A Simple and General Synthesis of Symmetrical and Unsymmetrical Bis(arylamino)methanes. Reactions of N,O-Acetals with Nitrogen Bases

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Bis(arylamino)methanes 4 free of amine contamination have been efficiently synthesized from N,O-acetals 1 following three different methodologies. The first two are useful for symmetrical aminals and involve the decomposition of an N,O-acetal by a base (phenyllithium or a lithium arylamide) and trapping of the resulting methyleneamine 2 by the equimolar amount of the corresponding arylamine. The third method allows the preparation of either symmetrical or unsymmetrical aminals and consists of decomposing the starting N,O-acetal 1 by heating in vacuo in the presence of the desired arylamine.

Ein einfacher und allgemeiner Zugang zu symmetrischen und unsymmetrischen Bis(arylamino)methanen. Reaktionen von N,O-Acetalen mit Stickstoffbasen

Bis(arylamino)methane 4 ohne Verunreinigung durch Amine werden aus N,O-Acetalen 1 nach drei verschiedenen Methoden dargestellt. Die ersten beiden Verfahren liefern symmetrische Aminale. Sie basieren auf der Spaltung von N,O-Acetalen 1 mit einer Base (Phenyllithium oder ein Lithiumamid) und Abfangen des entstandenen Methylenamins 2 mit der äquimolaren Menge des entsprechenden Arylamins. Die dritte Methode erlaubt die Darstellung sowohl von symmetrischen als auch von unsymmetrischen Aminalen 4 und besteht in der Spaltung des Ausgangs-N,O-Acetals 1 durch Erhitzen im Vakuum in Gegenwart eines Arylamins.

The reaction of formaldehyde with primary amines proceeds in several steps in which the products initially formed undergo a series of transformations. The final composition of the reaction mixture depends largely on the pH value of the reaction medium, the amine/formaldehyde molar ratio used, and the temperature[1-9]. The complexity of the reaction is particularly great in the case of aromatic amines since several types of products derived from annular C–N and C–C bond formation are then obtained.

Over the last century many reports have dealed with the synthesis of bis(arylamino)methanes **4**, a class of compounds that is accepted to be formed in the early stages of the amine/aqueous formaldehyde condensation process when it is carried out under neutral or slightly alkaline conditions[3]. The preparation of these compounds or their salts has been often claimed with correct elemental analysis as the only structural proof. However, elementary analysis does not permit a distinction between bis(arylamino)methanes and other amine-formaldehyde condensation products containing two amine groups linked by a methylene bridge. So the synthesis of dianilinomethane, the parent compound in this series, has been subject of contradictory reports[10-12]. Wagner[3-8] studied these condensation reactions and concluded that many of the compounds previously described cannot be authenticated. We reproduced the procedure given by Eberhardt[11] and Bischoff[12] for the preparation of dianilinomethane (**4a**) and obtained a solid melting at 66 °C but, in spite of the correct elemental analysis found, we observed by ^1H and ^{13}C NMR the presence of at least two different kinds of methylene groups in the product. Similar results were obtained when the synthesis of **4a** was attempted by the procedure described by Wakae[13].

More recently compounds **4** have attracted interest by the commercial importance of some of their derivatives[14] and also by their behavior in mass spectrometry[15]. While aminals derived from secondary amines are easily obtained[16], those derived from primary amines require the use of a 10:1 amine-formaldehyde ratio[14] to avoid, under the conditions described by Wakae et al.[13], the contamination of the aminals by other condensation products. When aminals are prepared following the above methodology, the yields in isolated products are always low since the aminal has to separate out by spontaneous precipitation in the reaction medium. When **4** derives from a solid amine both crystallize together, and in the case of liquid amines the presence of amine hampers the crystallization process. When the aminal **4** is a liquid or solid of low melting point it cannot be separated from the excess of amine due to its thermal and chemical unstability and, probably for this reason, the synthesis of bis(3-methylanilino)methane (**4d**) has to our best knowledge never been reported.

In the present paper we describe three new and efficient methods for the general synthesis of bis(arylamino)methanes free of amine contamination.

