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PREPARATION OF 1-FERROCENYL-2-METHYL-1-PROPYLAMINE, A HIGHLY EFFECTIVE CHIRAL TEMPLATE IN ASYMMETRICALLY INDUCED SYNTHESIS

GERHARD EBERLE, INGER LAGERLUND, IVAR UGI* and REINHARD URBAN
Institut für Organische Chemie, Technischen Universität, D-8000 München 2, Arcisstrasse 21, West Germany

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Abstract—The 1-ferrocenyl-2-methyl-1-propylamine (**2a**) is the most effective chiral template in asymmetrically induced peptide synthesis by stereoselective four component condensation (4CC). Two routes for the synthesis of this amine via its N,N-dimethyl derivative (**12a**) are described. One route involves the conversion of **12a** into the corresponding azide **14a** by treatment with methyl iodide/sodium azide in diglyme/water and subsequent reduction of the azide. The preferred other route consists of treating **12a** with thioglycolic acid/formic acid to yield the carboxymethylmercapto derivative **9a** and transformation of the latter into **2a** with aqueous ammonia/ammonium chloride/mercuric chloride. Some related reactions are also discussed.

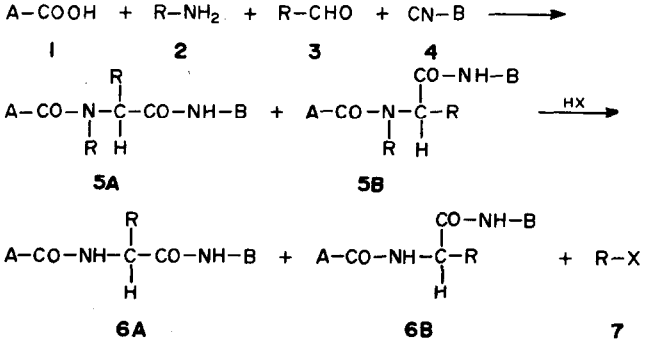
Zusammenfassung—1-Ferrocenyl-2-methyl-1-propylamin (**2a**) ist bis jetzt das wirksamste chirale Reagens in der asymmetrisch induzierten Peptidsynthese mittels Vierkomponentenkondensation (400). Für die Synthese des Amins **2a** über sein N,N-Dimethyl-Derivat **12a** werden zwei Wege beschrieben. Der eine geht von der Umwandlung von **12a** in das entsprechende Azid **14a** durch Behandeln mit Methyljodid/Natriumazid in Diglyme/Wasser aus mit nachfolgender Reduktion des Azids. Beim bevorzugten zweiten Weg behandelt man **12a** mit Thioglycolsäure/Ameisensäure und erhält das Carboxymethylmercapto-Derivat **9a**. Dieses wird mit wässrigen Ammoniak/Ammoniumchlorid/Quecksilberchlorid in **2a** übergeführt. Einige ähnliche Reaktionen werden ebenso diskutiert.

In the synthesis of peptide derivatives by stereoselective four component condensation (4CC)[1] according to Scheme 1 it is of critical importance to use a suitable amine component (**2**). The latter must be chiral and have strong asymmetric inducing power. The group R* of the amine (**2**) must also be replacable by hydrogen,[2] *i.e.* the conversion **5**→**6** must occur, under conditions which do not destroy or racemize peptide derivatives. Further, it is desirable that the rates of the processs **5A**→**6A** and **5B**→**6B** respectively differ substantially. One of the 4CC products (**5A** or **5B**) can then be selectively removed from the isomer mixture (**5**) by partial cleavage.[3] Since the chiral amines (**2**) generally are difficult to prepare, peptide synthesis by stereoselective 4CC will only be practically useful if the by-product (**7**) of the cleavage step **5**→**6** can be reconverted without racemization into the original amine component (**2a**)[3b,4]

