# A Simple Two-Step Synthesis of Diphenylmethyl Esters of 2-Oxo-1-azetidineacetic Acids

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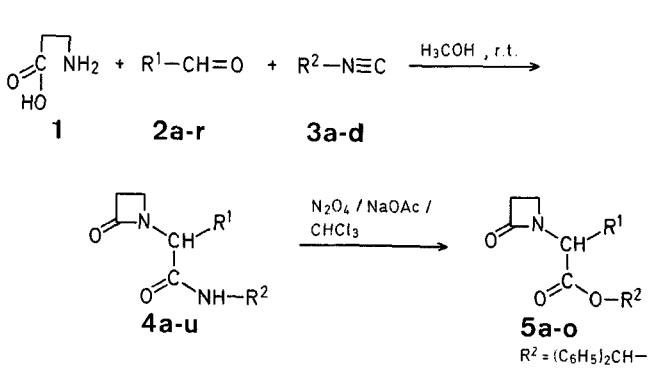
Nocardicin A, isolated in 1975, is the first monocyclic β-lactam with a potentially useful antibacterial activity[1,2]. In common with its seven minor congeners, nocardicin B–G[3], it features a 2-oxo-1-azetidineacetic acid nucleus. The synthesis of this β-lactam nucleus and of related structures merits attention since it could provide access to novel and structurally simple analogs of the nocardicins.

Several syntheses have recently been published[4-8] which permit the preparation of certain specific 2-oxo-1-azetidineacetic acids. None of these methods offers broad scope and preparative simplicity. The shortest and possibly the most efficient access to amides of the target compounds is given by the 4-component-condensation (4CC)[9]. Starting from β-amino acids **1**, aldehydes **2** (or ketones), and isocyanides **3**, this method leads in a single step to 2-oxo-1-azetidineacetamides **4** (Scheme **A**).

However, since conversion of amides into esters or free acids is difficult in the presence of a β-lactam ring, it is not surprising that this method has found little use in β-lactam chemistry[10-15]. The only successful further transformation of 4CC products is a conversion into methyl esters via imino chlorides claimed in a recent patent[14]. Since, in the presence of β-lactam rings, the cleavage of methyl esters is not trivial, this transformation does not improve substantially the practical utility of the 4CC.

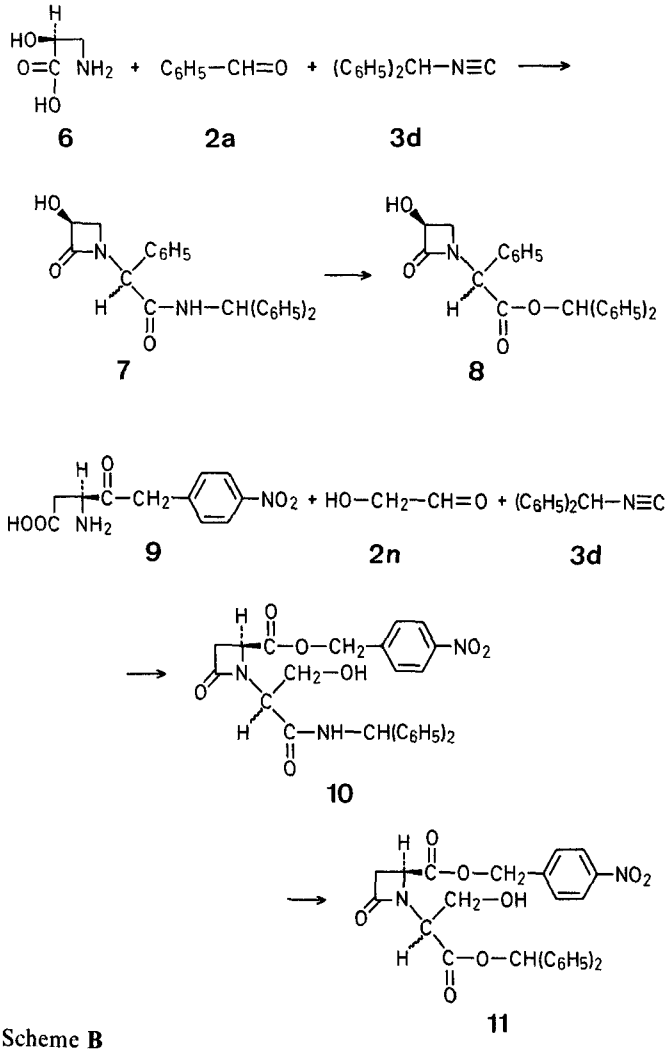
We now describe the convenient and high-yield conversion of *N*-(diphenylmethyl)-amides **4** obtained by 4CC with β-alanine (**1**), aldehydes **2**, and diphenylmethyl isocyanide (**3d**) into the corresponding esters **5** which are easily cleaved by a variety of methods into free acids. The crucial step of the sequence consists in formation of *N*-nitrosoamides from the 4CC products followed by thermal decomposition into esters.




