Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

α-Haloalkyl Haloformates and Related Compounds. II. Synthesis of Dichloromethyl Carbonates and Their Transformation to Carbamates

Tamás Patonay [a], László Hegedüs [a], Ferenc Mogyoródi [b] & László Zolnai [b]
[a] Department of Organic Chemistry, Kossuth Lajos University, H-4010, Debrecen, HUNGARY
[b] SAGROCHEM Ltd, H-3792, Sajóbàbony, HUNGARY
Published online: 16 Feb 2007.

SYNTHETIC COMMUNICATIONS, 24(17), 2507-2513 (1994)

α-HALOALKYL HALOFORMATES AND RELATED COMPOUNDS 21. SYNTHESIS OF DICHLOROMETHYL CARBONATES AND THEIR TRANSFORMATION TO CARBAMATES.

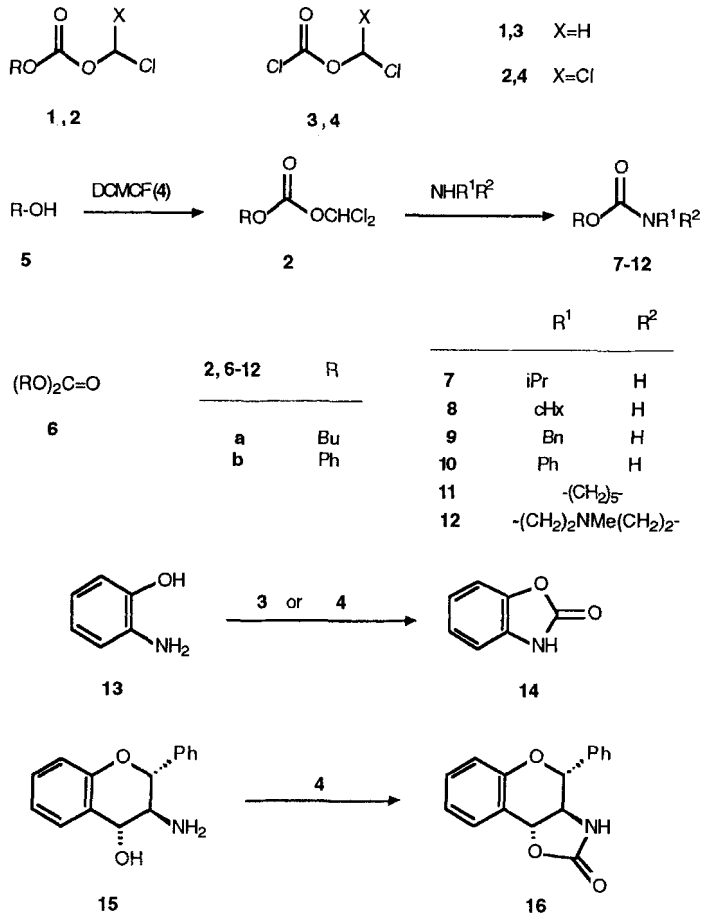
Tamás PATONAY*,[a], László HEGEDŰS[a], Ferenc MOGYORÓDI[b] and László ZOLNAI[b]

[a]Department of Organic Chemistry, Kossuth Lajos University, H-4010 Debrecen, HUNGARY
[b]SAGROCHEM Ltd, H-3792 Sajóbábony, HUNGARY

Abstract: *Dichloromethyl carbonates, easily available upon treatment alcohols with dichloromethyl chloroformate, react with various amines to give carbamates in high yield under mild conditions. Extension of the reaction for the synthesis of oxazolones from 2-aminoalcohols is also demostrated.*