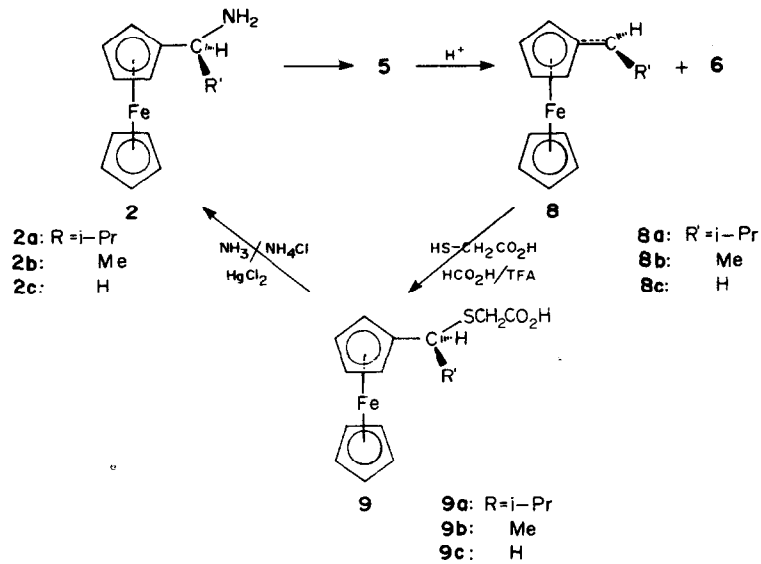
It was found that the amine **2a** fulfills the above-mentioned requirements. Under favorable conditions the 4CC of **2a** leads to a stereoisomer ratio of 200:1 of products **5**.[3a,b] These are cleaved by acidolysis, due to the stability of the α-ferrocenylcarbenium ion (**8a**).[5] This ionic intermediate is also responsible for the retention of configuration in S_N1 type nucleophilic substitutions[5] such as **5**→**9a** and **9a**→**2a**. (Scheme 2). The rates of the reactions **5A**→**6A**, and **5B**→**6B**, respectively have been observed to differ by a factor of ≤230.[3b] In the present paper we wish to report on the synthesis of the amine **2a** and some related reactions.

RESULTS

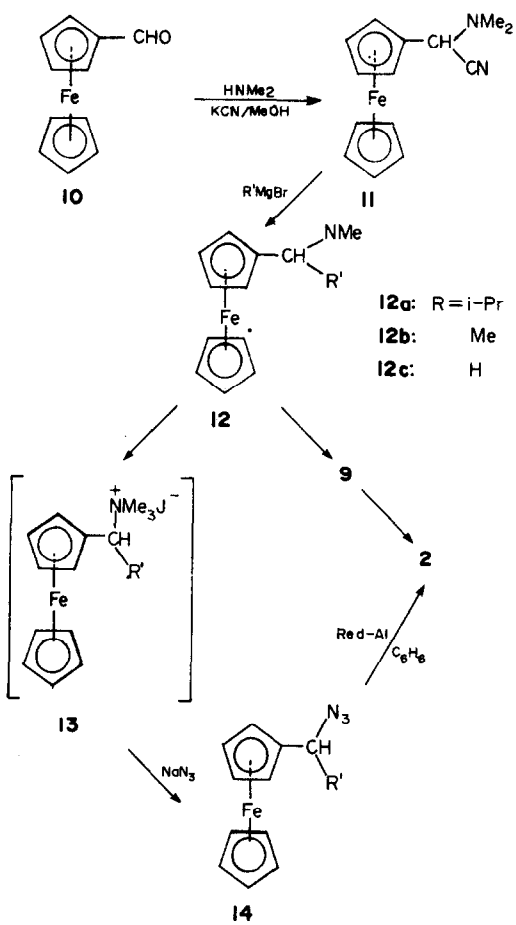
The chiral primary amine **2a** is prepared according to Scheme 3. In the synthesis of optically active **2a** the intermediate **12a** plays a key role, as hitherto the resolution into enantiomers has succeeded only at this stage. The racemic tertiary amine **12a** is best obtained from **10** via **11** and is resolved by crystallization of the tartrates from water.[6]



Scheme 1.



Scheme 2.



Scheme 3.

†However, in this case complete racemisation took place during the reaction, probably due to elimination-addition reactions.

Optically active **2a** can be prepared from the resolved **12a** by two different routes, namely via **9a** or via **13a** and **14a**.[6] The route via **9a** is preferable, particularly for large scale preparation, as this route, in contrast to the one via **14a**, does not require chromatography at any stage and also shows more reproducible yields.

