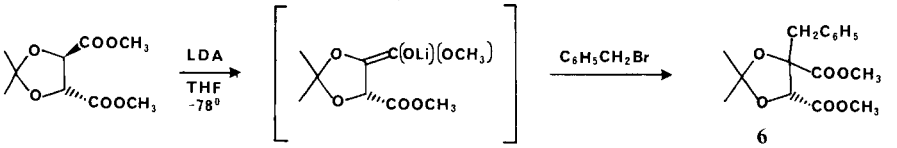
Scheme 5



(*Z*)-**5**+(*E*)-**5**

Cosolvent (% vol.)	(*Z*)-**5**/(*E*)-**5**
–	30:70
HMPT (23)	95:5 [17a]
DMPU (19)	94:6

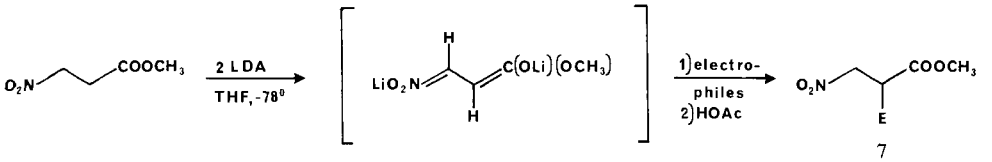
Scheme 6



6

Cosolvent (% vol.)	Yield of **6** (%)
–	< 5 [18]
HMPT (17)	54 [18]
DMPU (33)	52

Scheme 7



7

(Electrophiles: aldehydes, 1-iodoalkane)

Cosolvent (% vol.)	Yield of **7** (%)
–	< 5 [19]
HMPT (17)	50–85 [19]
DMPU (33)	50–80 [19]

the ^{1}H-NMR. and GC. analysis of the trapping products **5** obtained with *t*-butyldimethylsilyl chloride is fully reproduced by replacing HMPT by DMPU. The quite tricky generation of dimethyl tartrate acetonide enolate [18] and subsequent benzylation to **6** is equally possible in the two cosolvents DMPU and HMPT, and the same is true of the double deprotonation of methyl *β-aci*-nitro-ester intermediate (→ **7**), a process which has been described in full detail elsewhere [19].

It appears that DMPU can replace HMPT as a cosolvent in many synthetically useful reactions occurring under strongly basic and nucleophilic conditions. Generally, a somewhat larger amount of DMPU is necessary. It is to be hoped that no dangerous physiological properties of the cyclic urea will be discovered in future tests.

We thank the *Fluka AG* (Buchs) for supplying us with DMPU solvent. *T. M.* thanks the *Sandoz AG* (Basel) for a postdoctoral fellowship.

Experimental Part

All the reagents and solvents were purified by the usual methods. DMEU and DMPU were purified by distillation from calcium hydride under reduced pressure and stored in serum capped bottles under Ar over molecular sieves 4A. All reactions involving organolithium compounds were carried out under anhydrous conditions in Ar atmosphere. Spectra were recorded using the following instruments: IR.: *Perkin-Elmer*-Spectrophotometer 297; ^{1}H-NMR.: *Varian*-EM-390 (90 MHz) and *Bruker*-WM-300 (300 MHz); ^{13}C-NMR.: *Varian*-CFT-20 (20 MHz). IR. data are presented in cm^{-1}. NMR. data are reported in parts per million relative to internal tetramethylsilane standard (0 ppm). The following abbreviations are used to indicate the pattern of the signals: *s* = singlet, *d* = doublet, *t* = triplet, *st* = sextuplet, *m* = multiplet, and a prefix br. to indicate broadness. Gas chromatograms were obtained using *Fractovap* 2457 and 2150 *(Carlo Erba)*. Bulb-to-bulb distillations were carried out using *Büchi*-GKR-50 and reported boiling points are air bath temperatures.