Because of the importance of carbamates as industrial products (pesticides, drugs, plastics etc.) and as protecting groups in the organic synthesis, continuous efforts have been directed toward the development of new carbamate syntheses which work under mild conditions or avoid the use of toxic reagents such as isocyanates. A widely used approach utilizes carbonates containing electron-withdrawing groups (*activated* carbonates)[2]. Recently, we demonstrated the usefulness of chloromethyl carbonates (**1**) obtained by the reaction of alcohols/phenols and chloromethyl chloroformate (CMCF) (**3**) for the preparation of carbamates[1]. An evident opportunity to increase the reactivity of these carbonates is the incorporation of a second halogen into the leaving group as exemplified by dichloromethyl carbonates (**2**). The required starting material dichloromethyl chloroformate (DCMCF) (**4**) has been known for a long time[3] but the troublesome control of the successive photochlorination of methyl chloroformate and the difficult separation of the chlorinated products made compound **4** less available.Probably these difficulties may explain the limited number of publications[4] dealing with the reactivity of DCMCF (**4**). A recently developed procedure[5] for the preparation and separation of chlorinated methyl chloroformates including DCMCF allowed to initiate detailed studies on this field. We describe here the synthesis of dichloromethyl carbonates (**2**) and their transformation into carbamates under mild conditions.

* To whom correspondence should be addressed.



The reaction of model compounds 1-butanol (**5a**) and phenol (**5b**) with DCMCF (**4**) in the presence of acid scavengers (such as pyridine or triethyl amine) afforded the corresponding carbonates **2** in moderate yield. The lower yield (compared to the analogous reaction of CMCF[1]) may be interpreted on the basis of the enhanced reactivity of the carbonyl center which accelerates the secondary reaction resulting in the symmetric carbonates **6**. In the light of this increased reactivity, the comparable or even higher yield of **2** achieved under phase-transfer conditions (benzene-water, sodium hydroxide as base, Adogen 464® catalyst) is surprising.

As expected, treatment of dichloromethyl carbonates **2a,b** with various amines, such as primary and secondary aliphatic amines and aniline, afforded the appropriate carbamates **7-12** in good yield under mild conditions (in apolar solvents benzene or toluene and generally at room temperature). The comparison of data for preparation of N,O-diphenyl carbamate (**10b**) (75.4%

yield, toluene, room temperature starting from dichloromethyl carbonate **2d** *vs.* 37.5 % yield, refluxing dioxane using pyridine as co-base starting from chloromethyl carbonate **1b**[1]) clearly shows the higher reactivity of the carbonyl center in carbonates **2**. In accordance with the earlier results[1], no nucleophilic substitution of the chlorine atom was observed.

The simplicity and efficacy of the reported procedure prompted us to investigate the possible extension of this approach to the one-step preparation of cyclic carbamates starting from 1,2-bifunctional substrates. When 2-aminophenol (**13**) was reacted with DCMCF (**4**) either in dichlormethane solution using triethylamine as acid scavenger or under phase-transfer conditions (toluene-water, sodium hydroxide, triethylbenzylammonium chloride catalyst), 2(3H)-benzoxalone (**14**) was obtained in moderate yield. The repeated reaction using chloromethyl chloroformate (CMCF) (**3**) instead of DCMCF resulted in the formation of **14** in lower yield proving again the superior reactivity of the carbonyl functionalized with dichloromethoxy group. The one-step procedure was found to work in the case of more strained systems, as well. Thus, the reaction of 2,3-*trans*-3,4-*trans*-3-amino-4-hydroxyflavane (**15**) with DCMCF (**4**) in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) afforded the tricyclic carbamate **16**.

Further studies on the synthetic applicability of the highly reactive intermediates available from dichlormethyl chloroformate (**4**) are in progress.

Financial support of this work by OTKA (Grant # I/3 1723) is much appreciated.

EXPERIMENTAL

Mp's were determined on a Boetius hot-stage apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded with a Perkin-Elmer 16 PC FT-IR instrument. ^{1}H-NMR spectra were taken with a Bruker WP 200 SY instrument ($CDCl_3$ solution, internal standard TMS, δ=0 ppm). MS spectra were determined with a VG 7035 GC-MS-DS system (EI, 70 eV). $MgSO_4$ was used as drying agent, column chromatography was performed on Kieselgel 60 (Reanal). Dichloromethyl chloroformate (DCMCF) (**4**) was prepared by photochlorination of methyl formate[5].