Schema **A**

found to be exceptionally good substrates for the transformation into esters **5**. Nitrosation occurs fast and in high yield at 0 °C in various solvents and with various nitrosating agents. We regard dinitrogen tetroxide in chloroform as the reagent of choice and prefer it to nitrosyl chloride which occasionally gave rise to side reactions, i.e. chlorination of aromatic rings. *N*-Diphenylmethyl-nitrosoamides decompose into diphenylmethyl esters spontaneously and quantitatively between 0 °C and room temperature. *N*-Nitrosoamides have therefore not to be isolated and the whole operation is fast, safe and can be carried out in one-pot.

Other amides (i.e. **4s-u**) were found unsuitable because either nitrosation took place sluggishly or cleavage of the *N*-nitrosoamides required high temperatures. In particular, *N*-*t*-butylamides, in accordance with literature reports[18], gave no esters at all. Attemps to convert *N*-diphenylmethyl amides obtained by 4CC from β-amino acids and ketones into the corresponding esters also failed because these amides could not be nitrosated, probably for steric reasons.




Scheme **B**

Although the mechanism of the decomposition of *N*-nitrosoamides has been extensively studied[16], the reaction has only rarely been used for preparative purposes (i.e. Ref.[17]). In order to be useful in β-lactam chemistry, it is essential that the esters obtained from the amides can be converted without difficulty into free acids, e.g. *t*-butyl or diphenylmethyl esters. It was known that diphenylmethyl substituted *N*-nitrosoamides are cleaved into esters with particular ease[16]. It therefore appeared worthwhile to study the reaction sequence using diphenylmethyl isocyanide (**3d**) in the 4CC-step. As it turned out, diphenylmethyl isocyanide (**3d**) is a most satisfactory isocyanide component for 4CC. It is easily prepared, crystalline and odorless, and gives condensation products in much the same yields as other isocyanides (Table 1). The ensuing amides **4** were

The generality of the procedure is illustrated by the variety of products listed in Table 2 and by the preparation of compounds **8** and **11** (Scheme **B**). Yields are frequently moderate only. However, this disadvantage is compensated by ease of operation and cheapness of reactants and reagents. The following aldehydes and β-amino acids could not be used successfully as starting materials showing certain limitations of our method:

- α,β-unsaturated aliphatic aldehydes: they are poor substrates for 4CC.
- α-ketoaldehydes: although these aldehydes are excellent substrates for 4CC, the ensuing diphenylmethyl-amides contain

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enolizable β-keto groups which are easily *C*-nitrosated and, therefore, prevent clean transformation into esters (i.e. **4q** and **4r** in Table 2).

— $N^2$-benzyloxycarbonyl- and $N^2$,$N^2$-phthaloyl-2,3-diaminopropanoic acid: these amino acids, in contrast to **6** and **9**, invariably failed to undergo a 4CC with aldehydes and diphenylmethyl isocyanide **(3d)**.

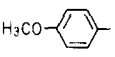
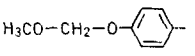
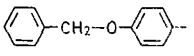
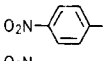
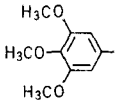
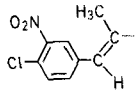
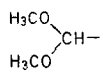
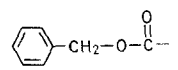
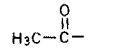
Despite these limitations, the present method appears to be a useful and convenient route to a large variety of 2-oxo-1-azetidineacetic acid diphenylmethyl esters. Some of the products are amenable to further transformations and may serve as intermediates for the synthesis of novel analogs of β-lactam antibiotics. A synthesis of nocardicins using the reaction sequence will be described in a separate paper[20].