The absolute configuration of optically active **2a** follows from the known absolute configuration of **12a** through the retentive nature of the reactions **12a** → **2a**.[5,6] Furthermore, the configuration of (*S*)-**2a** and (*S*)-**12a** have been correlated by methylation of (*S*)-**2a** with formaldehyde/sodium borohydride in analogy to Ref. 7. The attempt to transform other α-dimethylaminoalkylferrocenes as **12b** and **12c** into the corresponding thioglycolic acid derivatives (**9b** and **9c**) did not work satisfactorily. However, **9b** is formed in good yield from the quaternary ammonium salt **13b** by treatment with thioglycolic acid/formic acid.† The thioglycolic acid derivatives **9a** and **9b** can also be prepared in good yields from the corresponding α-ferrocenylalkyl alcohols[4,8] and are obtained by the cleavage of the 4CC products **5**.[3b,4]

The ammonium salt **13c** reacts neither with thioglycolic acid, nor with sodium azide in a corresponding manner.

DISCUSSION

In the synthesis of **2a** the route via **9a** is superior to that via **13a** and **14a** because of the pronounced tendency of the intermediate **13a** to eliminate trimethylammonium iodide to form 1-ferrocenyl-2-methylpropene **15**. The salt **13a** cannot, in contrast to the analogs **13b** and **13c**, be prepared by customary methods, due to its instability. This fact presumably accounts for the variations in yield when **14a** is prepared from **12a**. The yield of **9a** from the treatment of **12a** with thioglycolic acid/formic acid depends on reaction time and temperature according to Table 1. These data indicate that **9a**, once it is formed, is relatively stable, and that the losses in yield are due to side reactions of the tertiary amine **12a**. Since **15**, which is formed from **9a** by elimination, would add thioglycolic acid under the reaction conditions, this process would not lower the overall yield of **9a** but would lead to a partially racemized product. It is noteworthy that optic-

Table 1. Yield dependence of **9a** from the reaction of **12a** with thioglycolic acid/formic acid on reaction time and temperature.

Time (days)	Temp. (°C)	Isolated yield of **9a** (%)	Yield of recovered **12a** (%)
4	20	60	23†
6	20	80	7
12	20	78‡	—
17	5	35	25

†With optically active material the optical rotation is unchanged in the recovered amine.
‡Highly impured with difficultly separable impurities.

ally active **9a** undergoes some racemization on prolonged heating in solution. The transformation of **9a** into **2a** proceeds by treatment with mercuric chloride and ammonium chloride in supersaturated aqueous ammon.[4b] The mercuric chloride cannot be successfully replace(by mercuric acetate, copper(I) chloride, copper(II) tetrammin sulphate, cadmium chloride or bromide. It is also not possible to substitute the aqueous ammonia for liquid ammonia or ammonia in isopropanol, diethyl ether or THF. The presence of water, leading to α-ferrocenylisobutyl alcohol as a side product, is presumably necessary for solvation reasons for the formation of **8a** from **9a** under the influence of the mercuric ion.

EXPERIMENTAL

All m.ps are uncorrected. ^{1}HNMR spectra were recorded using a Varian A60 instrument. The chemical shifts are given as δ-values in ppm relative to TMS as internal standard. IR spectra were recorded using a Perkin–Elmer Model 521 spectrophotometer. Optical rotations were measured with a polar-meter Roussel–Jouan Model 71 in an 0.2 dm cell. Elemental analyses were carried out by the Organisch-Chemischen Institut der Technischen Universität München.

(1-Ferrocenyl-2-methylpropyl)dimethylamine (**12a**)[6]

A Grignard reagent was prepared by reacting Mg (5.8 g, 240 mmol) with 2-bromopropane (28.4 g, 240 mmol) in dry diethyl ether (100 ml). A soln of **11**[6] (32.2 g, 120 mmol) in diethyl ether (250 ml) was added drop-wise, so that the mixture was kept refluxing. The mixture was refluxed for 1 more hr and then hydrolyzed by adding sat. NH_4Cl aq. The aqueous phase was extracted with diethyl ether, whereupon the combined ethereal extracts were extracted with a 3% aqueous L-tartaric acid soln. The aqueous phase was left overnight, during which time orange crystals of amine tartrate precipitated. Those were filtered off and washed several times with diethyl ether. From this salt an amine **12a** could be set free with an optical rotation of $[\alpha]_D^{20} = -150°$ (c = 1, benzene), yield 13.0 g (38%).