Butyl dichloromethyl carbonate (2a)

Method A: A solution of 2.75 mL (30.05 mmol) 1-butanol (**5a**) and 4.2 mL (29.97 mmol) triethyl amine in CH_2Cl_2 (20 mL) was added dropwise to the stirred and cooled (0-5 °C) solution of 3.2 mL (29.97 mmole) DCMCF (**4**) in CH_2Cl_2 (10 mL) in 120 min. The stirring was continued for 70 min then the precipitated salts were filtered off and washed with CH_2Cl_2. The organic phase was successively washed with 10% $NaHCO_3$ solution (2x30 mL) and ice-cold water (2x20 mL), dried and evaporated *in vacuo*. The residue was purified by vacuum distillation to give 2.81 g (46.6%) **2a** carbonate. Bp: 57-58 °C/1.5 Hgmm. ^{1}H-NMR: 7.68 (s, 1H, $\mathbf{CHCl_2}$), 4.27 (t, 2H, $OCH_2CH_2CH_2CH_3$), 1.70 (m, 2H, $OCH_2CH_2CH_2CH_3$), 1.42 (m, 2H, $OCH_2CH_2CH_2CH_3$), 0.97 (t, 3H, $OCH_2CH_2CH_2CH_3$). MS: 145 (<1%), 144 (<1), 117 (<1), 109 (<1), 83 (28.5), 56 (100), 55 (25). Anal. Calcd. for $C_6H_{10}Cl_2O_3$ (201.05): C, 35.85; H, 5.01; Cl, 35.27. Found: C, 35.66; H, 4.89; Cl, 35.35.

Method B: A solution of 3.2 mL (29.97 mmol) DCMCF (**4**) in benzene (15 mL) and a solution of 1.20 g (30.00 mmol) NaOH in water (15 mL) was added dropwise simultaneously in 25 min to a cooled (0-5 °C) and vigorously stirred mixture of 2.75 mL (30.05 mmol) 1-butanol (**5a**) and 0.3 g Adogen 464® with benzene (15 mL) and water (15 mL). After a further 40 min stirring the layers were separated and the aqueous phase was extracted with benzene (2x30 mL). The combined benzene solutions were dried and concentrated. Vacuum distillation of the residue afforded 2.47 g (41.0 %) pure **2a** product.

Dichlormethyl phenyl carbonate (2b)

From 2.965 g (31.50 mmol) phenol (**5b**) using Method A (2.53 mL (31.40 mmol) pyridine as acid scavanger at -30°C 1.79 g (27.0%) **2b** carbonate and 590 mg (17.5%) diphenyl carbonate (**6b**)[6] was obtained by fractionated distillation. **2b.** Bp: 88-90 °C/3 Hgmm. IR (neat): 3073, 3022, 1784 (C=O), 1601, 1591, 1494, 1486, 1324, 1237 (C-O-C), 1054, 1023 (C-O-C), 774, 758, 701, 685. ^{1}H-NMR: 7.75 (s, 1H, $CHCl_2$), 7.41 (dd, 2H, 3,5-H), 7.32 (dd, 1H, 4-H), 7.21 (dd, 2H, 2,6-H). MS: 220 ($M^{+\cdot}$,3), 176 (1.5), 156 (1), 141 (27), 121 (15), 113 (4), 94 (12), 93 (6), 83 (71.5) 77 (100), 65 (15), 51 (11). Anal. Calcd. for $C_8H_6Cl_2O_3$ (221.04): C, 43.47; H, 2.74; Cl, 32.08. Found: C, 43.29; H, 2.92; Cl, 30.95.

Starting from 2.965 g (31.50 mmol) phenol (**5b**) and using Method B, 3.28 g (49.5%) **2b** product and 685 mg (20.3%) **6b** carbonate was obtained by vacuum distillation.

