Synthesis of β-Lactams from Imines and 1-Lithio-oxy-2-phenylacetylene

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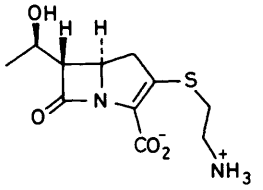
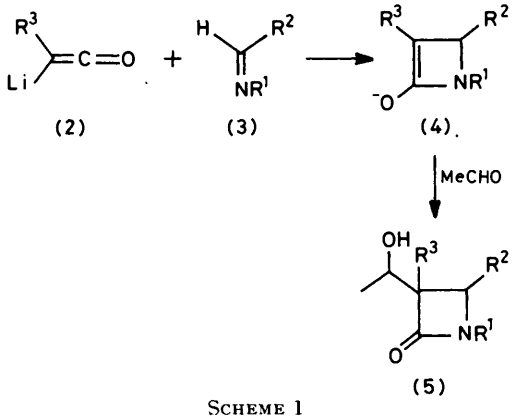
The ynolate 1-lithio-oxy-2-phenylacetylene, prepared from 3,4-diphenylisoxazole and n-butyl-lithium in tetrahydrofuran at −78 °C, condensed with the electron deficient imines ($R^1N{=}CHR^2$) to give the β-lactams [R^1NH-$CH(R^2)C(Ph)CON(R^1)CHR^2$] ($R^1$ = $C_6H_4NO_2$-4 and $C_6H_4CO_2Et$-4; R^2 = Ph, C_6H_4Me-3 and $C_6H_4NO_2$-4).

THE cycloaddition reaction of substituted ketens with imines provides a diverse array of β-lactams. The reaction is a most convenient synthetic entry to the penicillins, cephalosporins, norcardicins, *etc.* Thienamycin (1)



(1)

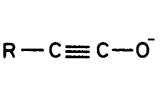
and related carbapenem antibacterials are notable for the presence of the non-classical hydroxyethyl side chain. Routinely, in synthesis this unusual substituent is incorporated *via* the condensation reaction of a β-lactam enolate with acetaldehyde or an acetylating reagent with subsequent reduction.[1] As a concise route to 3-(1-hydroxyethyl)azetidin-2-ones we sought to combine the versatile imine–keten cycloaddition with the enolate–acetaldehyde condensation (Scheme 1).[2] If realizable



SCHEME 1

this process would permit the direct imine to thienamycin anologue transformation, albeit in a stereochemically irrational [1] way. We thus attempted to prepare a lithiated keten (2) and condense this with an imine (3) to give the β-lactam enolate (4) directly. This would then be available for trapping *in situ* with acetaldehyde to give the β-lactam (5) (Scheme 1). Herein we report our attempts to realize this transformation.

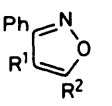
Although enolate chemistry is vast, studies of the related ynolate anions (6) are fragmentary.[3,4] Clearly, the ynolates (6) are metallated keten (2) [5] equivalents. In 1975 Schöllkopf and Hoppe reported [3] that the metallation of 3,4-diphenylisoxazole (7a) with n-butyl-lithium gave the anion (7b). This ring fragmented [6] to give benzonitrile and the ynolate anion (6a). We considered that the condensation of the ynolate (6a) with aldehydes and ketones to give, for example, the β-lactones (8) and (9), was a favourable auspice for the realization of Scheme 1.



