Monatshefte für Chemie 129, 671–677 (1998)

Monatshefte für Chemie
Chemical Monthly

Printed in Austria

Allylation and Heterocycloaddition Reactions of Aldimines: Furan- and Quinolinecarboxaldehydes

Vladimir Kouznetsov[2,*], **Nüket Öcal**[1,*], **Zuhal Turgut**[1], **Fedor Zubkov**[3], **Şeniz Kaban**[1], and **Alexei V. Varlamov**[3]

[1] Yıldız Technical University, Department of Chemistry, 80270 Şişli, İstanbul, Turkey
[2] School of Chemistry, Industrial University of Santander, Bucaramanga, Colombia
[3] Department of Organic Chemistry, Russian Peoples Friendship University, Moscow 117923, Russia

Summary. New derivatives of α-substituted furans were prepared in high yields from easily available α-furfurylidenbenzilamines *via* nucleophilic C-allylation. The homoallylamines obtained this way were used for the synthesis of some polyfunctional aminobutene derivatives. In addition, 4-thiazolidinones some of which are hetaryl substituted at the 2-position were prepared by the reaction of mercapto acids with quinoline carboxaldehydes and *p*-phenetidine. All new products were fully characterized.

Keywords. *Diels-Alder* adduct; α-Furfurylidenbenzilamine; Nitrone; α-Substituted furan; 4-Thiazolidinone.

Allylierungs- und Heterocycloadditionsreaktionen von Aldiminen: Furan- und Chinolincarboxaldehyde

Zusammenfassung. Aus den leicht zugänglichen α-Furfurylidenbenzilaminen wurden durch nucleophile C-Allylierung neue Derivative α-substituierter Furane mit hohen Ausbeuten dargestellt. Die dabei gewonnenen Homoallylamine wurden für die Synthese von polyfunktionalen Aminobutenderivaten eingesetzt. Darüber hinaus wurden durch Reaktion von Merkaptosäuren mit Chinolincarboxaldehyden und *p*-Phenetidin an der 2-Stelle heterosubstituierte 4-Thiazolidinone gebildet. Alle Produkte wurden entsprechend charakterisiert.

Introduction

Furans have been proven to be useful precursors for a wide variety of carbo- and heterocycles which are present in numerous natural products [1]. The preparation of 1,4-dicarbonyl compounds and cyclopentanones from furans is a well documented process [2]. Aldimines derived from furfural or furfurylamine have

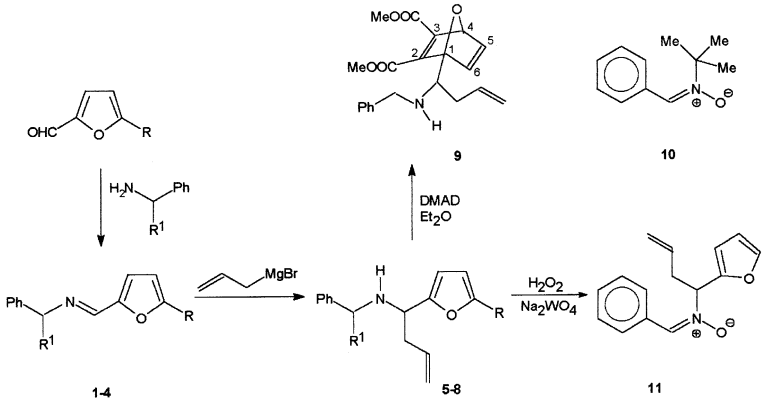
* Corresponding author

been successfully used in the synthesis of different β-lactams [3, 4]. Recently, such imines have been involved in Pd-catalyzed sequential and cascade[3+2]-cycloadditions to produce bicyclic β-lactams [5]. The ready availability of the starting materials and the simplicity of the procedures make N-allyl-α-furfurylamines attractive candidates for intramolecular *Diels-Alder* reactions [6, 7]. Furthermore, in the organometallic domain, the nucleophilic addition of allyl carbanions to aldimines to give homoallylamines [8, 9] is of particular interest owing to the many possible transformations of the double bond of the allyl group. However, these reactions have not been studied in the α-furfurylidenamine series so far. On the other hand, most of the 4-thiazolidinones display a large variety of activities such as antibiotic, diuretic, organoleptic, tuberculostatic, antileukemic, antibacterial, and antiparasitical [10, 11]. The biological significance of these compounds prompted us to study the synthesis of some 3-(4-ethoxyphenyl)-2-hetaryl-4-thiazolidinones.