**Table 1.** 4-Component-Condensation with Different Isocyanides **(1 + 2b + 3→4)**[a]

| Aldehyde **2** | Isocyanide **3** | | β-Lactam **4** | | | | |
|---|---|---|---|---|---|---|---|
| $R^1$ | No. | $R^2$ | No. | Yield [%][b] | m.p. [°C] | Molecular formula[c] | I.R. (KBr) ν [cm$^{-1}$] |
| 4-$H_3CO$—$C_6H_4$ | **3a** | *n*-$C_4H_9$ | **4s** | 50 | oil | $C_{16}H_{22}N_2O_3$ (290.4) | 1750 |
| 4-$H_3CO$—$C_6H_4$ | **3b** | *t*-$C_4H_9$ | **4t** | 51 | 111–112° | $C_{16}H_{22}N_2O_3$ (290.4) | 1744 |
| 4-$H_3CO$—$C_6H_4$ | **3c** | *c*-$C_6H_{11}$ | **4u** | 51 | 107–109° | $C_{18}H_{24}N_2O_3$ (316.4) | 1745 |
| 4-$H_3CO$—$C_6H_4$ | **3d** | $(C_6H_5)_2CH$ | **4b** | 50 | 163–167° | $C_{25}H_{24}N_2O_3$ (400.5) | 1730 |

[a] Standard reaction conditions: see general procedure.
[b] Yields of isolated pure products.
[c] Satisfactory microanalyses obtained: C ± 0.12, H ± 0.14, N ± 0.18.

**Table 2.** 4-CC with β-Alanine, Aldehydes, and Diphenylmethyl Isocyanide **(1 + 2 + 3d→4)** and conversion to Diphenylmethyl Esters **5**

| Aldehyde **2** | | β-Lactam **4** | | | | β-Lactam Ester **5** | | | |
|---|---|---|---|---|---|---|---|---|---|
| No. | $R^1$ | Yield [%][a] | m.p. [°C] | Molecular formula[b] | I.R. (KBr) ν [cm$^{-1}$] | Yield [%][a] | m.p. [°C] | Molecular formula[b] | I.R. (KBr) ν [cm$^{-1}$] |
| **a** |  | 49 | 190–191° | $C_{24}H_{22}N_2O_2$ (370.5) | 1733 | 81 | 105–106° | $C_{24}H_{21}NO_3$ (371.4) | 1760, 1733 |
| **b** |  | 50 | 163–167° | $C_{25}H_{24}N_2O_3$ (400.5) | 1730 | 68 | 87–88° | $C_{25}H_{23}NO_4$ (401.5) | 1766, 1738 |
| **c** |  | 47 | 145–146° | $C_{26}H_{26}N_2O_4$ (430.5) | 1740 | 83 | oil | $C_{26}H_{25}NO_5$ (431.5) | 1760, 1740[c] |
| **d** |  | 36 | 151–153° | $C_{31}H_{28}N_2O_3$ (476.6) | 1737 | 54 | 70–72° | $C_{31}H_{27}NO_4$ (477.6) | 1748, 1729 |
| **e** |  | 35 | 177–178° | $C_{24}H_{21}ClN_2O_2$ (404.9) | 1744 | 61 | 173–175° | $C_{24}H_{20}ClNO_3$ (405.9) | 1750, 1740 |
| **f** |  | 31 | 202–204° | $C_{24}H_{21}N_3O_4$ (415.5) | 1745 | 46 | 91–92° | $C_{24}H_{20}N_2O_5$ (416.4) | 1751, 1740 |
| **g** |  | 31 | 189–190° | $C_{24}H_{21}N_3O_4$ (415.5) | 1740 | 83 | 143–144° | $C_{24}H_{20}N_2O_5$ (416.4) | 1748, 1735 |
| **h** |  | 58 | 153–155° | $C_{27}H_{28}N_2O_5$ (460.5) | 1750 | 59 | 87–88° | $C_{27}H_{27}NO_6$ (461.5) | 1748, 1740 |
| **i** |  | 27 | 177–178° | $C_{22}H_{20}N_2O_3$ (360.4) | 1745 | 44 | 98–100° | $C_{22}H_{19}NO_4$ (361.4) | 1759 |
| **k** |  | 29 | 186–187° | $C_{27}H_{24}ClN_3O_4$ (480.0) | 1726 | 66 | 78–80° | $C_{27}H_{23}ClN_2O_5$ (490.9) | 1758, 1726 |
| **l** | H | 20[d] | 148–149° | $C_{18}H_{18}N_2O_2$ (294.4) | 1759 | 67 | 71–72° | $C_{18}H_{17}NO_3$ (295.3) | 1759, 1739 |
| **m** | *i*-$C_3H_7$ | 54 | 163–164° | $C_{21}H_{24}N_2O_2$ (336.4) | 1743 | 90 | oil | $C_{21}H_{23}NO_3$ (337.4) | 1750, 1740[c] |
| **n** | HO—$CH_2$ | 48 | 159–160° | $C_{19}H_{20}N_2O_3$ (324.4) | 1742 | 64 | 99–100° | $C_{19}H_{19}NO_4$ (325.4) | 1737, 1721 |
| **o** | Cl—$CH_2$ | 30[d] | 157–158° | $C_{19}H_{19}ClN_2O_2$ (342.8) | 1728 | 80 | oil | $C_{19}H_{18}ClNO_3$ (343.8) | 1740[c] |
| **p** |  | 48 | 164–165° | $C_{21}H_{24}N_2O_4$ (368.4) | 1752 | —[e] | — | — | — |
| **q** |  | 20 | 134–135° | $C_{26}H_{24}N_2O_4$ (428.5) | 1768, 1740 | 0 | — | — | — |
| **r** |  | 33[d] | 154–155° | $C_{20}H_{20}N_2O_3$ (336.4) | 1740 | 0 | — | — | — |