Preparation of 4-nonyne-2-ol (**1**). A solution of 1-hexyne (1.15 ml, 10 mmol) in THF (25 ml) was cooled by ice-salt bath and a hexane solution of butyllithium (6.4 ml, 10 mmol) was added dropwise, maintaining internal temperature below 5°. The ice-salt bath was replaced by ice bath and the reaction mixture was stirred for 2 h. The reaction mixture was cooled to −76°, the cosolvent (DMPU or HMPT – variable amount as indicated in *Scheme 1*) was added and then the reaction mixture was stirred for 10 min. Methyloxirane (0.72 ml, 10.3 mmol) was added and the reaction mixture was allowed to warm up to RT. over 6 h and then stirred at RT. for 12 h. After adding 30 ml 10% acetic acid the organic layer was separated and the aq. layer was extracted with ether (3 × 50 ml). The combined organic phases were washed with water (2 × 50 ml), sat. $NaHCO_3$-solution (1 × 25 ml) followed by water (1 × 50 ml), dried ($MgSO_4$) and the solvent flash evaporated. The pure product was obtained upon distillation, b.p. 110°/9 Torr, in the yields indicated in *Scheme 1*. – IR. (Film): 3350, 2960, 2920, 2860, 1450, 1430, 1370, 1350, 1320, 1210, 1115, 1080, 940, 885, 830. – ^{1}H-NMR. ($CDCl_3$): 0.7–1.07 (br. *t*, 3 H, 3 H–C(9)); 1.23 (*d*, *J* = 6, 3 H, 3 H–C(1)); 1.2–1.7 (*m*, 4 H, 2 H–C(7) and 2 H–C(8)); 2.0–2.4 (*m*, 5 H, 2 H–C(3), 2 H–C(6) and OH); 3.9 (*sext*, *J* = 6, 1 H, H–C(2)).

Preparation of 1-phenyl-3-hexene (**2**). a) *With cosolvent.* A stirred suspension of (3-phenylpropyl)-triphenylphosphonium bromide [20] (2.3 g, 5 mmol) in THF (15 ml) was cooled in an ice-salt bath and a hexane solution of butyllithium (3.2 ml, 5.06 mmol) was added dropwise maintaining the internal temperature below 0°. The cooling bath was removed and the reaction mixture was stirred at RT. for 1.5 h. The cosolvent (8 ml of DMPU or HMPT) was added and the reaction mixture was stirred for an additional period of 30 min. Propanal (0.38 ml, 5.3 mmol) was added to the orange ylid solution and the reaction mixture was stirred for 15 min. Water (40 ml) was added, the organic phase was separated and the aq. phase was extracted with ether (3 × 50 ml). The combined organic

phases were washed with water (3 × 50 ml), dried ($MgSO_4$), and the solvent flash evaporated. The crude product was filtered through a column of silica gel using hexane/benzene 1:1 to obtain a colourless liquid (for yield see *Scheme 2*). – IR. (Film): 3085, 3060, 3030, 3005, 2960, 2930, 2875, 2855, 1600, 1495, 1455, 1400, 1360, 1330, 1300, 1260, 1075, 1030, 965, 900, 870, 800, 770, 750, 720, 700. – ^{1}H-NMR. ($CDCl_3$): 0.89 (*t*, *J* = 7.5, 3 H, CH_3); 1.7–2.8 (3 *m*, 6 H, 3 CH_2); 5.17–5.6 (*m*, 2 H, HC=CH); 7.21 (*s*, 5 H, arom. H). – ^{13}C-NMR. ($CDCl_3$): 13.92 (CH_3 (*E*)-**2**); 14.23 (CH_3 (*Z*)-**2**); 20.58 (C(5) (*Z*)-**2**); 25.63 (C(5) (*E*)-**2**); 29.10 (C(2) (*Z*)-**2**); 34.16 (C(2) (*E*)-**2**); 36.14 (C(1)); 125.77, 128.26, 128.48, 132.31, 132.66 and 142.12 (olefinic and aromatic C-atoms). The isomer ratio given in *Scheme 2* is based on the ratio of the intensities of the corresponding signals in the ^{13}C-NMR. spectra for all three experiments (HMPT, DMPU, no cosolvent, see *b*)).

b) *Without cosolvent.* The procedure was identical to that described above, except that additional THF was used corresponding to the volume of the cosolvents above. For yield and ratio (*Z*)-**2**/(*E*)-**2** s. *Scheme 2.*

Preparation of 2-nitro-1-phenyl-1-butanol (**3**). The compound was prepared in 65% yield according to the published procedure [15] using 1-nitropropane (10 mmol), butyllithium (20 mmol) and benzaldehyde (10 mmol) in THF/DMPU 3:1 (60 ml). In case of the reaction without a cosolvent additional THF (equal to the volume of the cosolvent) was added following an otherwise identical procedure. For yield and ratio *threo*-**3**/*erythreo*-**3** s. *Scheme 3.*