(6)

a; R = Ph

b; R = $C_6H_3(MeO)_2$-3,4

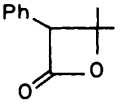


(7)

a; R^1 = Ph, R^2 = H

b; R^1 = Ph, R^2 = Li

c; R^1 = $C_6H_3(OMe)_2$-3,4, R^2 = H



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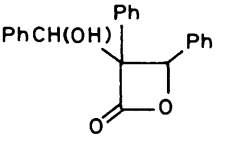
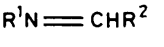


(9)



(10)

a; R^1 = R^2 = $C_6H_4NO_2$-4

b; R^1 = $C_6H_4CO_2Et$-4; R^2 = $C_6H_4NO_2$-4

c; R^1 = $C_6H_4NO_2$-4; R^2 = C_6H_4Me-3

d; R^1 = $C_6H_4NO_2$-4; R^2 = Ph

e; R^1 = $C_6H_4NO_2$-4; R^2 = C_6H_4OMe-4

f; R^1 = $C_6H_4NO_2$-4; R^2 = C_6H_4Cl-4

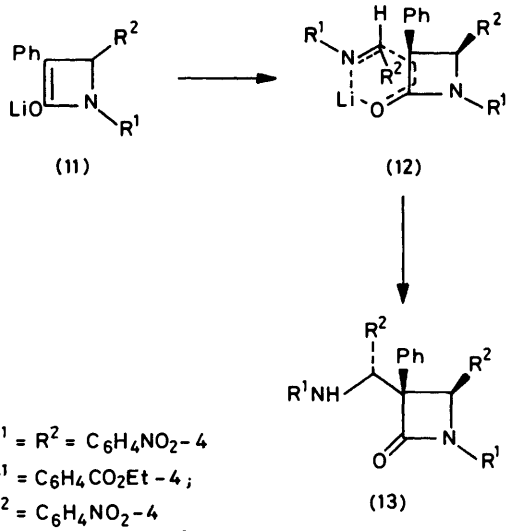
g; R^1 = C_6H_4CN-4; R^2 = $C_6H_4NO_2$-4

h; R^1 = Ph; R^2 = $C_6H_4NO_2$-4

i; R^1 = $C_6H_4CO_2Et$-4; R^2 = Ph

3,4-Diphenylisoxazole (7a) reacted with n-butyl-lithium in tetrahydrofuran (THF) at −78 °C to give an intense royal blue solution. Addition of the imines (10a)—(10d) resulted in slow discharge of this colour. Acidification at the orange-red end-point gave products which clearly were β-lactams ($\nu_{max.}$ 1 765—1 755 cm^{-1}). These four products all microanalysed as 2 : 1 imine–ynolate adducts and were assigned as the β-lactams (13a)—(13d). All spectral data were fully in agreement with these structures. In particular, the β-lactams (13c) and (13d) showed molecular ions in the mass spectra and all showed an amine NH proton ($\nu_{max.}$ 3 410—3 350 cm^{-1}) coupled

with an adjacent CH proton [for example (13a) δ 5.52 (1 H, d, *J* 8 Hz) and 5.9 (1 H, d, *J* 8 Hz)] and a single azetidin-2-one C-4 proton [for example (13a) δ 5.28 (1 H, s)]. The n.m.r. spectra showed that the β-lactams (13a)—(13d) were stereochemically homogeneous. However, none could be obtained crystalline, thus *X*-ray crystallographic structure determinations could not be carried out.

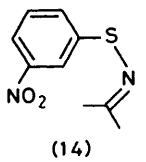


a; $R^1 = R^2 = C_6H_4NO_2$-4
b; $R^1 = C_6H_4CO_2Et$-4; $R^2 = C_6H_4NO_2$-4
c; $R^1 = C_6H_4NO_2$-4; $R^2 = C_6H_4Me$-3
d; $R^1 = C_6H_4NO_2$-4; R^2 = Ph

SCHEME 2

Tentatively, the β-lactams were assigned as structures (13a)—(13d) on the basis of assumed steric approach control and chelation *via* the intermediate (11) and transition state (12) (Scheme 2).

The imines (10e)—(10g) reacted with the ynolate (6a), but the product mixtures, although they contained β-lactams(s) (ν 1 760 cm^{-1}), were totally intractable. The imines (10h), (10i), (14), and the imino-chlorides (15a)—(15c) on attempted condensation with the ynolate (6a) all gave inseparable complex mixtures.



