

14. A New Method for the Preparation of (*E*)-3-Acylprop-2-enoic Acids¹⁾

by Daniel Obrecht* and Bettina Weiss

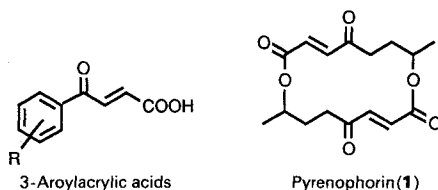
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Dedicated to Prof. R. E. Ireland on the occasion of his 60th birthday

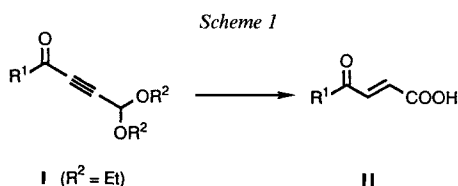
(28.XI.88)

A new method for the preparation of (*E*)-3-acylprop-2-enoic acids (= (*E*)-3-acylacrylic acids) of type **II** via acid-catalyzed isomerization of the corresponding 3-acylprop-2-ynal acetals of type **I** (*Scheme 1*) has been found. The described reaction gives a rapid and quite general access to these compounds known to exhibit a number of interesting biological activities. Some studies toward the elucidation of the reaction mechanism have been made, and a hypothetical mechanism is proposed.

1. Introduction. – In recent years, there has been a growing interest in (*E*)-3-acylprop-2-enoic acids. The 3-acylprop-2-enoic-acid moiety is thought to be the important part in many biologically active natural products, for instance such as pyrenophorin (**1**) [1] [2]. Recently, (*E*)-3-arylprop-2-enoic acids have been synthesized as antiulcer compounds [3a–d], and several new synthetic methods have been developed.



Since there is still a lack of generally applicable methods for the synthesis of (*E*)-3-acylprop-2-enoic acids in good yields, we have been looking for a simple and new approach to this kind of compounds. Our new method is based on the finding that 3-acylprop-2-ynal acetals of type **I** can be isomerized into the corresponding (*E*)-3-acylprop-2-enoic acids of type **II** under acidic conditions (*Scheme 1*).



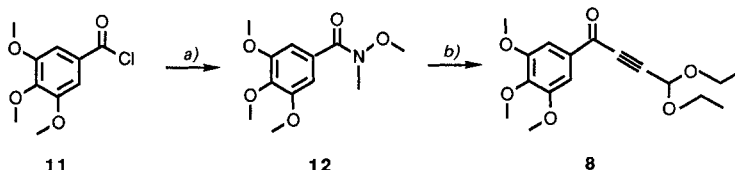
¹⁾ Presented in part at the autumn meeting of the Swiss Chemical Society in Bern on October 21, 1988.

2. 3-Acylprop-2-ynal Diethyl Acetals I. – The required acetals of type I, *i.e.* 7–10 (see Table 1), were easily accessible starting from either the *N*-methoxy-*N*-methylamide 12 [8] (11→12→8, Scheme 2) or from the corresponding aldehydes of type III, *i.e.* 3–6 (III→IV→I, Scheme 3). They reacted smoothly with the acetylide prepared from the commercially available 3,3-diethoxyprop-1-yne (2) and BuLi in THF at -78° [9]. In cases where the aldehyde III was available, we preferred the two-step procedure *via* the acetylenic alcohols IV because of slightly better overall yields.

Table 1. Synthesis of the 3-Acylprop-2-ynal Acetal I

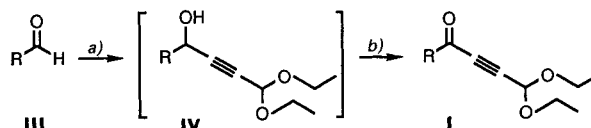
R ¹	Aldehyde III	Acetal I	Yield [%]
Ph	3	7	89
3,4,5-(MeO) ₃ C ₆ H ₂	4	8	89
CH ₃ (CH ₂) ₄	5	9	87
(<i>E</i>)-PhCH=CH	6	10	91

Scheme 2



a) $\text{CH}_3(\text{CH}_3\text{O})\text{NH} \cdot \text{HCl}$, $(i\text{-Pr})_2\text{EtN}$, CH_2Cl_2 (82%). b) BuLi, THF, $\text{CH} \equiv \text{CCH}(\text{OEt})_2$ (2), $-78^{\circ} \rightarrow 0^{\circ}$ (90%).