Results and Discussion

Bis(arylamino)methanes **4** result from the addition of amines to methyleneamines **2** in the course of the amine/formaldehyde condensation processes. In recent papers we described the preparation of *N*-(methoxymethyl)arylamines **1** and found that they are efficient precursors of methyleneamines **2**[17]. The reaction conditions used allow their trapping by nucleophiles such as organometallics[18] or metal hydrides[19]. The formation of methyleneamines **2** from *N*-(methoxymethyl)arylamines **1** implies the elimination of alcohol, and this reaction can be promoted under basic catalysis of by heating. On the basis of these observations we felt that this methodology could be applied to the synthesis

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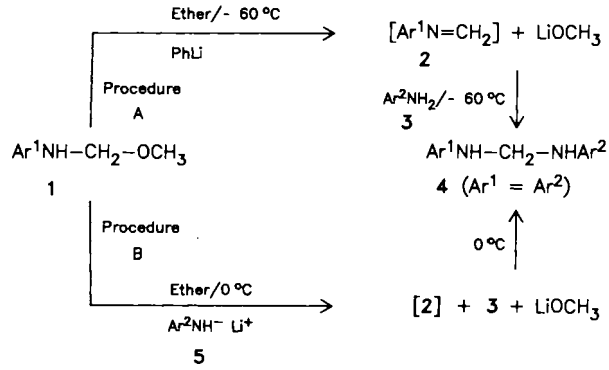
of bis(arylamino)methanes **4** by performing the generation of methyleneamines **2** in the presence of the stoichiometric amount of an aromatic amine **3**.

Synthesis of Symmetric Bis(arylamino)methanes 4 ($Ar^1 = Ar^2$) under Basic Conditions

Two alternative procedures were developed for the base-promoted generation of the intermediate methyleneamine **2**. In procedure A (Scheme 1) *N*-(methoxymethyl)aniline (**1a**) was treated with the equimolar amount of phenyllithium in dry ether solution at −60 °C, and then, once the elimination of lithium methoxide was complete, the stoichiometric amount of aniline (**3a**) was added. At this low temperature, compound **2a** is stable and does not undergo fast trimerization or polymerization processes, but it is able to add aniline to yield the expected dianilinomethane (**4a**) as the only product. By this new methodology for symmetrical aminals **4** ($Ar^1 = Ar^2$) the contamination of the reaction product by free amine is avoided. The method could be simplified from the experimental standpoint by promoting the elimination of lithium methoxide with the corresponding lithium amide **5** (Ar^2) as the base (procedure B, Scheme 1). For instance, in the synthesis of **4a** aniline was treated with phenyllithium and the resulting salt **5a** ($Ar^2 = C_6H_5$) allowed to react with **1a** in dry ether solution at 0 °C. After usual workup procedure excluding carefully the presence of any acid, pure dianilinomethane (**4a**) free of aniline contamination was obtained as determined by ^1H and ^{13}C NMR.

Scheme 1



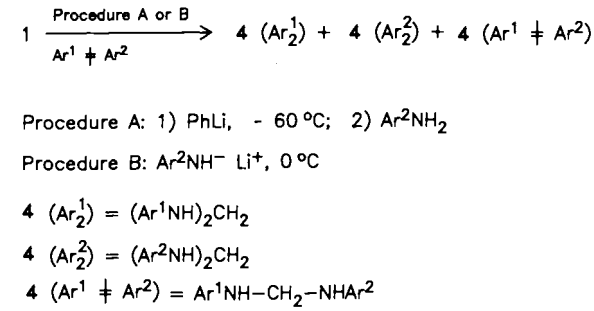
Unsymmetrical aminals **4** ($Ar^1 \neq Ar^2$) are an unknown class of compounds formally derived from the condensation of two different amines and formaldehyde. They are not accessible by the procedures for the synthesis of symmetrical aminals **4** ($Ar^1 = Ar^2$) since these methods, as it has been emphasized above, require the use of a large excess of amine in the condensation step. It is obvious that under these conditions only mixtures of aminals are obtained. In the procedures A and B for the synthesis of compounds **4** ($Ar^1 = Ar^2$) described here the stoichiometric amount of amine is used in a sequential addition, and it appeared to us that this could be also useful for the synthesis of the unsymmetrical compounds **4** ($Ar^2 \neq Ar^2$). However, when the aryl group in the amine **3** (Ar^2) (procedure A) or the lithium amide **5** (Ar^2) (procedure B) was different to that present in the precursor