The filtrate was washed with diethyl ether and made alkaline with 1N NaOH, then extracted with diethyl ether. The ethereal phase was washed with water, dried over Na_2SO_4, and the solvent was evaporated *in vacuo* at room temp. The residual amine **12a** (19.5 g, 57%) has an optical rotation of $[\alpha]_D^{20} = +104°$ (c = 1, benzene). The total yield of partially resolved amine **12a** is thus 95%, b.p. 112° 0.1 mm Hg. The further resolution of **12a** was carried out using aqueous L- and D-tartaric acid solns respectively according to Ref. 6 to give:

(*R*)-**12a**: $[\alpha]_D^{20} = -191.5°$, $[\alpha]_{546}^{20} = -319.8°$ (c = 1, benzene)

(*S*)-**12a**: $[\alpha]_D^{20} = +192.8°$, $[\alpha]_{546}^{20} = +320.8°$ (c = 1, benzene).

(R)-1-*Ferrocenyl-2-methyl-1-propyl azide* (R)-**14a** was prepared from (*R*)-**12a** by treatment with MeI/sodium azide in diglyme/water according to Ref. 6. The reaction time was 65 hr, yield 60–82%, b.p. 79° 0.1 mm Hg. $[\alpha]_D^{20} = -111.3°$ $[\alpha]_{546}^{20} = -168.5°$ (c = 1, benzene). (Found: C, 59.4: H, 5.8; N, 14.8. Calc. for $C_{14}H_{17}N_3Fe$: C, 59.4; H, 6.1; N, 14.8%), IR(film): 2100 cm^{-1} (−N_3);, ^{1}H NMR ($CDCl_3$): 0.85 (dd, 6H, $CH(CH_3)_2$), 1.60 (m, 1H, $CH(CH_3)_2$), 4.05 (d, 1H, CH–$CH(CH_3)_2$), 4.21 (s and m, 9H, C_5H_5 and C_5H_4).

(S)-1-*Ferrocenyl-2-methyl-1-propyl azide* (S)-**14a** was prepared analogously from (*S*)-**12a**. $[\alpha]_D^{20} = +111.9°$, $[\alpha]_{546}^{20} = +169.3°$ (c = 1, benzene).

(R)-1-*Ferrocenyl-2-methyl-1-propylamine* (R)-**2a** was prepared by reduction of (*R*)-**14a** with Red-Al ($NaH_2Al(OCH_2CH_2OCH_3)_2$) in benzene according to Ref. 6. The yield was 60–79%, b.p. 101.5° 0.4 mm Hg. $[\alpha]_D^{20} = -79.8°$, $[\alpha]_{546}^{20} = -97.4°$ (c = 1, benzene), IR: 3370, 3295 cm^{-1} (NH_2); ^{1}H NMR ($CDCl_3$): 0.77 (dd, 6H, $CH(CH_3)_2$, 1.41 (s, 2H, NH_2), 1.51 (m, 1H, $CH(CH_3)_2$), 3.45 (d, 1H, Fc–CH), 4.10 (s, 5H, C_5H_5) and 4.17 (m, 4H, C_5H_4). (Found: C, 65.4; H, 7.5; N, 5.5. Calc. for $C_{14}H_{19}NFe$: C, 65.4; H, 7.5; N, 5.5).

(S)-1-*Ferrocenyl-2-methyl-1-propylamine* (S)-**2a** was prepared analogously from (*S*)-**14a**. $[\alpha]_D^{20} = +79.5°$, $[\alpha]_{546}^{20} = +97.1°$ (c = 1, benzene).

Conversion of (S)-1-*ferrocenyl-2-methyl-1-propylamine* (S)-**2a** *into* (S)-(1-*ferrocenyl-2-methylpropyl)dimethylamine* (S)-**12a**. To a solution of (*S*)-**2a** (0.9 g, 3.5 mmol, $[\alpha]_D^{20} = +79.5°$) in MeOH (20 ml) 30% digeous formaldohyde (7 ml) was added. At 0° $NaBH_4$ (0.53 g, 14 mmol) was added with stirring, and the mixture was then stirred for 1 hr. After completion of the reaction water was added and the product was extracted with diethyl ether. The combined extracts were dried, and the solvent was removed under reduced pressure. The crude **12a** was chromatographed on basic alumina (Activity III) with benzene as eluent, yield 85%, $[\alpha]_D^{20} = +191.2°$, $[\alpha]_{546}^{20} = +319°$ (c = 1, benzene).