Butyl N-isopropyl carbamate (7a)

A solution of 1.4 mL (16.34 mmol) of isopropyl amine in abs. toluene (5 mL) was added dropwise to the stirred solution of 1.620 g (8.06 mmol) butyl dichloromethyl carbonate (**2a**) in abs. toluene (10 mL) in 45 min at room temperature. Stirring was continued for 8 hours then the reaction mixture was diluted with toluene (50 mL), washed successively with 4% HCl (100 mL), saturated $NaHCO_3$ solution (100 mL) and water (100 mL) and dried. Crude product obtained by evaporation *in vacuo* was purified by short-column chromatography (hexane-EtOAc=10:1) to give 879 mg (68.5%) **7a** carbamate as a colourless oil. IR (neat): 3336 (NH), 2964, 2936, 2874, 1698 (Amide-I), 1530 (Amide-II), 1462, 1386,1364 (Me), 1248 (Amide-III + C-O-C), 1090 (C-O-C). ^{1}H-NMR: 4.60 (br s, 1H, NH), 4.06 (t, 2H, $OCH_2CH_2CH_2CH_3$), 3.80 (m, 1H, $CHMe_2$), 1.58 (m, 2H, $OCH_2CH_2CH_2CH_3$), 1.41 (m, 2H, $OCH_2CH_2CH_2CH_3$), 1.16 (d, 6H, $CHMe_2$), 0.92 (t, 3H, $OCH_2CH_2CH_2CH_3$). Anal. Calcd. for $C_8H_{17}NO_2$ (159.23): C, 60.35; H, 10.76; N, 8.80. Found: C,60.59; H, 10.72; N, 8.97.

Phenyl N-cyclohexyl carbamate (8b)

A solution of 1.9 mL (15.69 mmol) cyclohexyl amine in benzene (5 mL) was dropped into the stirred solution of 1.623 g (7.34 mmol) dichloromethyl phenyl carbonate (**2b**) in benzene (10 mL) at room temperature in 45 min. The mixture was refluxed for 1 hr then stirred at room temperature for 18 hrs. The precipitated salts were filtered off and washed with benzene. The filtrate was washed successively with 4% HCl (100 mL), saturated $NaHCO_3$ solution (100 mL) and water (100 mL), dried and concentrated. The solid residue was triturated with hexane to give 1.437 g

(89.3%) **8b** carbamate. Mp: 134-136 °C. (Lit. mp[7]: 139-140 °C). Its IR (KBr) spectrum agreed with data reported previously[1].

Butyl N-benzyl carbamate (9a)

A solution of 2.5 mL (22.40 mmol) benzyl amine in toluene (5 mL) was added dropwise to the stirred solution of 1.656 g (8.24 mmol) of **2a** carbonate at room temperature in 75 min and stirred for 44 hrs. The mixture was worked up as given for **8b**. The residue obtained by evaporation was purified by short-column chromatography (hexane-EtOAc=10:1) to give 1.478 g (86.6%) **8a** product as a colourless oil. ^{1}H-NMR: 7.30 (m, 5H, Ph), 5.04 (br s, 1H, NH), 4.35 (d, 2H, PhCH_2), 4.09 (t, 2H, O$CH_2CH_2CH_2CH_3$), 1.60 (m, 2H, $OCH_2CH_2CH_2CH_3$), 1.39 (m, 2H, $OCH_2CH_2CH_2CH_3$), 0.92 (t, 3H, $OCH_2CH_2CH_2CH_3$). Anal. Calcd. for $C_{12}H_{17}NO_2$ (207.28): C, 69.54; H, 8.27; N, 6.76. Found: C, 69.88; H, 8.17; N, 6.89.