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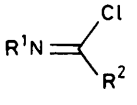
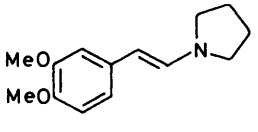


(15)

a; R^1 = Me; R^2 = Ph
b; R^1 = Me; $R^2 = C_6H_4NO_2$-4
c; $R^1 = R^2 = C_6H_4NO_2$-4



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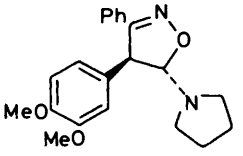

(17)

Since the ynolate (6a) condensed slowly with the imines (10a)—(10d) to give the β-lactams (13a)—(13d), the intermediate β-lactam enolates (11a)—(11d) must have been more nucleophilic. This unfavourable relative nucleophilicity of compounds (6a) and (11a)—(11d) prevented the realization of Scheme 1.

Briefly, we examined the preparation of the ynolate (6b) in the anticipation of this showing enhanced nucleophilicity. Thus, 4-(3,4-dimethoxyphenyl)-3-phenylisoxazole (7c) was prepared from 3,4-dimethoxyphenylacetaldehyde [7] *via* the enamine (16) and the isoxazoline (17).[8] The isoxazole (7c) reacted with n-butyl-lithium in THF solution at −78 °C to give a royal blue solution. The blue colour was discharged on the addition of the imines (10a), (10b), or (10d). Acidification in every case gave an intractable mixture of compounds that included β-lactam(s) (ν 1 760 cm^{-1}).

Although the ynolate anion (6a) could be used to prepare the β-lactams (13) the reaction was only successful for electron-deficient aromatic imines. This condensation reaction, although an extension of ynolate chemistry, is not to be recommended as a useful synthetic method: purification of the β-lactams (13) is non-trivial. Bergbreiter and Newcomb [9] have recently described the convenient synthesis of β-lactams from ester enolates and aryl aldimines.

EXPERIMENTAL

Melting points were determined with a Kofler hot stage apparatus and are uncorrected. Chromatographic absorbents refer to Merck products. All reagents and solvents were purified by standard techniques.[10] Tetrahydrofuran (THF) was freshly redistilled from potassium benzophenone ketyl. The following reagents were prepared by standard methods: α-chlorobenzaldoxime,[8] 3,4-dimethoxyphenylacetaldehyde,[7] 3,4-diphenylisoxazole (7a),[8] and compounds (10a),[11] (10b),[12] (10d),[11] (10f),[12] (10g),[13] (10h),[14] (10i),[15] (14),[16] (15a),[17] and (15c).[18]

All reactions were carried out under dry nitrogen.

Preparation of the Imines (10e) *and* (10c).—4-Methoxybenzaldehyde (2.99 g) and 4-nitroaniline (2.76 g) in ethanol (50 ml) were refluxed for 1 h and cooled to give N-4-*methoxybenzylidene*-4-*nitroaniline* (10e) (3.66 g, 71%), m.p. 123—124 °C (EtOH); $\nu_{max.}$ (Nujol) 1 510 and 1 345 cm^{-1}; δ($CDCl_3$) 3.95 (3 H, s), 7.07 (2 H, d, *J* 9 Hz), 7.37 (2 H, d, *J* 9 Hz), 7.92 (2 H, d, *J* 9 Hz), 8.27 (2 H, d, *J* 9 Hz), and 8.38 (1 H, s); *m/e* 256 ($M^{+\cdot}$) (Found: C, 65.75; H, 4.7; N, 10.9. $C_{14}H_{12}N_2O_3$ requires C, 65.6; H, 4.7; N, 10.95%). 4-Nitroaniline (1.38 g) and 3-methylbenzaldehyde (1.2 g) in dry benzene (20 ml) were heated under nitrogen for 12 h (Dean–Stark). Evaporation and crystallization from benzene–light petroleum gave N-3-*methylbenzylidene*-4-*nitroaniline* (10c) (1.18 g, 49%), m.p. 87—88 °C; $\nu_{max.}$ ($CHCl_3$) 1 520 and 1 350 cm^{-1}; δ($CDCl_3$) 2.42 (3 H, s), 7.23 (2 H, d, *J* 9 Hz), 7.34—7.47 (2 H, m), 7.62—7.82 (2 H, m), 8.22 (2 H, d, *J* 9 Hz), and 8.4 (1 H, s); *m/e* 240 ($M^{+\cdot}$) and 138 (Found: C, 69.9; H, 5.05; N, 11.6. $C_{14}H_{12}N_2O_2$ requires C, 70.0; H, 5.05; N, 11.65%).