Results and Discussion

As part of an ongoing project aiming at the use of homoallylamines in the synthesis of various nitrogen heterocycles of biological interest, we required α-substituted furans comprising an N-benzylaminobutenyl radical. For this purpose, we performed some *Grignard* allylation reactions on aldimines derived from substituted furfurals and benzylamines using allyl bromide and magnesium.

Addition of allyl magnesium bromide to aldimines **1**–**4** gave homoallylamines **5**–**8** as shown in Scheme 1. In each case, the reaction was conducted in diethyl ether with initial addition of aldimines to the *Grignard* reagent at 0°C. After stirring at the same temperature for 0.5 hours, the reaction mixture was allowed to warm to room temperature, and stirring was continued for 1 hour before standard work-up. The homoallylamines **5**–**8** were isolated as stable yellow oils in 65–86% yield after distillation under reduced pressure. Their structure was established using IR, NMR, and mass spectroscopy. The IR spectra showed the bands of the



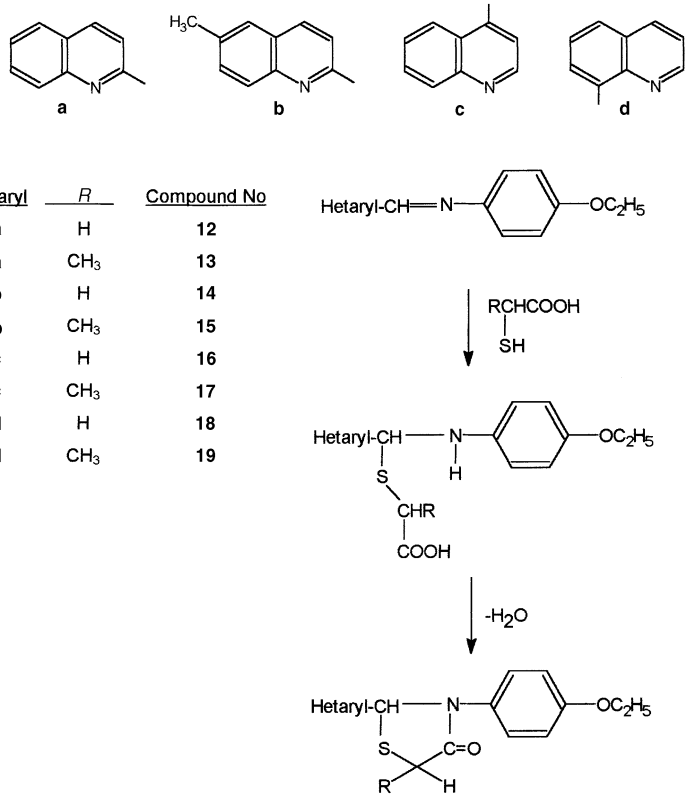
1, **5**: $R = R^1 = H$; **2**, **6**: R = H, R^1 = Me; **3**, **7**: R = Me, R^1 = H; **4**, **8**: R = Br, R^1 = H

Scheme 1

amine group in the region of 3325–3340 cm^{-1}; the molecular ions in the mass spectra corresponded to their formulas. In the ^1H NMR spectra, the protons of the allyl residue gave rise to three groups of signals: the triplet of the CH_2-group was observed in the region of 2.49–2.57 ppm, and the multiplet signals of the $=CH_2$ and CH= groups, respectively, appeared at low field, *i.e.* between 4.98–5.14 and 5.57–5.70 ppm. Compound **6** is formed as a mixture of two pairs of diastereoisomers which was confirmed by its ^1H NMR spectrum.

Reaction of compound **5** with dimethyl acetylenedicarboxylate (*DMAD*) carried out in diethyl ether at 0°C afforded a polyfunctional *Diels-Alder* adduct (**9**) as colorless crystals in high yields. Under these conditions, we did not observe the formation of any products resulting from nucleophilic NH-addition to the triple bond. The ^1H NMR spectrum of this adduct shows doublet and triplet signals at 6.27 and 7.34 ppm corresponding to 6-H and 5-H. The protons of the allyl group resonate between 5.08 and 5.74 ppm as two characteristic multiplets.