Table 1. Synthesis of bis(arylamino)methanes **4**

Product	Ar^1	Ar^2	Procedure (Yield %)
4a	C_6H_5	C_6H_5	A (97) B (96) C (99)
4b	4-$H_3C-C_6H_4$	4-$H_3C-C_6H_4$	A (97) B (95) C (98)
4c	2-$H_3C-C_6H_4$	2-$H_3C-C_6H_4$	A (97) B (96) C (99)
4d	3-$H_3C-C_6H_4$	3-$H_3C-C_6H_4$	A (97) B (96) C (98)
4e	2-$H_3CO-C_6H_4$	2-$H_3CO-C_6H_4$	A (97) B (95) C (98)
4f	2-$C_2H_5O-C_6H_4$	2-$C_2H_5O-C_6H_4$	A (97) B (94) C (98)
4g	C_6H_5	2-$H_3C-C_6H_4$	C (99)
4h	C_6H_5	3-$H_3C-C_6H_4$	C (98)
4i	C_6H_5	4-$H_3C-C_6H_4$	C (98)

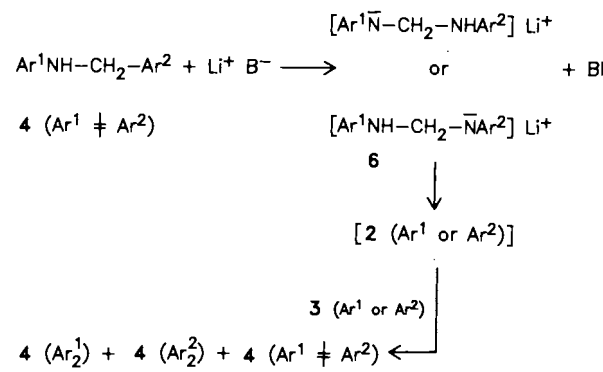
N,O-acetal **1** (Ar^1), then a mixture of the three possible aminals **4** (Ar^1_2), **4** (Ar^2_2), and **4** ($Ar^1 \neq Ar^2$) was always obtained (Scheme 2).

Scheme 2



This result can be easily rationalized by assuming that aminals **4** are unstable species that undergo a β-elimination of lithium amide upon deprotonation promoted by lithium methoxide, a byproduct in the first step of the reaction (Scheme 3).

Scheme 3



Synthesis of Symmetrical (4, $Ar^1 = Ar^2$) and Unsymmetrical Bis(arylamino)methanes (4, $Ar^1 \neq Ar^2$) under Neutral Conditions

The above difficulty could only be overcome by generating methyleneamines **2** (Ar^1) under neutral conditions and trapping them by a second amine **3** (Ar^2). Recently we have shown that aromatic N,O-acetals **1** when heated at 30°C for several hours are quantitatively converted into the corresponding aryltriazinane by trimerization of the intermediate methyleneamine **2**. This transformation is particularly efficient and fast when carried out under vacuum since the alcohol eliminated in the formation of the intermediate **2** is removed, and hence the reverse process of addition of alcohol to the imine C=N bond is prevented. On the basis of these observations we mixed equimolecular amounts of compound **1a** and aniline (**3a**) and allowed the mixture to stand at room temperature for 10 hours in vacuo (0.5 Torr, procedure C). The ^{1}H-NMR analysis of the resulting waxy solid revealed the presence of a single methylene group centered at $\delta = 4.45$ as well as the absence of the methoxy group; the product was identified as dianilinomethane (**4a**) ($Ar^1 = Ar^2 = Ph$). This shows that methyleneamines **2** when generated by this procedure undergo the nucleophilic attack of amines faster than the trimerization reaction to aryltriazinanes. It is to be noted that under our reaction conditions the concentration in compounds **2** (Ar^1) built up in the solution is very low. When the amine **3** (Ar^2) added was different to that from which the starting N,O-acetal **1** (Ar^1) was derived, the corresponding unsymmetrical aminal **4** ($Ar^1 \neq Ar^2$) was obtained. Since the elemental analysis does not allow to distinguish between an equimolecular mixture of the symmetrical aminals **4** (Ar^1_2) and **4** (Ar^2_2) and the unsymmetrical **4** ($Ar^1 \neq Ar^2$), the product was carefully examined by ^{1}H and ^{13}C NMR. A single methylene group was detected while the aromatic signals due to both amines appeared with the expected relative intensities in all the cases. Since the range for the resonance values in aminals **4** is very narrow, to ascertain this characterization, mixtures of aminals **4** ($Ar^1 \neq Ar^2$), **4** (Ar^1_2), and **4** (Ar^2_2) were examined by NMR. The two latter compounds were prepared independently by procedures A and B. It was found that the methylene groups, are not identical in NMR and their signals do not overlap.