Scheme 3



a) BuLi, THF, $\text{CH} \equiv \text{CCH}(\text{OEt})_2$ (2). b) MnO_2 , CH_2Cl_2 , $0^{\circ} \rightarrow \text{r.t.}$

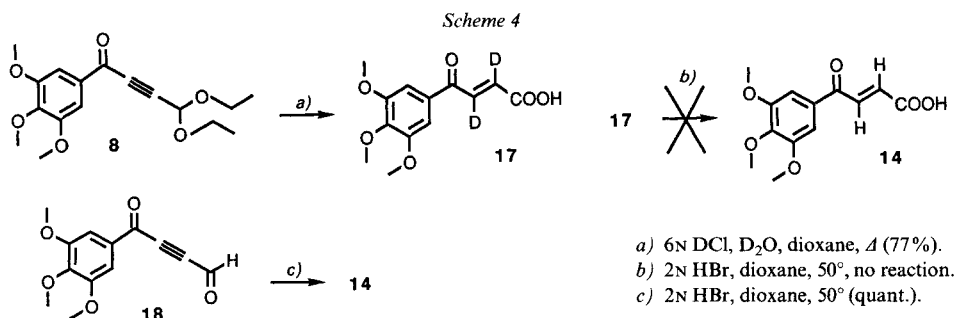
3. (*E*)-3-Acylprop-2-enoic Acids II. – The desired acids of type II were obtained by treatment of the corresponding acetals of type I with either 2N aq. HBr or 4N aq. HCl in dioxane (Scheme 1). The optimum conditions in our hands turned out to be 2N aq. HBr/dioxane 1:3 at temperatures ranging from 30 to 80° (Table 2). It is worth noting that only the (*E*)-isomers were formed.

Table 2. Isomerization of the 3-Acylprop-2-ynal Diethyl Acetals I

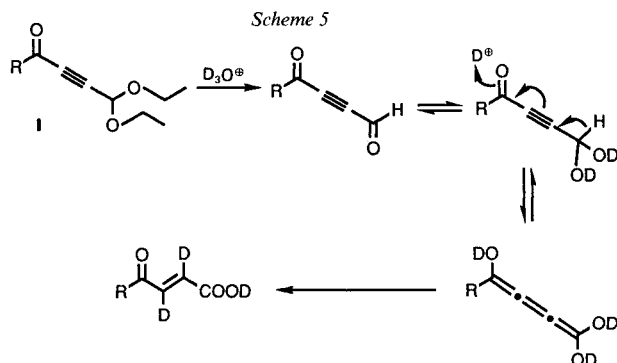
Acetal I	R ¹	Solvent	Time [h]	Temp. [$^{\circ}$]	Acid II	Yield [%]
7	Ph	2N aq. HBr/dioxane 1:3	12	50	13	79 ^{a)}
8	3,4,5-(MeO) ₃ C ₆ H ₂	2N aq. HBr/dioxane 1:3	2.5	50	14	91 ^{a)}
8	3,4,5-(MeO) ₃ C ₆ H ₂	4N aq. HCl/dioxane 1:3	7	50	14	80 ^{b)}
9	CH ₃ (CH ₂) ₄	2N aq. HBr/dioxane 1:3	30	80	15	82 ^{a)}
10	(<i>E</i>)-PhCH=CH	2N aq. HBr/dioxane 1:3	30	30	16	78 ^{b)} , 41 ^{c)}

^{a)} Isolated yield. ^{b)} Crude yield. ^{c)} Purified as the Na salt.

4. Mechanistic Aspects. – In order to elucidate the possible mechanism of the reaction **I**→**II**, we performed three experiments (*Scheme 4*). When **8** was treated with 6N DCl/D₂O in dioxane at 50°, the corresponding (D₂)acid **17** was obtained in 77% isolated yield (97% D₂ by ¹H-NMR). When **17** was treated with 2N aq. HBr in dioxane at 50°, there was no loss of D observable, which indicated that the D-incorporation is not reversible. The quantitative transformation of the aldehyde **18**²⁾ into the corresponding acid **14** using 2N aq. HBr in dioxane at 50° showed that hydrolysis of the acetal is most probably the first step of the transformation.