(R)-1-*Ferrocenyl-2-methyl-1-propylamine* (R)-**2a**. A mixture of formic acid (120 ml), thioglycolic acid (15 ml) and trifluoracetic acid (0.5 ml) was cooled in an ice-bath. The amine (*R*)-**12a** (5.0 g, 17.5 mmol) ($[\alpha]_D^{20} = -189°$) was added, and the soln was stirred in the dark for 6 days at room temp., during which time the colour changed from dark red-brown to dark green. The mixture was then poured on ice-water and extracted with diethyl ether. The combined extracts were then washed with water until neutral (several times), and extracted with Na_2CO_3 aq. The aqueous phase was acidified with 10% H_3PO_4-soln and extracted with diethyl ether. The combined ether extracts were washed with water, dried over Na_2SO_4 and the solvent was removed *in vacuo* to give crude (*R*)-**9a** (6.1 g). A sample was recrystallized from diisopropyl ether/hexane to give (*R*)-**9a** (see below).

The crude (*R*)-**9a** was dissolved in conc aqueous ammonia (200 ml). The soln was cooled and, after addition of NH_4Cl (1.85 g, 35 mmol), saturated with gaseous ammonia at −10°, Mercuric chloride (9.5 g, 35 mmol) was added, the mixture was stirred overnight and extracted with diethyl ether. The combined ethereal phases were washed with ice-water until neutral, and then extracted with an ice-cold 1% L-tartaric acid soln. The aqueous phase was made alkaline with an ice-cold 1N NaOH and extracted with diethyl ether. The ethereal extracts were washed with ice-water and dried over Na_2SO_4. The solvent was evaporated *in vacuo* at low temp. to yield the amine (*R*)-**2a** (1.98 g, 45%). $[\alpha]_D^{20} = -79°$, $[\alpha]_{546}^{20} = -96°$ (c = 1, benzene), m.p. 17–20°, bp. 101.5° 0.4 mm Hg.

(S)-1-*Ferrocenyl-2-methyl-1-propylamine* (S)-**2a** was prepared similarly from (*S*)-**12a** ($[\alpha]_D^{20} = +185°$, (c = 1, benzene). The yield was 44%. $[\alpha]_D^{20} = +79°$, $[\alpha]_{546}^{20} = +98°$ (c = 1, benzene).

(R/S)-S-(1-*Ferrocenyl-2-methylpropyl)thioglycolic acid* **9a**, was prepared from 1-ferrocenyl-2-methylpropanol analogous to the procedure above (see also Ref. 8). The reaction time was 24 hr, yield 92%. (Found: C, 57.8; H, 6.0. Calc. for $C_{16}H_{20}O_2SFe$: C, 57.8; H, 6.1), m.p. 80°. ^{1}H NMR($CDCl_3$): 0.88 (dd, 6H, $CH(CH_3)_2$). 2.16 (m, 1H, $CH(CH_3)_2$), 3.31 (s, 2H, CH_2), 3.83 (d, 1H, CH–$CH(CH_3)_2$), 4.17–4.25 (s and m, 9H, C_5H_5 and C_5H_4) and 11.2 (d, 1H, *COOH*).

The recemic product **9a** was resolved by crystallization of its

d-ψ-ephedrine salt from MeOH mp. 141°. From this salt **9a** could be set free with an optical rotation $[\alpha]_D^{25} = +50.5°$ ($c = 1$, MeOH). The conversion of this acid into **2a** (see above) yielded a product with $[\alpha]_D^{25} = +68.2°$ ($c = 1$, benzene) i.e. 83% enantiomer excess. Thus, complete resolution of the acid **9a** could not be achieved by this method.

(R)-S-(1-*Ferrocenyl-2-methylpropyl*)*thioglycolic acid* (R)-**9a** *by the cleavage of the 4CC product Phth-Gly-(N-(R)-1-ferrocenylisobutyl)-Val-Gly-OtBu.* The 4CC product (0.67 g, 1 mmol) was dissolved in trifluoroacetic acid (20 ml) and thioglycolic acid (8 ml). After 48 hr KOH aq was added until pH 4 and the mixture was extracted with EtoAC. The extract was washed with water, dried, and the solvent was evaporated. From the residue the thioether derivative **9a** was dissolved in a mixture of diethyl ether/pentane 1/1 and this soln was worked up as above to give (*R*)-**9a** (0.28 g, 87%). $[\alpha]_D^{25} = -67.7°$ ($c = 1$, MeOH). From this product optically pure (*R*)-**2a** could be obtained according to the procedure above.