Preparation of N-*Methyl*-4-*nitrobenzimidoyl Chloride* (15b).—*N*-Methyl-4-nitrobenzamide (5 g) and phosphorus pentachloride (5.75 g) were heated together until melted. After a further 20 min at 100 °C phosphorus oxychloride was

removed under reduced pressure and the residue was distilled to give the *title compound* (15b), b.p. 110 °C/0.05 mmHg (short-path distillation), m.p. 71—73 °C, $\nu_{max.}$ (Nujol) 1 660, 1 610, 1 535, 1 465, 1 365, 900, 865, and 848 cm^{-1}; δ($CDCl_3$) 3.33 (3 H, s) and 8.03 (4 H, s); *m/e* 200, 198 ($M^{+\cdot}$) 180, 163, and 117 (Found: C, 48.55; H, 3.75; N, 14.0. $C_8H_7ClN_2O_2$ requires C, 48.4; H, 3.55; N, 14.1%).

Preparation of (E)-1-(3,4-*Dimethoxyphenyl*)-2-*pyrrolidinylethene* (16).—Freshly redistilled pyrrolidine (0.54 g) was added to 3,4-dimethoxyphenylacetaldehyde (1.36 g) and toluene-4-sulphonic acid (10 mg) in dry benzene (50 ml) at 0 °C. The mixture was refluxed overnight (Dean–Stark trap) and the benzene removed under reduced pressure to leave the crude enamine (16); $\nu_{max.}$ 1 640, 1 515, 1 420, 1 370, 1 220—1 260, 1 150, 1 025, and 680 cm^{-1}; δ($CDCl_3$) 1.81—2.15 (4 H, m), 3.06—3.37 (4 H, m), 3.83 (3 H, s), 3.88 (3 H, s), 5.04 (1 H, d, *J* 14 Hz), 6.70 (3 H, s), and 6.94 (1 H, d, *J* 14 Hz); *m/e* 233 ($M^{+\cdot}$), 218, and 151.

Preparation of trans-4 (3,4-*Dimethoxyphenyl*)-3-*phenyl*-5-*pyrrolidin*-1-*yl*-2-*isoxazoline* (17).—The enamine (16) (1.69 g) and dry triethylamine (1.05 ml) in dry diethyl ether (50 ml) were added, with stirring, over 20 min to α-chlorobenzaldoxime (1.19 g) in dry diethyl ether (50 ml) at 0 °C. The mixture was further stirred at 0 °C for 2 h when water (100 ml) was added. The organic phase was washed with water (3 × 25 ml), dried ($MgSO_4$), evaporated, and the residue chromatographed on Kieselgel H [10 g; eluant, benzene–dichloromethane (1 : 1)] to give the title compound (17) as a white foam. A *sample* was purified by p.l.c. (Kieselgel GF_{254} developed in dichloromethane); $\nu_{max.}$ ($CHCl_3$) 1 530, 1 465, 1265, 1 250, and 910 cm^{-1}; δ($CDCl_3$) 1.6—1.73 (4 H, m), 2.43—2.83 (4 H, m), 3.7 (6 H, s), 4.1 (1 H, d, *J* 2.5 Hz), 5.12 (1 H, d, *J* 2.5 Hz), 6.5—6.66 (3 H, m), and 7.03—7.56 (5 H, m); *m/e* 352 ($M^{+\cdot}$) 350, 281, 253, and 218 (Found: C, 71.55; H, 6.85; N, 7.95. $C_{21}H_{24}N_2O_3$ requires C, 71.25; H, 7.0; N, 7.7%).