It is well known that nitrones [12, 13] are useful synthons in natural products synthesis and are effective spin traps (for example, phenyl *tert*-butyl nitrone (**10**) [14]). To our knowledge there are no reports on the synthesis of such compounds bearing an α-furfuryl moiety. Thus, the first nitrone of this series (**11**) was conveniently prepared by oxidation with 30% H_2O_2 in the presence of a catalytic amount of Na_2WO_4 in acetone at room temperature. It was isolated as a stable,



Hetaryl	R	Compound No
a	H	12
a	CH_3	13
b	H	14
b	CH_3	15
c	H	16
c	CH_3	17
d	H	18
d	CH_3	19

Scheme 2

colorless solid which could be purified on a chromatographic column and was recrystallized from hexane. The presence of four multiplet signals, *i.e.* HC=C ($\delta = 5.8$ ppm), CH_2=CH_{cis} ($\delta = 5.1$ ppm), CH_2=CH_{trans} ($\delta = 5.2$ ppm), and -CH_2- ($\delta = 3.25$ ppm) in its ^{1}H spectra proves that the allyl fragment is not oxidized under these reaction conditions. The signal of the aldiminic proton (HC=N) appears at 7.41 ppm.

In conclusion, allylation of easily available α-furfurylidenbenzylamines constitutes a convenient procedure for the preparation of the corresponding homoallylamines. It should be noted that the new compounds **9** and **11** obtained from these amines still contain the allylic fragment which might be used in intramolecular cyclization reactions.

On the other hand, 4-thiazolidinones have been prepared by the reaction of thioglycolic acid or thiolactic acid with *Schiff* bases derived from quinoline-2-, 6-methylquinoline-2-, quinoline-4-, and quinoline-8-carboxaldehydes with *p*-phenetidine [15]. The biological activities of these compounds are under investigation at the *Karl Franzens* University in Graz, Austria.

The structures of the new compounds were firmly established on the basis of their IR, NMR, and mass spectra. In general, the strong sharp band at 1610–1620 cm^{-1} in the IR spectra of the *Schiff* bases was absent in the spectra of the thiazolidinones, and a characteristic ν(C=O) appeared in the region of 1710–1680 cm^{-1}.

Experimental

Melting points are uncorrected and were measured in open capillaries with an Electrothermal IA 9100 melting point apparatus. IR spectra were recorded on Perkin Elmer 599B-FT and Philips PU 9714 spectrometers in KBr pellets unless otherwise indicated. The NMR spectra were determined on Bruker WP-200 (compounds **5**–**8**), Bruker WH-400 (compounds **9**, **11**), and Varian Gemini 200 (compounds **12**–**19**) spectrometers in $CDCl_3$ with tetramethylsilan (*TMS*, $\delta = 0$ ppm) as internal standard. Mass spectra were obtained from an LKB-9000 spectrometer with 70 eV electron impact ionization. Elemental analyses were performed on a Leco CHN-600 analyzer. The purities of the obtained substances and the compositions of the reaction mixtures were monitored by TLC on Alufol 60, and Silufol UV254 plates and Eastman Kodak Chromatogram 13181 silica gel sheets with fluorescent indicator. Elemental analyses were in satisfying agreement with the calculated data.

Allylation of aldimines **1**–**4**; *general procedure*

A solution of **1**–**4** (0.1 mol) dissolved in dry ether (30 ml) was added dropwise to a stirred suspension of allyl magnesium bromide prepared from allyl bromide (0.3 mol) and magnesium (0.6 mol) in dry ether (100 ml) at 0°C. After stirring at 0°C for a 0.5 h, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. Work-up with a cold saturated solution of NH_4Cl, extraction with ether (3×50 ml), and vacuum distillation of the dried extracts (Na_2SO_4) afforded the homoallylfurfurylamines **5**–**8** as yellow oils.

4-N-Benzylamino-4-(2-furyl)-1-butene (**5**; $C_{15}H_{17}NO$)

Yield: 82%; b.p.: 115–118°C/2 mm Hg; IR (KBr): $\nu = 3330$, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$, δ, 200 MHz): 7.35 (1H, d, α-Fu), 7.30–7.05 (5H, m, Ph), 6.27 (1H, d, β-Fu), 6.13 (1H, t, β'-Fu), 5.69

(1H, ddt, =CH–), 5.05–4.99 (2H, m, $=CH_2$), 3.74 (1H, t, CH–Fu), 3.72 and 3.56 (2H, dd, CH_2–N), 2.49 (2H, t, CH_2–CH=), 1.70 (1H, br s, NH) ppm; MS: $m/z = 227$ (M^+).