[a] Yield of pure, isolated product.
[b] Satisfactory microanalyses obtained for all solid products: C ± 0.39, H ± 0.23, N ± 0.29, Cl ± 0.09.
[c] Film.
[d] Aqueous solution used.
[e] Experiment was not carried out.

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**Diphenylmethyl Isocyanide (3d):**
A solution of thionyl chloride (73.3 ml, 1.0 mol) in dimethylformamide (330 ml) is added to a stirred solution of *N*-(diphenylmethyl)-formamide[21] (211 g, 1.0 mol) in dimethylformamide (2 l) at −55 °C under argon. The mixture is warmed to −35 °C within 30 min. Sodium carbonate (212 g, 2.0 mol) is added at −70 °C, the cooling bath is removed, and stirring is continued for 3.5 h. The mixture is poured into well-stirred ice/water (10 l), the precipitated isocyanide is filtered off and washed with water; yield: 153 g (79%); m.p. 49–51 °C (Ref.[19], m.p. 35–36 °C); b.p. 104–107 °C/0.05 torr.

| | | | | |
|---|---|---|---|---|
| $C_{14}H_{11}N$ | calc. | C 87.02 | H 5.74 | N 7.25 |
| (193.3) | found | 86.77 | 5.79 | 7.33 |

I.R. (KBr): $\nu = 2142$ cm$^{-1}$.

***N*-(Diphenylmethyl)-2-oxo-1-azetidineacetamides 4; General Procedure:**
β-Alanine (**1**; 8.9 g, 0.1 mol), aldehyde **2** (0.1 mol), and diphenylmethyl isocyanide (**3d**; 19.3 g, 0.1 mol) are stirred for 1–3 days in 96% methanol (200 ml) at 25 °C. The reaction is followed by T.L.C. on silica gel using ethyl acetate/cyclohexane (2:1) and stopped when the isocyanide is consumed. The mixture is evaporated and chromatographed through a short column of silica gel using ethyl acetate/cyclohexane (2:1) as eluent, affording the product in sufficient purity for crystallization from the same solvent mixture.

**Diphenylmethyl 2-oxo-1-azetidineacetates 5; General Procedure:**
Dinitrogen tetroxide (9.3 ml, 0.15 mol) in dry chloroform (50 ml) is added to a stirred suspension of sodium acetate (16.4 g, 0.2 mol) in dry chloroform (120 ml) at 0 °C. A solution of the amide **4** (0.05 mol) in dry chloroform (50–200 ml, depending on the solubility) is added to the yellow suspension over 15 min. After 1 h at 0 °C, the cooling bath is removed and the stirring is continued for 1–3 h [the reaction can be followed by T.L.C. on silica gel using ethyl acetate/cyclohexane (1:4)]. A solution of sodium hydrogen carbonate (16.8 g, 0.2 mol) in water (200 ml) is added, the chloroform is evaporated in vacuo, and the remaining water phase is extracted with ethyl acetate (2 × 200 ml). The extract is washed with water, dried with sodium sulfate, and evaporated to dryness. Normally the product can be crystallized directly from ethyl acetate/cyclohexane. In a few cases chromatography through a short column of silica gel with ethyl acetate/cyclohexane (1:4) is advisable.