Addition of 2-lithio-1,3-dithiane to 2-cyclohexen-1-one (preparation of 3-(1,3-dithian-2-yl)-1-cyclohexanone (**4a**) *and 1-(1,3-dithian-2-yl)-2-cyclohexen-1-ol* (**4b**)). a) *In the presence of DMPU.* To a cold (−76°) solution of 1,3-dithiane (1.2 g, 10 mmol) in THF (25 ml) was added butyllithium (6.3 ml, 9.95 mmol). After stirring for 15 min, the dry ice-acetone bath was replaced by an ice-salt bath and the reaction mixture was stirred at about −20° for 1 h. The reaction mixture was recooled to −76° and DMPU (4.8 ml, 40 mmol – or 2.4 ml, 20 mmol as the case may be) was added. After stirring for 10 min cyclohexenone (1 ml, 10.4 mmol) was added and the reaction mixture was stirred for 15 min at −76°. Sat. NH_4Cl-solution (5 ml) was added and the reaction mixture was allowed to warm up to RT. Ether (20 ml) and water (20 ml) were added. The organic phase was separated and the aq. phase was extracted with ether (3 × 25 ml). The combined organic phases were washed with water (5 × 30 ml), dried ($MgSO_4$), and concentrated. The crude product thus obtained was chromatographed on silica gel using benzene followed by CH_2Cl_2 as eluant to obtain **4a** and **4b** as pure compounds (yields see *Scheme 4*). The ratio **4a**/**4b** was determined from the 300 MHz ^{1}H-NMR. spectrum of the crude reaction mixture. – ^{1}H-NMR. ($CDCl_3$) of **4a**: 1.55–2.62 (*m*, 11 H, 9 cyclohexan H-atoms and CH_2CH_2–S); 2.82–2.96 (*m*, 4 H, 2 SCH_2); 4.1 (*d*, *J* = 5, 1 H, SCHS). – ^{1}H-NMR. ($CDCl_3$) of **4b** [21]: 1.68–2.15 (*m*, 8 H, $(CH_2)_3$ of the cyclohexene ring and CH_2CH_2S); 2.27 (br. *s*, 1 H, OH); 2.82–2.98 (*m*, 4 H, 2 SCH_2); 4.25 (*s*, 1 H, SCHS); 5.78 (br. *d*, *J* = 11, 1 H, H–C(2)); 5.94–6.02 (*m*, 1 H, H–C(3)).

b) *In the absence of cosolvent.* The procedure was identical to that described above except that no DMPU was added (*cf.* [21]).

Preparation of (Z/E)-3-(t-butyldimethylsilyloxy)-2-pentene (**5**). The procedure was identical to the published one [17a], except for the use of DMPU (volume-% as in *Scheme 5*) instead of HMPT. The product ratio was determined by GC. (see *Scheme 5*).

Preparation of a cis/trans *mixture of 4-benzyl-2,2-dimethyl-4,5-bis(methoxycarbonyl)-1,3-dioxolane* (**6**). A solution of diisopropylamine (1.5 ml, 10.6 mmol) in THF/DMPU 2:1 (40 ml) was cooled to −35° and a hexane solution of butyllithium (6.6 ml, 10.4 mmol) was added dropwise. After stirring for 20 min, the solution of LDA thus obtained was cooled to −76° and a solution of (4*R*,5*R*)-2,2-dimethyl-4,5-bis(methoxycarbonyl)-1,3-dioxolane [22] (2.18 g, 10 mmol) in THF (2 ml) was added dropwise. The resulting yellow solution was stirred at −76° for 1 h. Benzyl bromide (1.6 ml, 13.5 mmol) was added. The reaction mixture was stirred for 12 h during which period the temperature rose to −60° and then at RT. for 8 h. Ether (200 ml) was added to the reaction mixture, and the suspension was washed with water (5 × 100 ml), dried ($MgSO_4$), and concentrated in a rotatory evaporator. The residue, a highly viscous oil, was carefully fractionally distilled (and redistilled, if necessary) to give **6** as a colourless oil (1.6 g, 52%), b.p. 120°/0.01 Torr, identical with an authentic sample of the mixture of the two *cis*/*trans*-isomers. – ^{1}H-NMR. ($CDCl_3$)[10]: 1.0 and 1.4 (2 *s*,

[10]) The first chemical shift value of a pair corresponds to the minor isomer.

$H_3C-C(2)$); 1.55 and 1.7 (2 *s*, $H_3C-C(2)$); 2.89 (*d*, *AB*-system, $J = 13.5$, *H*C–Ph, major isomer); 3.09 (*d*, *AB*-system, $J = 13.5$, *H*C–Ph, major isomer); 3.20 (*d*, *AB*-system, $J = 14$, *H*C–Ph, minor isomer); 3.34 (*d*, *AB*-system, $J = 14$, *H*C–Ph, minor isomer); 3.68 and 3.62 (2 *s*, OCH_3); 3.82 (*s*, OCH_3 of both isomers); 4.38 and 4.93 (2 *s*, H–C(5)).