(R/S)-S-(1-*Ferrocenylethyl*)*thioglycolic acid* **9b**[8] was prepared from 1-ferrocenylethanol as described for **9a**. The reaction time was 24 hr, yield 93%, m.p. 85°. The racemic product was resolved according to Ref. 8 by crystallization of its *d*-ephedrine salt. mp. 172°. From this salt an acid could be released with $[\alpha]_D^{25} = -33.2°$ ($c = 1$, MeOH). The conversion of this resolved acid **9b** into **2b** (see below) gave a product with $[\alpha]_D^{25} = +18.2°$ ($c = 1$, benzene), *i.e.* 87% enantiomer excess. Thus, it is not possible to obtain complete resolution of **9b** into enantiomers by this procedure.

(R)-S-(1-*Ferrocenylethyl*)*thioglycolic acid* **9b** *from the cleavage of the 4CC product For-Val-(N-1-ferrocenylethyl)-Val-Val-OMe.* The 4CC product (0.45) g, 1 mmol) was dissolved in acetone (20 ml) then thioglycolic acid (2.0 g, 20 mmol) and trifluoroacetic acid (5 drops) were added and the mixture was stirred for 24 hr at room temp. Diethyl ether (100 ml) was added and the ethereal phase was washed with water until neutral. Further work-up gave **9b** (0.28 g, 94%). $[\alpha]_D^{25} = +37.9°$ ($c = 1$, MeOH). From this product optically pure (*R*)-**2b** could be obtained by the procedure described below.

(±)-S-(1-*Ferrocenylethyl*)*thioglycolic acid* (±)-**9b** *from trimethyl-1-ferrocenylethylammonium iodide* (–)-**13b**. Compound **13b**[5] (1.3 g, 3.25 mmol) and thioglycolic acid (6 ml) in formic acid (50 ml) were stirred at room temp. for 12 hr. The mixture was worked up as described above to give the thioglycolic acid derivative (±)-**9b** (0.79, 81%); $[\alpha]_D^{25} = \pm 0°$ ($c = 1$, MeOH).

(R)-1-*Ferrocenylethylamine* (R)-**2b**[5] was prepared from (*R*)-**9b** according to the procedure described for (*R*)-**2a**. The reaction time was 7 hr, yield 78%, b.p. 81° 0.01 mm Hg, $[\alpha]_D^{25} = -20.8°$ ($c = 1$, EtOH).

REFERENCES

[1]a I. Ugi, *Rec. Chem. Progr.* **30**, 289 (1969); b G. Gokel, P. Hoffmann, H. Kleimann, G. Lüdke, D. Marquarding and I. Ugi, *Isonitrile Chemistry* (Edited by I. Ugi), p. 201. Academic Press, New York (1971); c I. Ugi, *Intra-Sci. Chem. Reps* **5**, 229 (1971); [d]I. Ugi *et al.*, *Peptides* 1974 (Edited by Y. Wolman) p. 71 Wiley, New York, Israel University Press, Jerusalem (1975); [e]I. Ugi *et al.*, *Peptides* 1976, *Proc. 14th Europ. Peptide Symp.* (Edited by A. Loffet) in press.

[2]D. Marquarding, P. Hoffmann, H. Heitzer and I. Ugi, *J. Am. Chem. Soc.* **92**, 1969 (1970).

[3a]R. Urban and I. Ugi, *Angew. Chem* **87**, 67 (1975); *Ibid.* Internat. Edit. **14**, 61 (1975); [b]R. Urban, G. Eberle, D. Marquarding, D. Rehn, H. Rehn and I. Ugi, *Ibid.* **88**, 644 (1976); *Ibid.* Internat Edit. **15**, 627 (1976); [c]J. Brandt, C. Jochum, I. Ugi and P. Jochum, *Tetrahedron* **33**, 1353 (1977).

[4]G. Eberle and I. Ugi, *Angew. Chem.* **88**, 509 (1976); *Ibid* Internat. Edit. **15**, 1976).

[5]G. Gokel, D. Marquarding and I. Ugi, *J. Org. Chem.* **37**, 3052 (1972).

[6]D. Marquarding, H. Burghard, I. Ugi, R. Urban and H. Klusacek, *J. Chem. Res.* (S) 82 (1977), (M) 915 (1977).

[7]G. Gokel, P. Hoffmann, H. Klusacek, D. Marquarding, E. Ruch and I. Ugi, *Angew. Chem.* **82**, 77 (1970); *Ibid.* Internat. Ed. to be published.

[8]A. Ratajczak and B. Misterkiewicz, *J. Organometal. Chem.* **91**, 73 (1975).