4-N-Benzylamino-4-(5-methyl-2-furyl)-1-butene (**6**; $C_{16}H_{19}NO$)

Yield: 70%; b.p.: 140–142°C/10 mm Hg; IR (KBr): $\nu = 3325$, 1641 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 7.36 (1H, d, α-Fu), 7.35–7.15 (5H, m, Ph), 6.27 (1H, d, β-Fu), 6.13 (1H, t, β'-Fu), 5.70–5.60 (1H, m, =CH–), 5.10–4.98 (2H, m, $=CH_2$), 3.75 and 3.65 (1H, q, CH–N), 3.45 (1H, t, CH–Fu), 2.55 and 2.49 (2H, t, CH_2–CH=), 1.68 (1H, br s, NH), 1.42 and 1.35 (1H, d, Me) ppm; MS: $m/z = 241$ (M^+).

4-N-Benzylamino-4-(5-bromo-2-furyl)-1-butene (**7**; $C_{16}H_{19}NO$)

Yield: 86%; b.p.: 124–126°C/2 mm Hg; IR (KBr): $\nu = 3340$, 1648 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 7.35–7.25 (5H, m, Ph), 6.09 (1H, d, β-Fu), 5.93 (1H, d, β'-Fu), 5.57 (1H, ddt, =CH–), 5.14–5.09 (2H, m, $=CH_2$), 3.74 (1H, t, CH–Fu), 3.82 and 3.65 (2H, dd, CH_2–N), 2.57 (2H, m, CH_2–C=), 2.32 (3H, s, Me), 1.75 (1H, br s, NH) ppm; MS: $m/z = 241$ (M^+).

4-N-(α-Methylbenzyl)amino-4-(2-furyl)-1-butene (**8**; $C_{15}H_{16}BrNO$)

Yield: 64%; viscous oil; IR (KBr): $\nu = 3326$, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 7.35–7.30 (5H, m, Ph), 6.26 (1H, d, β-Fu), 6.09 (1H, d, β'-Fu), 5.74 (1H, ddt, =CH–), 5.11–5.09 (2H, m, $=CH_2$), 3.80 and 3.63 (2H, dd, CH_2–N), 3.74 (2H, t, CH–Fu), 2.54 (2H, m, CH_2–C=) ppm; MS: $m/z = 306$ (M^+).

1-(4′-N-Benzylamino-1′-butenyl-4′)-2,3-dimethoxycarbonyl-7-oxabicyclo[2.2.1]hepta-2,3-diene (**9**; $C_{21}H_{23}NO_5$)

A solution of **5** (0.026 mol) and dimethyl acetylenedicarboxylate (*DMAD*, 0.029 mol) in Et_2O (40 ml) was allowed to stand in a loosely stoppered flask for 12 h. The resulting solid was filtered and recrystallized from hexane with a small amount of ethyl acetate to give **9** as colorless crystals.

Yield: 85%; m.p.: 67–69°C; IR (KBr): $\nu = 3375$, 1736, 1697 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 7.34 (1H, t, 5-H; $J_{4,5} = J_{6,5} = 1.3$ Hz), 7.28–7.18 (3H, m, Ph), 7.07–7.03 (2H, m, Ph), 6.27 (2H, d, 4-H, 6-H; $J_{4,5} = J_{6,5} = 1.3$ Hz), 5.74 (1H, ddt, =CH–), 5.12–5.08 (1H, m, $=CH_2$), 4.65 (1H, t, CH–N; $J_{4,3} = 7.8$ Hz), 4.59 (1H, br s, NH), 4.36 and 4.19 (2H, AB, CH_2–N; $J_{A,B} = 16.8$ Hz), 3.96 and 3.55 (3H, s, COOMe), 2.70 (2H, m, CH_2–C=) ppm; MS: $m/z = 369$ (M^+).