Based on the experiments, we believe that the acetal **8** is first hydrolyzed to the aldehyde **18** which probably exists to a great extent in the hydrated form under the acidic reaction conditions. Then, **18** or its hydrated form isomerizes *via* vinylogous enolization and H⁺ (D⁺) transfers to the corresponding acid **14** (**17**). The incorporation of 2 D-atoms at C(2) and C(3) of **17** (*Scheme 4*) clearly rules out a mechanism involving a [1,2]-H shift from C(1) to C(2). The overall mechanism in DCl in D₂O/dioxane is given in *Scheme 5*.



5. Conclusions. – Our new method of preparing (*E*)-3-acylprop-2-enoic acids **II** (*Scheme 1*) is especially well suited for molecules which tolerate dilute-acid conditions. It is worth mentioning that the method gives high yields in preparing various (*E*)-3-arylprop-2-enoic acids, compounds which exhibit interesting antisecretory and cytoprotective activities [3a–d].

²⁾ Prepared in 45% yield by oxidation of the corresponding alcohol using MnO₂ in CH₂Cl₂.

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Experimental Part

(The authors wish to thank Mr. *O. Heitzelmann* for his excellent experimental work)

General. All reactions with air- and moisture-sensitive reactants and solvents were carried out in oven- or flame-dried glassware under a positive pressure of dry Ar. Reaction solvents and liquid reagents were purified by distillation shortly before use: THF was distilled under Ar from Na with benzophenone ketyl as indicator. CH_2Cl_2 and (i-Pr) $_2\text{EtN}$ (Hünig's base) were distilled from powdered CaH_2 . All other reactants were 'reagent grade' unless described otherwise. Anal. TLC: 2.5×10 cm precoated TLC plates, SiO_2 60F-254, layer thickness 0.25 mm (*E. Merck & Co.*, Darmstadt, FRG). Flash chromatography: *E. Merck* SiO_2 60 (230–400 mesh ASTM), according to [11]. M.p.: Büchi SMP-20 apparatus; uncorrected. IR: Nicolet 7199 FT-IR spectrometer; solids in KBr pellets, liquids as thin films; indication of characteristic bands in cm^{-1} . $^1\text{H-NMR}$: at 250 MHz (*Bruker* 250), TMS as internal standard; chemical shifts δ of signal centres or ranges in ppm, *J* in Hz.

1. General Procedures. – 1.1. *Acetals of Type I, Method A.* To a stirred soln. of 1.43 ml (10.0 mmol) of 3,3-diethoxyprop-1-yne (**2**) in THF (30 ml), BuLi (6.25 ml, 10.0 mmol; 1.6M in hexane) was slowly added at -78° and stirred for 30 min at -78° . Then, aldehyde **III** (10.0 mmol) in THF (10 ml) was added and stirred for 30 min at -78° . The mixture was allowed to warm up to r.t. and quenched with sat. HN_4Cl soln. (50 ml), ice (20 g), and Et_2O (100 ml), the aq. phase extracted twice with Et_2O (100 ml), and the combined org. phase extracted with brine (50 ml), dried (MgSO_4), and evaporated. The remaining oil in CH_2Cl_2 (30 ml) was slowly added to a mechanically stirred suspension of MnO_2 (26 g) in CH_2Cl_2 (50 ml) at 0° , vigorously stirred at 0° for 1 h, and slowly warmed up to r.t. until the reaction was completed (1–2 h). The suspension was filtered, the filtrate evaporated, and the residue chromatographed on SiO_2 (200 g) with AcOEt /hexane 1:3 to 1:5 or crystallized as indicated to give **I**.

1.2. *Acids of Type II, Method B.* To a stirred soln. of 1.0 mmol of **I** in dioxane (3 ml), 2N aq. HBr (1 ml) was added at r.t. The mixture was heated to 30 – 80° for 7–18 h (see Table 2), then quenched at 0° by addition of sat. NaHCO_3 soln. (10 ml) and Et_2O (10 ml). The org. layer was extracted with sat. NaHCO_3 soln. (2×5 ml), the combined aq. phase carefully acidified to pH 2 with 4N aq. HCl and extracted with AcOEt (3×10 ml), the combined org. phase dried (MgSO_4) and evaporated, and the product **II** crystallized and dried.