Preparation of 4-(3,4-*Dimethoxyphenyl*)-3-*phenylisoxazole* (7c).—The isoxazoline (17) (2.1 g) in methanol and concentrated hydrochloric acid (1 : 2 v/v; 65 ml) was refluxed for 90 min under nitrogen. When cold, diethyl ether (50 ml) was added and the aqueous phase was neutralized with saturated sodium hydrogencarbonate. The aqueous phase was extracted with diethyl ether (3 × 50 ml), and the total organic phase was washed with saturated sodium hydrogencarbonate (10 ml), dried ($MgSO_4$), and evaporated. Chromatography of the residue on Kieselgel H [10 g; eluant, dichloromethane–benzene (1 : 1)] gave the *title compound* (7c) (1.01 g, 60%), m.p. 97.5—98.5 °C (from ethanol); $\nu_{max.}$ (Nujol) 1 230 and 810 cm^{-1}; δ($CDCl_3$) 3.42 (3 H, s), 3.64 (3 H, s), 6.1 (1 H, m), 6.8 (2 H, m), 7.2—7.55 (5 H, m), and 8.47 (1 H, s); *m/e* 281 ($M^{+\cdot}$), 266, 166, 155, and 151 (Found: C, 72.5; H, 5.35; N, 4.8. $C_{17}H_{15}NO_3$ requires C, 72.6; H, 5.35; N, 5.0%).

Preparation of 3-(4-*Nitroanilino*-4-*nitrophenylmethyl*)-1,4-*di*-(4-*nitrophenyl*)-3-*phenylazetidin*-2-*one* (13a).—n-Butyllithium (1.60M, 1.50 ml) was added, with stirring, to 3,4-diphenylisoxazole (7a) (552.5 mg) in dry THF (20 ml) at −78 °C under nitrogen. Instantly, a royal blue solution was produced. After 10 min the imine (10a) (682.5 mg) in dry THF (5 ml) was added as drops, the temperature being kept at −78 °C. After 2 h at −78 °C the royal blue colour had discharged and acetic acid (150 mg) was added to the deep red-orange solution. The mixture was allowed to warm to room temperature, the solvent was evaporated off, and the residue leached with dichloromethane (2 × 25 ml). The extract was chromatographed on Kieselgel H (10 g; eluant, dichloromethane) to give the title β-lactam (13a) (741 mg, 89%) as a bright yellow foam. A *sample* was purified by p.l.c. on Kieselgel GF_{254} (6-developments in dichloromethane); $\nu_{max.}$ ($CHCl_3$) 3 410br, 1 765, 1 600, 1 525, 1 520, 1 380, 1 350—1 320br, 1 270, 1 115, 900, 860, 840, 790, 740, and 705 cm^{-1}; δ($CDCl_3$–[$^2H_6$]acetone, 9 : 1 v/v), 5.28 (1 H, s), 5.52 (1 H, d, *J* 8 Hz), 5.9 (1 H, d, *J* 8 Hz), 6.35 (2 H, d, *J*, 9 Hz), 6.6—7.1 (9 H, m), and 7.5—7.9 (10 H, m); *m/e* $M^{+\cdot}$ absent, 538, 481, 295, 279, 236, 221, and 162 (Found: C, 61.5; H, 3.9; N, 12.45. $C_{34}H_{24}N_6O_9$ requires C, 61.8; H, 3.65; N, 12.7%).