Phenyl-(4′-α-furyl-1′-butenyl-4′)nitrone (**11**; $C_{15}H_{15}NO_2$)

To a suspension of **1** (5 mol) and $Na_2WO_4 \cdot 2H_2O$ (0.25 mol) in acetone (50 ml), 30% H_2O_2 (20 mol) was added dropwise. The mixture was stirred at room temperature for 5 h (TLC control) and then diluted with H_2O (100 ml). The organic products were extracted with Et_2O (4×50 ml) and purified on a chromatographic column (Al_2O_3, hexane/ethyl acetate, 10:1). The residue was crystallized from hexane and afforded **11** as colorless crystals.

Yield: 43%; m.p.: 91–92°C; IR (KBr): $\nu = 1644$, 1579, 1565, 1155, 930 cm^{-1}; ^1H NMR ($CDCl_3$, δ, 200 MHz): 8.22 (2H, m, *o*-Ph), 7.43–7.35 (3H, m, Ph), 7.43 (2H, d, α-Fu), 7.41 (1H, s, HC=N), 6.41 (4H, d, β,β'-Fu), 5.79 (1H, ddt, =CH–), 5.23–5.11 (2H, m, $=CH_2$), 5.05 (1H, t, CH–Fu), 3.25 (2H, ddd, CH_2–C=) ppm; MS: $m/z = 241$ (M^+).

Preparation of 3-(4-ethoxyphenyl)-2-hetaryl-4-thiazolidinones **12–19**

To a solution of the *Schiff* bases derived from quinolinecarboxaldehydes (0.01 mol) in 15 ml dry benzene, thioglicolic acid or thiolactic acid (0.01 mol) was added. The mixture was refluxed on a water bath for 8 h, then cooled and poured into water. The upper organic layer was washed with $NaHCO_3$ solution (15 ml, 10%) and then with H_2O, dried (Na_2SO_4), and the benzene was distilled off. Upon crystallization of the residue from petroleum ether (40–60°C)/ethanol (1:1), the thiazolidinones were obtained as yellow crystals (exceptions: **18** and **19**).

3-(4-Ethoxyphenyl)-2-(2-quinolinyl)-4-thiazolidinone (**12**; $C_{20}H_{18}N_2O_2S$)

Yield: 89%; m.p.: 114°C; IR (KBr): $\nu = 1660\,cm^{-1}$; ^1H NMR ($CDCl_3$, δ, 200 MHz): 6.70–8.20 (10H, m, ArH), 6.20 (1H, s, CH), 4.10 (2H, d, CH_2), 3.80 (2H, q, OCH_2CH_3), 1.30 (3H, q, OCH_2CH_3) ppm; MS: $m/z = 350$ (M^+).

3-(4-Ethoxyphenyl)-5-methyl-2-(2-quinolinyl)-4-thiazolidinone (**13**; $C_{21}H_{20}N_2O_2S$)

Yield: 78%; m.p.: 126°C; IR (KBr): $\nu = 1660\,cm^{-1}$; ^1H NMR ($CDCl_3$, δ, 200 MHz): 6.70–8.20 (10H, m, ArH), 6.20 (1H, s, CH), 4.20 (2H, q, OCH_2CH_3), 3.80 (1H, q, $CHCH_3$), 1.60 (3H, d, $CHCH_3$), 1.30 (3H, q, OCH_2CH_3) ppm; MS: $m/z = 364$ (M^+).

3-(4-Ethoxyphenyl)-2-(6-methyl-2-quinolinyl)-4-thiazolidinone (**14**; $C_{21}H_{20}N_2O_2S$)

Yield: 72%; m.p.: 117°C; IR (KBr): $\nu = 1665\,cm^{-1}$; ^1H NMR ($CDCl_3$, δ, 200 MHz): 6.69–8.07 (9H, m, ArH), 6.23 (1H, s, CH), 4.06 (2H, d, CH_2), 3.70 (2H, q, OCH_2CH_3), 2.50 (3H, s, CH_3), 1.33 (3H, q, OCH_2CH_3) ppm; MS: $m/z = 364$ (M^+).

3-(4-Ethoxyphenyl)-5-methyl-2-(6-methyl-2-quinolinyl)-4-thiazolidinone (**15**; $C_{22}H_{22}N_2O_2S$)

Yield: 68%; m.p.: 93°C; IR (KBr): $\nu = 1660\,cm^{-1}$; ^1H NMR ($CDCl_3$, δ, 200 MHz): 6.70–7.60 (9H, m, ArH), 6.15 (1H, s, CH), 4.20 (2H, q, OCH_2CH_3), 3.80 (1H, q, $CHCH_3$), 2.50 (3H, s, CH_3), 1.60 (3H, d, $CHCH_3$), 1.30 (3H, q, OCH_2CH_3) ppm; MS: $m/z = 378$ (M^+).