***N*-(Diphenylmethyl)-3-hydroxy-2-oxo-α-phenyl-1-azetidineacetamide (7):**
A mixture of isoserine (**6**; 52.5 g, 0.5 mol), benzaldehyde (**2a**; 53 g, 0.5 mol), and diphenylmethyl isocyanide (**3d**; 96.5 g, 0.5 mol) is refluxed for 2 days under argon in 90% aqueous methanol (750 ml). After evaporation of the solvent in vacuo, the residue is taken up in dichloromethane (500 ml). Unreacted isoserine (16 g, 0.15 mol) remains insoluble and is removed by filtration. The filtrate is evaporated and the residue dissolved in toluene (2 × 500 ml) and evaporated again. The residue is crystallized from hot toluene (1 l); yield: 56 g (44%, based on consumed isoserine). An analytical sample is recrystallized from ethyl acetate/cyclohexane; m.p. 185–189 °C (mixture of diastereomers ≈ 1:1).

| | | | | |
|---|---|---|---|---|
| $C_{24}H_{22}N_2O_3$ | calc. | C 74.59 | H 5.74 | N 7.25 |
| (386.5) | found | 74.70 | 5.62 | 7.25 |

**Diphenylmethyl 3-Hydroxy-2-oxo-α-phenyl-1-azetidineacetate (8):**
Compound **7** is converted to the diphenylmethyl ester **8** as described in the general procedure; yield: 71% (mixture of diastereomers ≈ 1:1); m.p. 126–127 °C (from ethyl acetate/cyclohexane).

| | | | | |
|---|---|---|---|---|
| $C_{24}H_{21}NO_4$ | calc. | C 74.40 | H 5.46 | N 3.62 |
| (387.4) | found | 74.36 | 5.47 | 3.58 |

I.R. (KBr): $\nu = 1748$ cm$^{-1}$.

***p*-Nitrobenzyl (*S*)-1-{1-[(Diphenylmethyl)-aminocarbonyl]-2-hydroxyethyl}-4-oxo-2-azetidinecarboxylate (10):**
A mixture of L-aspartic acid α-*p*-nitrobenzyl ester (**9**; 26.8 g, 0.1 mol), hydroxyacetaldehyde (**2n**; 6.0 g, 0.1 mol), and diphenylmethyl isocyanide (**3d**; 19.3 g, 0.1 mol) is stirred for 6 h in 96% methanol (300 ml) at 25 °C. After filtration over Celite and evaporation, a dark red oil (50 g) is obtained, which is chromatographed on silica gel (1.5 kg, Merck, Kieselgel 60, 0.04–0.063 mm; Jobin Yvon Chromatospac Prep 100) using ethyl acetate/cyclohexane (2:1); yield (isomer I): 16 g (32%); yield (isomer II): 8.4 g (17%). Both isomers are amorphous solids; total yield of **10**: 49%.

*Isomer I:* I.R. (KBr): $\nu = 1755$; 1676 cm$^{-1}$.

$^1$H-N.M.R. ($CDCl_3$): $\delta = 8.17$ (d, 2H, $J = 9$ Hz); 7.45 (d, 2H, $J = 9$ Hz); 7.25 (s, 10H); 6.14 (d, 1H, $J = 8$ Hz); 5.22 (s, 2H); 4.54 (dd, 1H, $J = 5$ Hz, $J = 3$ Hz); 4.38 (t, 1H, $J = 4.5$ Hz); 3.9 (m, 3H); 3.22 (dd, 1H, $J = 14$ Hz, $J = 5$ Hz); 2.93 ppm (dd, 1H, $J = 14$ Hz, $J = 3$ Hz).

*Isomer II:* I.R. (KBr): $\nu = 1755$; 1676 cm$^{-1}$.