Preparation of 3-[(4-*Ethoxycarbonylanilino*)-(4-*nitrophenyl*)*methyl*]-1-(4-*ethoxycarbonylphenyl*)-4-(4-*nitrophenyl*)-3-*phenylazetidin*-2-*one* (13b).—In the same way the imine (10b) gave the title β-lactam (13b) (79%) as a pale yellow *foam*; $\nu_{max.}$ (CH_2Cl_2) 3 350, 1 755, 1 700, 1 605, 1 525, 1 370, 1 350, 1 280, 1 270, 1 175, 1 110, 1 015, 850, 770, 740, and 700 cm^{-1}; δ($CDCl_3$) 1.32 (3 H, t, *J* 7 Hz), 1.38 (3 H, t, *J* 7 Hz), 4.28 (2 H, q, 7 Hz), 4.38 (2 H, q, *J* 7 Hz), 4.74 (1 H, d, *J* 9.5 Hz), 4.9 (1 H, d, *J* 9.5 Hz), 5.61 (1 H, s), 6.12 (2 H, d, *J* 9 Hz), 7.2 (2 H, d, *J* 9 Hz), 7.3 (3 H, m), 7.4 (4 H, m), 7.64 (4 H, m), 7.9 (2 H, d, *J* 9 Hz), and 8.06 (4 H, m), *m/e* $M^{+\cdot}$ absent, 519, 398, 369, 298, 253, and 165 (Found: C, 67.4; H, 4.95; N, 7.7. $C_{40}H_{34}N_4O_9$ requires C, 67.2; H, 4.8; N, 7.85%).

Preparation of 4-(3-*Methylphenyl*)-3-[(3-*methylphenyl*)-(4-*nitroanilino*)*methyl*]-1-(4-*nitrophenyl*)-3-*phenylazetidin*-2-*one* (13c).—In the same way the imine (10 c) gave the β-lactam (13c) (58%) as a pale yellow *foam*; $\nu_{max.}$ (CH_2Cl_2) 3 400, 1 755, 1 600, 1 520, 1 500, 1 380, 1 320, 1 265, 1 180, 1 110, 895, 850, 835, 790, and 750 cm^{-1}; δ($CDCl_3$) 2.13 (3 H, s), 2.27 (3 H, s), 4.83 (1 H, s), 5.03 (1 H, d, *J* 7.5 Hz), 6.0 (1 H, d, *J* 7.5 Hz), 6.4 (2 H, d, *J* 9 Hz), 6.67 (2 H, m), 6.9—7.4 (13 H, m), 7.87 (2 H, d, *J* 9 Hz), and 8.04 (2 H, d, *J* 9 Hz); *m/e* 598 ($M^{+\cdot}$), 481, 358, 328, 240, and 210 (Found: C, 72.25; H, 5.25; N, 9.25. $C_{36}H_{30}N_4O_5$ requires C, 72.25; H, 5.05; N, 9.35%).

Preparation of 3-[(4-*Nitroanilino*)*phenylmethyl*]-1-(4-*nitrophenyl*)-3,4-*diphenylazetidin*-2-*one* (13d).—In the same way, the title compound (13d) was obtained as a *foam* (66%); $\nu_{max.}$ (CH_2Cl_2) 3 410, 1 760, 1 600, 1 520, 1 502, 1 384, 1 328, 1 180, 1 150, 1 112, 1 072, 1 030, 1 000, 900, 850, and 830 cm^{-1}; δ($CDCl_3$) 4.97 (1 H, s), 5.12 (1H , d, *J* 7 Hz), 5.97 (1 H, d, *J* 7 Hz, NH), 6.35 (2 H, d, *J* 9.5 Hz), 6.8—7.65 (17 H, m), 7.77 (2 H, d, *J* 9.5 Hz), and 7.93 (2 H, d, *J* 9.5 Hz); *m/e* 570 ($M^{+\cdot}$) 554, 432, 343, 328, 315, 297, 269, 227, 180, 119, and 117 (Found: C, 71.65; H, 4.7; N, 9.7. $C_{34}H_{26}N_4O_5$ requires C, 71.55; H, 4.6; N, 9.8%).