Scheme 4

Procedure C

$$1\ (Ar^1) + 3\ (Ar^1) \xrightarrow[-\ CH_3OH]{30\ °C,\ 0.5\ Torr} 4\ (Ar^1_2)$$

$$1\ (Ar^1) + 3\ (Ar^2) \xrightarrow[-\ CH_3OH]{30\ °C,\ 0.5\ Torr} 4\ (Ar^1 \neq Ar^2)$$

It can be concluded that N,O-acetals are efficient and clean precursors for bis(arylamino)methanes in reactions that do not require the use of any excess of amine. Under basic conditions (procedure A and B) only the symmetrical products **4** ($Ar^2 = Ar^2$) can be synthesized. However, under neutral conditions (procedure C) the until now unavailable unsymmetrical aminals **4** ($Ar^1 \neq Ar^2$) are easily obtained selectively.

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Experimental

General Methods: Infrared spectra: Perkin-Elmer 781 spectrometer. – NMR Spectra: Varian FT80A and Bruker WP80SY. – Ether was dried with sodium-potassium amalgam and distilled as needed. All reagents were purified by distillation before use. *N*-(Alkoxymethyl)amines were prepared following our procedure[17]. Discrepant values of the melting points have been reported elsewhere for compounds **4a**, **4b**, and **4c**. All of them are summarized for each compound. Since compounds **4** decompose on heating, their melting points have little significance, and the values found might change even with the rate of heating of each sample.

Synthesis of Dianilinomethane (**4a**)

General Procedure A: A solution of *N*-(methoxymethyl)aniline (1.37 g, 10 mmol) in anhydrous ether under inert gas was cooled to −70°C, and then 7.7 ml of an 1.3 N ethereal solution of phenyllithium (10 mmol) was added dropwise maintaining carefully the temperature and stirring. Once the addition was complete the reaction mixture was allowed to stand 10 min at −70°C, and then aniline (0.93 g, 10 mmol) was added. The reaction mixture was allowed to warm up to 25°C and maintained 30 additional min at this temperature.

The mixture was hydrolyzed with water at 0°C and extracted three times with ether. The organic layer was dried with sodium sulfate, and the solvents were evaporated in vacuo yielding 1.94 g (98%) of a waxy solid identified as **4a**.

General Procedure B: To a 1.3 N ethereal solution of phenyllithium (7.7 ml, 10 mmol) at 0°C under inert gas aniline (0.93 g, 10 mmol) was given. Then *N*-(methoxymethyl)aniline (1.37 g, 10 mmol) was added. After 1 h the reaction mixture was hydrolyzed with ice/water and extracted three times with ether. The organic layer was dried with sodium sulfate, and the solvent was evaporated in vacuo yielding 1.88 g, (95%) of a waxy solid identified as **4a**.

General Procedure C: A flask containing a mixture of *N*-(methoxymethyl)aniline (0.68 g, 5 mmol) and aniline (0.46 g, 5 mmol) at room temperature was connected to the vacuum (10^{-2} Torr) and maintained 10 h at this pressure to give 1.96 g (99%) of a waxy solid identified as **4a**.

Dianilinomethane (**4a**): Procedures A, B, and C; m.p. 44°C (56.3–57°C[5] 64–65°C[13]). – ^{1}H NMR ($DCCl_3$, TMS): $\delta = 4.5$ (s, 2H), 3.4 (s, 2H), 6.5–7.2 (m, 10H). – ^{13}C NMR ($DCCl_3$, TMS): $\delta = 54.8$ (t), 113.8 (d), 118.4 (d), 129.6 (d), 146.9 (s). – IR (Nujol): 700 cm^{-1}, 760, 1190, 1260, 1320, 1510, 1530, 1610, 3050, 3420.

Bis(4-methylphenylamino)methane (**4b**): Procedures A, B, and C: m.p. 64–65°C (66°C[5], 63–65°C[7]). – ^{1}H NMR ($DCCl_3$, TMS): $\delta = 2.2$ (s, 6H), 3.4 (s, 2H), 4.6 (s, 2H), 6.4–7.1 (m, 8H). – ^{13}C NMR ($DCCl_3$, TMS): $\delta = 19.6$ (t), 113.1 (d), 126.1 (s), 129.0 (d), 143.3 (s). – IR (Nujol): 810 cm^{-1}, 1260, 1300, 1380, 1470, 1530, 1620, 3390.