3-(4-Ethoxyphenyl)-2-(4-quinolinyl)-4-thiazolidinone (**16**; $C_{20}H_{18}N_2O_2S$)

Yield: 92%; m.p.: 118°C; IR (KBr): $\nu = 1665\,cm^{-1}$; ^1H NMR ($CDCl_3$, δ, 200 MHz): 6.72–8.87 (11H, m, ArH and CH), 4.01 (2H, d, CH_2), 3.80 (2H, q, OCH_2CH_3), 1.25 (3H, q, OCH_2CH_3) ppm; MS: $m/z = 350$ (M^+).

3-(4-Ethoxyphenyl)-5-methyl-2-(4-quinolinyl)-4-thiazolidinone (**17**; $C_{21}H_{20}N_2O_2S$)

Yield: 84%; m.p.: 142°C; IR (KBr): $\nu = 1660\,cm^{-1}$; ^1H NMR ($CDCl_3$, δ, 200 MHz): 6.60–8.80 (11H, m, ArH and CH), 4.20 (2H, q, OCH_2CH_3), 3.92 (1H, q, $CHCH_3$), 1.70 (3H, d, $CHCH_3$), 1.30 (3H, q, OCH_2CH_3) ppm; MS: $m/z = 364$ (M^+).

3-(4-Ethoxyphenyl)-2-(8-quinolinyl)-4-thiazolidinone (**18**; $C_{20}H_{18}N_2O_2S$)

Yield: 92%; m.p.: 127°C; IR (KBr): $\nu = 1660\,cm^{-1}$; ^1H NMR ($CDCl_3$, δ, 200 MHz): 6.72–8.96 (11H, m, ArH and CH), 4.02 (2H, d, CH_2), 3.77 (2H, q, OCH_2CH_3), 1.20 (3H, q, OCH_2CH_3) ppm; MS: $m/z = 350$ (M^+).

3-(4-Ethoxyphenyl)-5-methyl-2-(8-quinolinyl)-4-thiazolidinone (**19**; $C_{21}H_{20}N_2O_2S$)

Yield: 85%; m.p.: 134°C; IR (KBr): $\nu = 1660\,cm^{-1}$; ^1H NMR ($CDCl_3$, δ, 200 MHz): 6.60–8.90 (11H, m, ArH and CH), 4.20 (2H, q, OCH_2CH_3), 3.85 (1H, q $CHCH_3$), 1.70 (3H, d, $CHCH_3$), 1.30 (3H, q, OCH_2CH_3) ppm; MS: $m/z = 364$ (M^+).

References

[1] Maier ME (1993) Nachr Chem, Tech Lab **41**: 696, 698, 704
[2] Piancatelli G, D'Auria M, D'Onofrio F (1994) Synthesis **9**: 867
[3] Brown AD, Colvin EW (1991) Tetrahedron Lett **32**: 5187
[4] Burwood DA, Gallucci J, Hart DJ (1985) J Org Chem **50**: 5120
[5] Burwood M, Davies B, Diaz E, Grigg R, Molina P, Sridharan V, Hughes M (1995) Tetrahedron Lett **6**: 9053
[6] Hernandez JE, Fernandez S, Arias G (1988) Synth Commun **18**: 2055
[7] Mance AD, Jakopcick K, Sindler-Kulyk M (1996) Synth Commun, **26**: 923
[8] Yamamoto Y (1987) Acc Chem Res **20**: 243
[9] Yamamoto Y, Asao N (1993) Chem Rev **93**: 2207
[10] Singh VP, Upadhyay GS, Singh H (1992) Asian J Chem Rev **3**: 12
[11] Pandya D, Nair KB (1993) Pharmazie **48**: 414
[12] Hamer J, Macaluso A (1964) Chem Rev **64**: 473
[13] Black DSC, Crozier RF, Davis VC (1975) Synthesis **2**: 205
[14] Philips JW, Clough-Helfman C (1990) Med Sci Res **18**: 403
[15] Kaban Ş, Fidaner Z (1990) Monatsh Chem **121**: 525

Received January 12, 1998. Accepted (revised) February 28, 1998