Butyl N-phenyl carbamate (10a)

Starting from 1.627 g (8.09 mmol) **2a** carbonate and 3.0 mL (32.93 mmol) aniline and using the same procedure as given for **9a** (addition of amine: 25 min, stirring: 9.5 hrs), evaporation afforded a red oil which recrystallized on standing with hexane (5mL). The crude product (771 mg, 49.3%, mp: 47-52 °C) was purified by crystallizing from hexane to yield 520 mg (33.2%) pure **9a** carbamate. Mp: 55-57 °C. (Lit. mp[8]: 61.5-62 °C). IR (KBr): 3324 (NH), 3134, 3058, 3028, 2964, 2932, 2898, 2870, 1704 (Amide-I), 1600, 1502, 1484, 1540 (Amide-II), 1442 (CH_2), 1234 (Amide-III + C-O-C), 1064 (C-O-C), 748, 698. ^{1}H-NMR: 7.30-7.42 (m, 4H, 2,3,5,6-H), 7.07 (m, 1H, 4-H), 6.63 (s, 1H, NH), 4.18 (t, 2H, O$CH_2CH_2CH_2CH_3$), 1.68 (m, 2H, $OCH_2CH_2CH_2CH_3$), 1.42 (m, 2H, $OCH_2CH_2CH_2CH_3$), 0.96 (t, 3H, $OCH_2CH_2CH_2CH_3$). Anal. Calcd. for $C_{11}H_{15}NO_2$ (193.25): C, 68.37; H, 7.82; N, 7.25. Found: C, 68.11; H, 7.81; N, 7.32.

N,O-Diphenyl carbamate (10b)

Starting from 1.623 g (7.34 mmol) **2b** carbonate and 3.0 mL (32.93 mmol) aniline and using the same procedure as given for **9a** (addition of amine: 35 min, stirring: 2.5 hrs), evaporation afforded a solid residue which was treated with hexane-benzene (10:1) mixture and filtered. The crude product was crystallized from hexane-benzene (10:1) mixture to give 1.180 g (75.4%) **10b** product. Mp: 125-126.5 °C. (Lit.mp[9]: 126 °C). Its IR (KBr) spectrum agreed with data reported previously[1].

1-(Phenoxycarbonyl)piperidine (11b)

Starting from 1.623 g (7.34 mmol) **2b** carbonate and 1.5 mL (15.19 mmol) piperidine and using the same procedure as given for **9a** (addition of amine: 35 min, stirring: 3.5 hrs), evaporation afforded a colourless oil (1.44 g, 95.6%) which recrystallized on standing. Trituration with hexane yielded 1.195 g (79.3%) pure **11b** product. Mp: 76-77 °C. (Lit. mp[10]: 81 °C). Its IR (KBr) spectrum was agreed with data reported previously[1].

1-(Butoxycarbonyl)-4-methylpiperazine (12a)

A solution of 1.7 mL (15.31 mmol) 1-methylpiperazine in toluene (5 mL) was dropped to the

stirred solution of 1.620 g (8.06 mmol) **2a** carbonate in toluene (10 mL) at room temperature in 30 min. After 150 min stirring the precipitated salts were filtered off, dissolved in water (100 mL), pH was adjusted to 9 by using diluted NaOH and the aqueous solution was extracted with CH_2Cl_2 (3x40 mL). The toluene filtrate was extracted with 4% HCl (2x50 mL). pH of acidic extract was adjusted to 9 and extracted with CH_2Cl_2 (3x40 mL).The combined CH_2Cl_2 solutions were dried, evaporated *in vacuo* , the residue was purified by short-column chromatography (hexane-EtOAc=95:5) to give 686 mg (42.5%) **12a** as a pale yellow liquid. IR (neat): 2958, 2936, 2864, 2792 (NMe), 1704 (Amide-I), 1460 (CH_2), 1428,1378 (CH_3), 1262, 1236 (Amide-III + C-O-C), 1150 (piperazine ring), 1074 (C-O-C), 1004, 770. ^{1}H-NMR: 4.09 (t, 2H, $OCH_2CH_2CH_2CH_3$), 3.50 (t, 4H, 2,6-H), 2.48 (t, 4H, 3,5-H), 2.41 (s, 3H, 4-Me), 1.62 (m, 2H, $OCH_2CH_2CH_2CH_3$), 1.40 (m, 2H, $OCH_2CH_2CH_2CH_3$), 0.95 (t, 3H, $OCH_2CH_2CH_2CH_3$). MS: 200 ($M^{+\cdot}$,28%), 199 (4), 143 (5), 127 (14), 99 (10), 97 (4), 87 (7), 70 (100), 58 (62), 57 (23), 56 (19), 43 (35), 42 (22.5), 41 (15).