2. Acetals of Type I. – 2.1. *N,3,4,5-Tetramethoxy-N-methylbenzamide (12).* To a stirred soln. of 5.0 g (21.7 mmol) of 3,4,5-trimethoxybenzoyl chloride (**11**) (*Fluka*) and 2.12 g (21.7 mmol) of *N,O*-dimethylhydroxylamine·HCl (*Fluka*) in dry CH_2Cl_2 (70 ml), 3.36 g (26.04 mmol) of (i-Pr) $_2\text{EtN}$ were slowly added at 0° . The mixture was stirred at 0° for 1 h and allowed to warm up to r.t. After addition of ice/ H_2O , the org. phase was dried (MgSO_4) and evaporated. The remaining solid was crystallized from AcOEt /hexane yielding 4.54 g (82%) of **12** as a pale yellow solid. M.p. 61 – 62° . IR (KBr): 2940m, 1660s, 1585s, 1510m, 1420s, 1375s, 1245s, 1135s, 1010s. $^1\text{H-NMR}$ (250 MHz, CDCl_3): 6.98 (s, 2 arom. H); 3.89, 3.60, 3.37 (3s, 4 CH_3O , CH_3N). MS: 255 (6, M^+), 195 (100). Anal. calc. for $\text{C}_{12}\text{H}_{17}\text{NO}_5$: C 56.46, H 6.71, N 5.49; found: C 56.34, H 6.77, N 5.47.

2.2. *4,4-Diethoxybut-2-ynophenone (7)* [10]. A soln. of 6.54 g (51.0 mmol) of **2** was treated following Method A with 5.95 g (56.06 mmol) of benzaldehyde (**3**) to yield 10.56 g (89.1%) of **7** as a colourless oil. IR (film): 2978m, 2932w, 2887w, 2150w, 1649s, 1559w, 1448w, 1261s, 1175w, 1119m, 1055s, 702m. $^1\text{H-NMR}$ (250 MHz, CDCl_3): 8.15–8.1 (m, 2 arom. H); 7.65–7.6, 7.55–7.45 (2m, 3 arom. H); 5.52 (s, $\text{CH}(\text{OCH}_2\text{CH}_3)_2$); 3.85–3.65 (m, $\text{CH}(\text{CH}_2\text{CH}_3)_2$); 1.29 (t, $J = 7.2$, $\text{CH}(\text{CH}_2\text{CH}_3)_2$). MS: 231 (1, $M^+ - \text{H}$), 187 (96), 159 (100), 105 (46), 77 (43). Anal. calc. for $\text{C}_{14}\text{H}_{16}\text{O}_3$: C 72.39, H 6.94; found: C 72.17, H 7.05.

2.3. *4,4-Diethoxy-3',4',5'-trimethoxybut-2-ynophenone (8)*. 2.3.1. *From 12:* To a stirred soln. of 1.0 ml (6.98 mmol) of **2** in dry THF (15 ml), 4.6 ml of BuLi (1.6M in hexane) were added at -78° and stirred for 30 min at -78° . After addition of a soln. of 1.62 g (6.35 mmol) of **12** in THF (10 ml), the mixture was stirred for 30 min at -78° , slowly warmed up to 0° , and quenched with 5% HCl soln. in EtOH and ice. After addition of AcOEt (20 ml), the aq. phase was extracted with AcOEt (2×10 ml), the combined org. phase dried (MgSO_4) and evaporated, and the residue chromatographed on SiO_2 (60 g) with Et_2O /hexane 1:2 yielding 1.85 g (90%) of **8** as white crystals after recrystallization from isooctane. M.p. 54° . IR (KBr): 2960m, 2930w, 2230w, 1645s, 1505m, 1460m, 1412m, 1335s, 1215m, 1128s, 1065m, 740m. $^1\text{H-NMR}$ (250 MHz, CDCl_3): 7.42 (s, 2 arom. H); 5.51 (s, $\text{CH}(\text{CH}_2\text{CH}_3)_2$); 3.95, 3.93

(2s, 3 CH₃O); 3.85–3.65 (m, CH(CH₂CH₃)₂); 1.29 (t, *J* = 7.9, CH(CH₂CH₃)₂). MS: 322 (100, *M*⁺), 277 (45), 249 (62), 195 (28), 168 (22). Anal. calc. for C₁₇H₂₂O₆: C 63.34, H 6.88; found: C 63.27, H 6.92.

2.3.2. From 3,4,5-Trimethoxybenzaldehyde (4). A soln. of 1.43 ml (10.0 mmol) of **2** was treated following *Method A* with 1.96 g (10.0 mmol) of **4** yielding 2.87 g (88.9%) **8** after recrystallization from isooctane. M.p. 54°. Spectra: identical to 2.3.1.