Bis(2-methylphenylamino)methane (**4c**): Procedures A, B, and C: m.p. 55°C (52°C[5]). – ^{1}H NMR ($DCCl_3$, TMS): $\delta = 2.0$ (s, 6H), 3.7 (s, 2H), 4.5 (s, 2H), 6.5–7.0 (m, 8H). – ^{13}C NMR ($DCCl_3$, TMS): $\delta = 16.5$ (q), 54.7 (t), 110.1 (d), 116.8 (d), 121.9 (d), 126.1 (d), 129.5 (s), 143.9 (s). – IR (Nujol): 755 cm^{-1}, 1050, 1140, 1250, 1310, 1450, 1505, 1520, 1590, 1610, 1700, 2920, 3010, 3450.

Bis(3-methylphenylamino)methane (**4d**): Procedures A, B, and C: Oil. – ^{1}H NMR ($DCCl_3$, TMS): δ = 2.2 (s, 6H), 3.6 (s, 2H), 4.5 (s, 2H), 6.4–7.1 (m, 8H). – ^{13}C NMR ($DCCl_3$, TMS): δ = 20.6 (q), 53.8 (t), 109.7 (d), 113.6 (d), 118.3 (d), 128.3 (d), 138.0 (s), 145.7 (s). – IR (Nujol): 700 cm^{-1}, 790, 1190, 1390, 1520, 1620, 3000, 3450.

$C_{15}H_{18}N_2$ (226.3) Calcd. C 79.60 H 8.02 N 12.38
Found C 78.95 H 8.10 N 12.01

Bis(2-methoxyphenylamino)methane (**4e**): Procedures A, B, and C; m.p. 87°C. – ^{1}H NMR ($DCCl_3$, TMS): δ = 3.7 (s, 6H), 4.7 (s, 2H), 4.8 (s, 2H), 6.7 (s, 8H). – ^{13}C NMR ($DCCl_3$, TMS): δ = 53.8 (t), 54.9 (q), 109.4 (d), 110.1 (d), 116.5 (d), 120.9 (d), 136.2 (s), 146.7 (s). – IR (Nujol): 750 cm^{-1}, 1030, 1240, 1600, 2900, 3400.

$C_{15}H_{18}N_2O_2$ (258.3) Calcd. C 69.74 H 7.02 N 10.84
Found C 69.52 H 7.03 N 10.61

Bis(2-ethoxyphenylamino)methane (**4f**): Procedures A, B, and C; m.p. 77°C. – ^{1}H NMR ($DCCl_3$, TMS): δ = 1.3 (t, 6H), 3.9 (q, 4H), 4.7 (s, 2H), 4.8 (s, 2H), 6.7 (s, 8H). – ^{13}C NMR ($DCCl_3$, TMS): δ = 14.5 (q), 54.4 (t), 63.4 (t), 110.6 (d), 110.6 (d), 117.1 (d), 120.8 (d), 136.4 (s), 146.1 (s). – IR (Nujol): 740 cm^{-1}, 1050, 1250, 1610, 2900, 3400.

$C_{17}H_{22}N_2O_2$ (286.4) Calcd. C 71.30 H 7.74 N 9.78
Found C 71.16 H 7.82 N 9.61

(2-Methylphenylamino)(phenylamino)methane (**4g**): Procedure C; Oil. – ^{1}H NMR ($DCCl_3$, TMS): δ = 2.0 (s, 3H), 4.0 (s, 2H), 4.8 (s, 2H), 6.2–7.2 (m, 9H). – ^{13}C NMR ($DCCl_3$, TMS): δ = 16.8 (q), 54.5 (t), 110.7 (d), 113.3 (d), 117.8 (d), 118.2 (d), 126.7 (d), 130.2 (s), 144.4 (s), 146.5 (s). – IR (KBr): 700 cm^{-1}, 760, 1420, 1620, 2940, 3040, 3440.

$C_{14}H_{16}N_2$ (212.3) Calcd. C 79.20 H 7.60 N 13.20
Found C 79.20 H 7.62 N 12.97

(3-Methylphenylamino)(phenylamino)methane (**4h**): Procedure C; Oil. – ^{1}H NMR (neat, TMS): δ = 2.2 (s, 3H), 3.8 (s, 2H), 5.0 (s, 2H), 6.3–7.4 (m, 9H). – ^{13}C NMR (neat, TMS): δ = 20.6 (q), 53.7 (t), 109.5 (d), 112.4 (d), 113.4 (d), 117.1 (d), 118.1 (d), 128.2 (d), 137.3 (d), 145.5 (s), 145.7 (s). – IR (film): 690 cm^{-1}, 750, 770, 1500, 1600, 2870, 2930, 3060, 3420.