2(3H)-Benzoxazolone (14)

A) A solution of 1.0 mL (9.37 mmol) DCMCF (**4**) in CH_2Cl_2 (10 mL) was added dropwise to the stirred and cooled (0 °C) solution of 1.091 g (9.98 mmol) 2-aminophenol (**13**) and 2.9 mL (20.72 mmol) dry triethyl amine in CH_2Cl_2 (20 mL) in 30 min. The mixture was stirred for 1 hr then the precipitation was filtered off and washed with CH_2Cl_2.The filtrate was successively washed with saturated $NaHCO_3$ solution (50 mL), 4% HCl (50 mL) and water (2x50 mL), dried and evaporated. Recrystallization of the crude product afforded 690 mg (51.1%) **14** product. Mp: 138-139 °C.(hexane-EtOAc) (Lit. mp[11]: 142-143 °C). IR (KBr): 3222 (NH), 1772,1734 (Amide-I), 1480 (Amide-II), 1400, 1306, 1254 (Amide-III + C-O-C), 1146, 942, 742, 696. ^{1}H-NMR (DMSO-d_6): 11.60 (br s, 1H, NH), 7.29 (dd, 1H, 4-H), 7.20-7.04 (m, 3H, 5,6,7-H).

B) A solution of 1.4 mL (13.11 mmol) DCMCF (**4**) in toluene (5 mL) and a 8% NaOH solution (13 mL, 26 mmol) was added dropwise simultaneously in 75 min to a cooled (0-5 °C) and vigorously stirred mixture of 1.091 g (9.98 mmol) 2-aminophenol (**13**), 0.23 g (1.01 mmol) triethylbenzylammonium chloride (TEBAC), 5mL toluene and 5 mL water. The mixture was stirred for 60 min, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3x25 mL). The combined organic layers were successively washed with saturated $NaHCO_3$ solution (50 mL), 4% HCl (50 mL) and water (2x50 mL), dried and evaporated. Purification of the residue by column chromatography (PhMe-abs. MeOH=10:1) yielded 598 mg (44.3%) **14** product. Mp: 136-139 °C.

C) When the A) reaction was repeated using 1.0 mL (11.43 mmol) chloromethyl chloroformate (CMCF) (**3**) instead of DCMCF (**4**), column chromatography resulted in 281 mg (20.8%) **14** product. Mp: 136-137 °C.

***trans,trans*-3a,9b-Dihydro-4H-[1]Benzopyrano[3,4-d]oxazol-2-one (16)**

To a stirred and cooled (0-5°C) solution of 1.690 g (7.00 mmol) of 2,3-*trans*-3,4-*trans*-3-amino-4-hydroxyflavane (**15**) and 1.00 g (8.91 mmol) 1,4-diazabicyclo[2.2.2]octane (DABCO) in dry CH_2Cl_2 (20 mL), a solution of 0.8 mL (7.49 mmol) dichloromethyl chloroformate (**4**) in