We thank the S.E.R.C. for a studentship (to P. Q.)

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Note added in proof: A most elegant synthesis of ynolates from the dimetallation of dibromomethyl ketones and rearrangement has recently been reported (C. J. Kowalski and K. W. Fields, *J. Org. Chem.*, 1982, **104**, 321).

REFERENCES

[1] For example, see F. A. Bouffard, D. B. R. Johnson, and B. G. Christensen, *J. Org. Chem.*, 1980, **45**, 1130; F. A. Bouffard and B. G. Christensen, *ibid.*, 1981, **46**, 2208.

[2] Preliminary publication: R. M. Adlington, A. G. M. Barrett. P. Quayle, A. Walker, and M. J. Betts, *J. Chem. Soc., Chem. Commun.*, 1981, 404.

[3] U. Schöllkopf and I. Hoppe, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 765; I. Hoppe and U. Schöllkopf, *Liebigs Ann. Chem.*, 1979, 219.

[4] For related sulphur and nitrogen anions see, R. Raap, *Can. J. Chem.*, 1971, **49**, 1792; U. Schöllkopf and I. Hoppe, *Liebigs Ann. Chem.*, 1974, 1655; L. Brandsma, H. J. T. Bos, and J. F. Arens, in 'Chemistry of Acetylenes,' ed. H. G. Viehe, Dekker, New York, 1969, ch. 11; E. Schaumann and F.-F. Grabley, *Tetrahedron Lett.*, 1977, 4307; N. Miyaura, T. Yanagi, and A. Suzuki, *Chem. Lett.*, 1979, 535.

[5] R. P. Woodbury, N. R. Long, and M. K. Rathke, *J. Org. Chem.*, 1978, **43**, 376.

[6] T. L. Gilchrist and D. P. J. Pearson, *J. Chem. Soc., Perkin Trans. 1*, 1976, 989.

[7] Y. Ban and T. Oishi, *Chem. Pharm. Bull.*, 1958, **6**, 574.

[8] K. Bast, M. Christl, R. Huisgen, W. Mack, and R. Sustmann, *Chem. Ber.*, 1973, **106**, 3258; R. Huisgen, *J. Org. Chem.*, 1976, **41**, 403 and references therein.

[9] C. Gluchowski, L. Cooper, D. E. Bergbreiter, and M. Newcomb, *J. Org. Chem.*, 1980, **45**, 3413.

[10] D. F. Perrin, W. L. F. Amarego, and D. R. Perrin, 'Purification of Laboratory Chemicals,' Pergamon Press, London, 1966.

[11] A. Roe and J. A. Montgomery, *J. Am. Chem. Soc.*, 1953, **75**, 910.

[12] J. S. Dave, P. R. Patel, and K. L. Vasanth, *Ind. J. Chem.*, 1966, **4**, 505.

[13] J. A. Castellano, J. E. Goldmacher, L. A. Barton, and J. S. Kane, *J. Org. Chem.*, 1968, **33**, 3501.

[14] O. Fischer, *Chem. Ber.*, 1881, **14**, 2520.

[15] K. Tabei and E. Saitou, *Bull. Chem. Soc. Jpn.*, 1969, **42**, 1440.

[16] F. A. Davis, W. A. R. Slegeir, S. Evans, A. Schwartz, D. L. Goff, and R. Palmer, *J. Org. Chem.*, 1973, **38**, 2809.

[17] J. von Braun, *Chem. Ber.*, 1904, **37**, 2812.

[18] F. Feichtmayr and F. Würstlin, *Festschrift Carl Wurster Zum 60, Geburtstag*, 1960, 177; *Chem. Abstr.*, 1961, **55**, 24172 h.