$^1$H-N.M.R. ($CDCl_3$): $\delta = 8.15$ (d, 2H, $J = 9$ Hz); 7.41 (d, 2H, $J = 9$ Hz); 7.26 (s, 5H); 7.22 (s, 5H); 6.13 (d, 1H, $J = 8$ Hz); 5.21 (d, 1H, $J = 13$ Hz); 5.09 (d, 1H, $J = 13$ Hz); 4.49 (dd, 1H, $J = 5$ Hz, $J = 3$ Hz); 3.8–4.3 (m, 4H); 3.27 (dd, 1H, $J = 15$ Hz, $J = 5$ Hz); 2.96 ppm (dd, 1H, $J = 15$ Hz, $J = 3$ Hz).

**Diphenylmethyl α-(Hydroxymethyl)-2-[(*p*-nitrobenzyloxy)carbonyl]-4-oxo-1-azetidineacetate (11):**
Isomer I of **10** is converted into the diphenylmethyl ester **11** as described in the general procedure; yield: 73% (amorphous solid).

I.R. (film): $\nu = 1758$ cm$^{-1}$ (broad).

$^1$H-N.M.R. ($CDCl_3$): $\delta = 8.19$ (d, 2H, $J = 9$ Hz); 7.46 (d, 2H, $J = 9$ Hz); 7.31 (s, 10H; 6.86 (s, 1H); 5.19 (s, 2H); 4.69 (dd, 1H, $J = 5$ Hz, $J = 3.5$ Hz); 4.55 (t, 1H, $J = 3$ Hz); 4.0 (m, 2H); 3.31 (dd, 1H, $J = 14$ Hz, $J = 5$ Hz); 3.04 ppm (dd, 1H, $J = 14$ Hz, $J = 3.5$ Hz).

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[1] H. Aoki et al., *J. Antibiotics* **29**, 492 (1976).
[2] M. Hashimoto, T. Komori, T. Kamiya, *J. Am. Chem. Soc.* **98**, 3023 (1976).
[3] J. Hosoda et al., *Agric. Biol. Chem.* **41**, 2013 (1977).
[4] D. Reuschling, H. Pietsch, A. Linkies, *Tetrahedron Lett.* **1978**, 615.
[5] T. Kamiya et al., *Tetrahedron Lett.* **1978**, 5119.
[6] H. H. Wasserman, D. J. Hlasta, *J. Am. Chem. Soc.* **100**, 6780 (1978).
[7] H. H. Wasserman, D. J. Hlasta, A. W. Tremper, J. S. Wu, *Tetrahedron Lett.* **1979**, 549.
[8] H. H. Wasserman, A. W. Tremper, J. S. Wu, *Tetrahedron Lett.* **1979**, 1089.
[9] I. Ugi, *Angew. Chem.* **74**, 9 (1962).
[10] I. Ugi, C. Steinbrückner, *Chem. Ber.* **94**, 2802 (1961).
[11] I. Ugi, E. Wischhöfer, *Chem. Ber.* **95**, 136 (1962).
[12] A. Schutz, I. Ugi, *J. Chem. Research (S)* **1979**, 157.
[13] A. Schutz, I. Ugi, H.-J. Kabbe, *Z. Naturforsch.* [b] **34**, 1303 (1979).
[14] T. Hirata, A. Sato, N. Nakamizo, *German Patent (DOS)* 2842466 (1979), Kyowa Hakko Kogyo Co. Ltd.; *C.A.* **91**, 39300 (1979).
[15] T. Ishimaru, M. Hatanaka, N. Noguchi, *Japan. Patent* 125.651-79 (1979) Sangyo Kagaku Kenkyu Kyokai, *C.A.* **92**, 146583 (1980).
[16] E. H. White, D. J. Woodcock, *The Chemistry of the Amino Group*, S. Patai, Ed., Interscience Publishers, London, New York, Sydney, Toronto, 1968, p. 440.
[17] F. P. Schmidtchen, P. Rauschenbach, H. Simon, *Z. Naturforsch.* [b] **32**, 98 (1977).
[18] E. H. White, *J. Am. Chem. Soc.* **77**, 6014 (1955).
[19] I. Ugi et al., *Angew. Chem.* **77**, 492 (1965); *Angew. Chem. Int. Ed. Engl.* **4**, 472 (1965).
[20] H. P. Isenring, W. Hofheinz, *Helv. Chim. Acta*, in press (1981).
[21] V. J. Webers, W. F. Bruce, *J. Am. Chem. Soc.* **70**, 1422 (1948).


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