dichloromethane (10 mL) is added dropwise. After stirring for 6 hrs a further batch of DABCO (1.00 g, 8.91 mmol) followed by 0.8 mL (7.49 mmol) **4** was added and stirred for 2 hrs. The precipitated salts were filtered off and washed with CH_2Cl_2, the organic filtrate was successively washed with 4% HCl (100 mL), saturated $NaHCO_3$ solution (100 mL) and water (100 mL) and dried. The residue obtained by evaporation *in vacuo* was purified by column chromatography (hexane-EtOAc=4:1) to give 0.461 g (24.6%) **16** oxazolone. Mp: 190-193 °C. IR (KBr): 3260 br (NH), 1754 br (Amide-I), 1633,1612, 1576,1559, 1457 (Amide-II), 1354, 1263 br (Amide-III + C-O-C), 1198(benzopyran skeleton), 1118, 999, 871, 769, 709. ^{1}H-NMR: 7.43 (m, 5H, 4-Ph), 7.33 (dd, 1H, 9-H),7.28 (ddd, 1H, 7-H), 7.03-6.97 (m, 2H, 6,8-H), 5.48 (d, 1H, 4-H), 5.38 (d, 1H, 9b-H), 5.15 (s, 1H, 3-H), 3.88 (dd, 1H, 3a-H); $J_{3a\text{-}H,9b\text{-}H}$=10.4 Hz, $J_{3a\text{-}H,4\text{-}H}$=11.2 Hz.

REFERENCES

1. Part 1: Patonay, T., Patonay-Péli, E. and Mogyoródi, F. *Synth. Commun.*, **1990**, *20*, 2865.
2. For some leading references see: Pedersen, U. *Methoden der Organischen Chemie (Houben-Weyl) E4.*, Ed. Hagemann, H., Thieme Verlag, Stuttgart-New York, **1983**, pp. 144-192 and Ref. 1.
3. (a) Kling, A., Florentin, D. Lassieur, A. and Schmutz, R. *C. R. Sceances Acad. Sci.*, **1919**, *169*, 1074; *Chem. Abstr.*, **1920**, *14*, 738, (b) Grignard, V., Rivat, G. and Urbain, E.,*C. R. Sceances Acad. Sci.*, **1919**, *169*, 1143; *Chem. Abstr.*, **1920**, *15*, 1937, (c) Yura, S. *J. Chem. Soc. Jpn,.,Ind. Chem. Sect.*, **1948**, *51*, 157; *Chem. Abstr*, **1951**, *45*, 5457.
4. (a) EMV-Magyar Szenhidrogenipari Kutato-Fejleszto Intezet *Neth. Pat.* 80 02896 (1981); *Chem. Abstr.*, **1982**, *96*, 162311, (b) Ide, J. and Kitano, N. *Eur. Pat. Appl.* 142.969 (1985); *Chem. Abstr.*, **1986**, *104*, 5710, (c) Folkmann, M. and Lund, F.J. *Synthesis*, **1990**, 1159.
5. Mogyorodi, F., Koppany, E., Berczes, T., Dobe, S., Tasi, L., Zolnai, L. et al. , *Ger. Pat.*. 3.826.584 (1989); *Chem. Abstr.* ,**1989**, *111*, 117289.
6. *Dictionary of Organic Compounds, Vol. 2., 5th Ed.* Ed. Buckingham, J., Chapman & Hall, New York - London, **1982**, 2304.
7. Gysin, H. and Knuesli, E. *US Pat.* 2.776.197 (1957); *Chem. Abstr.*, **1957**, *51*, 11647.
8. Whitehead, C.W. and Traverso, J.J., *J. Am. Chem. Soc.*, **1955**,*77*, 5872.
9. Nekrasov, V. and Melnikov, N., *J. Prakt. Chem.*, **1930**, *126*, 81; *Chem. Abstr.*, **1930**, *24*, 27210.
10. Barcelo, G., Senet, J-P., Sennyey, G., Bensoam, J. and Loffet, A., *Synthesis*, **1986**, 627.
11. Bywater, W.G., Coleman, W.R., Kamm, O. and Merrit, H.H., *J. Am. Chem. Soc.* , **1945**, *67*, 905.

(Received in the USA 07 February 1994)