2.4. 1,1-Diethoxynon-2-yn-4-one (9). A soln. of 1.43 ml (10.0 mmol) of **2** was treated following *Method A* with 1.0 g (10.0 mmol) of hexanal (5) yielding 1.98 g (86.7%) of **9** as a colourless oil. IR (film): 2930m, 2870m, 2225w, 1685s, 1460w, 1405w, 1355m, 1330m, 1230m, 1155s, 1120s, 1060s. ¹H-NMR (250 MHz, CDCl₃): 5.39 (s, CH(CH₂CH₃)₂); 3.8–3.6 (m, CH(CH₂CH₃)₂); 2.59 (t, *J* = 7.3, CH₂CO); 1.75–1.6 (m, 2 H–C(6)); 1.4–1.15 (m, 2 H–C(7), 2 H–C(8)); 1.25 (t, *J* = 7.1, CH(CH₂CH₃)₂); 0.9–0.85 (m, 3 H–C(9)). MS: 225 (1, *M*⁺ – H), 181 (83), 111 (68), 83 (100), 55 (41). Anal. calc. for C₁₃H₂₂O₃: C 68.99, H 9.80; found: C 68.91, H 9.69.

2.5. (E)-6,6-Diethoxy-1-phenylhex-1-en-4-yn-3-one (10). A soln. of 1.43 ml (10.0 mmol) of **2** was treated following *Method A* with 1.40 g (10.59 mmol) of cinnamaldehyde (6) yielding 2.36 g (91.6%) of **10** as a pale yellow oil. IR (film): 2980m, 2930w, 2880w, 2225w, 1638s, 1600m, 1450w, 1330w, 1255s, 1120m, 960s. ¹H-NMR (250 MHz, CDCl₃): 7.74, 6.80 (2d, *J* = 16.2, H–C(1), H–C(2)); 7.6–7.55, 7.5–7.4 (2m, 5 arom. H); 5.49 (s, CH(CH₂CH₃)₂); 3.9–3.65 (m, CH(CH₂CH₃)₂); 1.29 (t, *J* = 7.2, CH(CH₂CH₃)₂). MS: 258 (13, *M*⁺), 213 (100), 185 (82), 129 (78), 103 (50), 787 (51). Anal. calc. for C₁₆H₁₈O₃: C 74.40, H 7.02; found: C 74.59, H 7.39.

3. Acids of Type II. – 3.1. (E)-4-Oxo-4-phenylbut-2-enoic Acid (13) [3d]. A soln. of 3.0 g (12.9 mmol) of **7** was treated following *Method B* for 12 h at 50° to yield 1.78 g (79%) of **13** after recrystallization from AcOEt/hexane. M.p. 94–95°. IR (KBr): 3430w, 3070m, 2822m, 2675w, 2581w, 1704s, 1671s, 1501m, 1440m, 1408m, 1301s, 1130m, 1008m, 929m. ¹H-NMR (250 MHz, CDCl₃): 11.50 (br. s, COOH); 8.02, 6.91 (2d, *J* = 15.6, H–C(2), H–C(3)); 8.05–8.0, 7.7–7.65, 7.55–7.5 (3m, 5 arom. H). MS: 176 (20, *M*⁺), 105 (100), 77 (53). Anal. calc. for C₁₀H₈O₃: C 68.18, H 4.58; found: C 67.97, H 4.58.

3.2. (E)-4-Oxo-4-(trimethoxyphenyl)but-2-enoic Acid (14) [3b]. A soln. of 500 mg (1.55 mmol) of **8** was treated following *Method B* for 2.5 h at 50° to yield 375 mg (90.8%) of **14** after recrystallization from AcOEt/hexane. M.p. 144° ([3b]: 144°). IR (KBr): 3075w, 2965m, 2580m, 1700s, 1670s, 1585s, 1415s, 1340s, 1230m, 1165s, 1130s, 1000m. ¹H-NMR (250 MHz, CDCl₃): 7.98, 6.92 (2d, *J* = 15.5, H–C(2), H–C(3)); 7.26 (s, 2 arom. H); 3.96, 3.95 (2s, 3 CH₃O). MS: 266 (100, *M*⁺), 251 (24), 220 (25), 195 (42), 163 (11), 99 (16). Anal. calc. for C₁₃H₁₄O₆: C 58.65, H 5.30; found: C 58.53, H 5.53.