$C_{14}H_{16}N_2$ (212.3) Calcd. C 79.20 H 7.60 N 13.20
Found C 79.05 H 7.71 N 12.83

(4-Methylphenylamino)(phenylamino)methane (**4i**): Procedure C; Oil. – ^{1}H NMR (CCl_4, TMS): δ = 2.2 (s, 3H), 4.0 (s, 2H), 4.6 (s, 2H), 6.3–7.2 (m, 9H). – ^{13}C NMR (neat, TMS): δ = 20.3 (q), 54.8 (t), 113.6 (d), 113.9 (d), 117.3 (d), 127.2 (s), 129.0 (d), 129.1 (d), 144.2 (s), 146.6 (s). – IR (KBr): 700 cm^{-1}, 760, 810, 1380, 1550, 1600, 2900, 3030, 3390, 3510.

$C_{14}H_{16}N_2$ (212.3) Calcd. C 79.20 H 7.60 N 13.20
Found C 78.95 H 7.58 N 13.35

CAS Registry Numbers

1a: 88933-19-1 / **1b**: 88919-94-2 / **1c**: 88919-92-0 / **1d**: 88919-93-1 / **1e**: 115163-00-3 / **1f**: 88919-96-4 / **3a**: 62-53-3 / **3b**: 106-49-0 / **3c**: 95-53-4 / **3d**: 108-44-1 / **3e**: 90-04-0 / **3f**: 94-70-2 / **4a**: 622-14-0 / **4b**: 17450-22-5 / **4c**: 54560-77-9 / **4d**: 115162-95-3 / **4e**: 39809-85-3 / **4f**: 115162-96-4 / **4g**: 115162-97-5 / **4h**: 115162-98-6 / **4i**: 115162-99-7

[1] M. M. Sprung, *Chem. Rev.* **26** (1940) 297.
[2] J. F. Walker, in *Formaldehyde*, 3rd ed. (P. C. Krieger, Ed.), Huntington N.Y., USA, 1975.
[3] E. C. Wagner, *J. Org. Chem.* **19** (1954) 1862.
[4] P. J. McLaughlin, E. C. Wagner, *J. Am. Chem. Soc.* **66** (1944) 251.
[5] W. C. Hunt, E. C. Wagner, *J. Org. Chem.* **16** (1951) 1792.
[6] E. C. Wagner, *J. Org. Chem.* **2** (1937) 157.
[7] J. R. Feldman, E. C. Wagner, *J. Org. Chem.* **7** (1948) 31.
[8] E. C. Wagner, *J. Am. Chem. Soc.* **54** (1932) 660.
[9] C. K. Ingold, H. A. Piggott, *J. Chem. Soc.* **123** (1923) 2745.
[10] L. Pratesi, *Gazz. Chim. Ital.* **14** (1884) 351.
[11] C. Eberhardt, A. Welter, *Ber. Dtsch. Chem. Ges.* **27** (1894) 1804.
[12] C. A. Bischoff, F. Reinfeld, *Ber. Dtsch. Chem. Ges.* **36** (1903) 41.
[13] M. Wakae, K. Konishi, *Osaka Furitsu Kogyo-Shoreikan Hokoku* **29** (1963) 47 [*Chem. Abstr.* **59** (1963) 6280].
[14] H. Ulrich, R. Richter, P. J. Whitman, A. A. R. Sayigh, *J. Org. Chem.* **39** (1974) 2897.
[15] [15a] H. J. Shine, D.-H. Bae, J. Lazar, F. C. Maseles, *Org. Mass. Spectrom.* **16** (1981) 191. – [15b] D.-H. Bae, H. J. Shine, *J. Org. Chem.* **45** (1980) 4448.
[16] [16a] A. Chimirri, S. Grasso, P. Monforte, G. Fenech, *Farmaco* **XXXIX** (1984) 797. – [16b] K. Matsumoto, S. Hashimoto, Y. Ikemi, S. Otani, *Heterocycles* **22** (1984) 1417.
[17] J. Barluenga, A. M. Bayón, P. J. Campos, G. Asensio, E. González-Núñez, Y. Molina, *J. Chem. Soc., Perkin Trans. 1*, in press.
[18] J. Barluenga, A. M. Bayón, G. Asensio, *J. Chem. Soc., Chem. Commun.*, **1983** 1109.
[19] J. Barluenga, A. M. Bayón, G. Asensio, *J. Chem. Soc., Chem. Commun.* **1984** 1334.

[89/88]