Hydroxyalkylation and alkylation of the dilithio derivative of methyl 3-nitropropanoate (preparation of 7). Details are described elsewhere [19].

REFERENCES

[1] a) *H. Normant,* Bull. Soc. Chim. Fr. *1968*, 791, and references cited therein; b) *M. Fieser & L. F. Fieser,* 'Reagents for Organic Synthesis' *1–7*, John Wiley & Sons, N.Y.; c) *M. Fieser,* 'Reagents for Organic Synthesis' *8*, John Wiley & Sons, N.Y. 1980; d) *M. Fieser, R. L. Danheiser & W. Roush,* 'Reagents for Organic Synthesis' *9*, John Wiley & Sons, N.Y. 1981.

[2] *W. R. Gilkerson & M. D. Jackson,* J. Am. Chem. Soc. *101*, 4096 (1979).

[3] *J. F. Schmutz,* Chem. Eng. News *16th Jan. 1978*, 39.

[4] *H. Spencer,* Chem. Ind. *1979*, 728.

[5] *A. Lüttringhaus & H. W. Dirksen,* Angew. Chem. *75*, 1059 (1963); *ibid.* Int. Ed. Engl. *3*, 260 (1964).

[6] *B. J. Barker, J. Rosenfarb & J. A. Caruso,* Angew. Chem. *91*, 560 (1979); *ibid.* Int. Ed. Engl. *18*, 503 (1979).

[7] *H. G. Richey, jr., R. D. Smith, B. A. King, T. C. Kester & E. P. Squiller,* J. Org. Chem. *46*, 2823 (1981).

[8] *R. E. Doolittle,* Org. Prep. Proc. Int. *12*, 1 (1980).

[9] *E. J. Lien & W. D. Kumler,* J. Med. Chem. *11*, 214 (1968).

[10] a) *H. E. Zaugg,* J. Am. Chem. Soc. *83*, 837 (1961); b) *H. Sakurai & F. Kondo,* J. Organomet. Chem. *92*, C 46 (1975); c) *idem, ibid. 117*, 149 (1976).

[11] a) *J. E. Shaw, D. C. Kunerth & J. J. Sherry,* Tetrahedron Lett. *1973*, 689; b) *J. E. Shaw & D. C. Kunerth,* J. Org. Chem. *39*, 1968 (1974).

[12] *G. Cardillo, M. Orena & S. Sandri,* Synthesis *1976*, 394.

[13] a) *P. E. Sonnet,* Org. Prep. Proc. Int. *6*, 269 (1974); b) *R. M. Waters, D. J. Voaden & J. D. Warthen, jr.,* Org. Prep. Proc. Int. *10*, 5 (1978); c) *G. Magnusson,* Tetrahedron Lett. *1977*, 2713.

[14] *D. Seebach,* Angew. Chem. *91*, 259 (1979); *ibid.* Int. Ed. Engl. *18*, 239 (1979).

[15] *F. Lehr, J. Gonnermann & D. Seebach,* Helv. Chim. Acta *62*, 2258 (1979).

[16] *C. A. Brown & A. Yamaichi,* J. Chem. Soc., Chem. Commun. *1979*, 100.

[17] a) *R. E. Ireland, R. H. Mueller & A. K. Willard,* J. Am. Chem. Soc. *98*, 2868 (1976); b) *Z. A. Fataftah, I. E. Kopka & M. W. Rathke,* J. Am. Chem. Soc. *102*, 3959 (1980).

[18] *R. Naef & D. Seebach,* Angew. Chem. *93*, 1113 (1981); *ibid.* Int. Ed. Engl. *20*, 1030 (1981); and unpublished results, *R. Naef,* ETH Zürich 1980.

[19] *D. Seebach, R. Henning & T. Mukhopadhyay,* Chem. Ber., in press.

[20] *H. J. Bestmann & H. Hartung,* Chem. Ber. *99*, 1198 (1966).

[21] *D. Seebach & E. J. Corey,* J. Org. Chem. *40*, 231 (1975).

[22] *M. Carmack & C. J. Kelley,* J. Org. Chem. *33*, 2171 (1968); *D. Seebach, H.-O. Kalinowski, B. Bastani, G. Crass, H. Daum, H. Dörr, N. P. Du Preez, V. Ehrig, W. Langner, Ch. Nüssler, H.-A. Oei & M. Schmidt,* Helv. Chim. Acta *60*, 301 (1977).