3.3. (E)-4-Oxonon-2-enoic Acid (15). A soln. of 1.0 g (4.42 mmol) of **9** was treated following *Method B* for 30 h at 80° to yield 617 mg (82%) of **15** after recrystallization from AcOEt/hexane. M.p. 105–106°. IR (KBr): 3440w, 2950s, 2925s, 1720s, 1680s, 1660s, 1625w, 1415w, 1290w, 1180m. ¹H-NMR (250 MHz, CDCl₃): 9.0 (br. s, COOH); 7.15, 6.68 (2d, *J* = 15.9, H–C(2), H–C(3)); 2.66 (t, *J* = 7.25, 2H–C(5)); 1.75–1.6, 1.45–1.25, 0.95–0.85 (3m, 9 aliph. H). MS: 171 (5, *M*⁺ + 1), 152 (10), 123 (36), 114 (100), 99 (87), 96 (36), 71 (37), 43 (70). Anal. calc. for C₉H₁₄O₃: C 63.51, H 8.29; found: C 63.07, H 8.29.

3.4. Sodium (all-E)-4-Oxo-6-phenylhexa-2,5-dienoate (Na Salt of 16). A soln. of 3.24 g (12.7 mmol) of **10** was heated following *Method B*, for 30 h at 30°, to afford 2.02 g (78.5%) of crude **16** as an oil. This material was dissolved in THF (5 ml) and solid Na₂CO₃ added at 0° until CO₂ formation ceased. After addition of Et₂O (15 ml), the precipitate was filtered, washed with Et₂O, and dried: 1.17 g (41%) of Na salt of **16** as a pale yellow solid. M.p. 200° (dec.). IR (KBr): 3440w (br.), 3060w, 3030w, 1662m, 1605s, 1570s, 1500w, 1425s, 1345m, 1200m, 990m, 785m, 695m. ¹H-NMR (250 MHz, (D₆)DMSO): 7.9–7.7 (m, 2 arom. H); 7.63, 7.34 (2d, *J* = 16.8, H–C(2), H–C(3)); 7.55–7.2 (m, 3 arom. H); 6.90, 6.82 (2d, *J* = 15.8, H–C(5), H–C(6)).

3.5. (E)-4-Oxo-4-(trimethoxyphenyl)(2,3-D₂)but-2-enoic Acid (17). A soln. of 500 mg (1.55 mmol) of **8** in dioxane (5 ml) and 6*N* DCl in D₂O (1.5 ml) was stirred for 12 h at 30° following *Method B* to yield 380 mg (91.4%) of crude **17** as an oil which crystallized from AcOEt/hexane: 320 mg (77%) of **17**. M.p. 137–139°. IR (KBr): 3430w (br.), 2990w, 2945w, 2660w, 2555w, 1700s, 1660s, 1585s, 1508m, 1470m, 1420s, 1340s, 1295m, 1218m, 1133s, 1005m, 780m. ¹H-NMR (250 MHz, CDCl₃): 7.26 (s, 2 arom. H); 3.96, 3.95 (2s, 3 CH₃O) (97% D₂). MS: 268 (100, *M*⁺), 195 (41).

REFERENCES

- [1] S. Nozoe, K. Hirai, K. Tsuda, K. Ischibashi, M. Shiraska, J. F. Grove, *Tetrahedron Lett.* **1965**, 4675.
- [2] M. Petrini, R. Ballini, G. Rosini, E. Marotta, *Tetrahedron Lett.* **1986**, 151.
- [3] a) M. Bianchi, F. Barzaghi, 1983, GB 2 108 500 A; b) C. Yani, R. Fournex, 1982, DE 32114082 A1; c) C. Yani, R. Tournemine, R. Fournex, 1981, FR 2481118 A1; d) M. Bianchi, F. Barzaghi, 1983, DE 3239189 A1.
- [4] H.-J. Bestmann, R. Schobert, *Angew. Chem.* **1985**, 97, 784.
- [5] M. d'Auria, A. de Mico, F. d'Onofri, A. Scettri, *Synthesis* **1985**, 988.
- [6] M. Asoaka, H. Takei, *J. Synth. Org. Chem. Jpn.* **1986**, 819.
- [7] W. Roush, J. W. Coe, *Tetrahedron Lett.* **1987**, 931.
- [8] S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, 3815.
- [9] F. Barbot, P. Miginiac, *Bull. Chem. Soc. Fr.* **1983**, 41.
- [10] A. Gorgues, A. Le Coq, *Tetrahedron Lett.* **1979**, 4825.
- [11] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, 43, 2923.