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TRIISOBUTYLALUMINUM ASSISTED REDUCTIVE REARRANGEMENT OF 2-ETHOXY-4-ALKYL-2,3-DIHYDROFURANS

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Abstract: The reaction of $AlBu^i_3$ with the title compounds was investigated. The reductive rearrangement of 2-ethoxy-4-alkyl-2,3-dihydrofurans proceeds in the same way as that of the corresponding dihydropyran compounds although a complete lack of stereocontrol was observed. On the basis of the experimental results obtained, a likely mechanism for this reductive rearrangement is suggested.

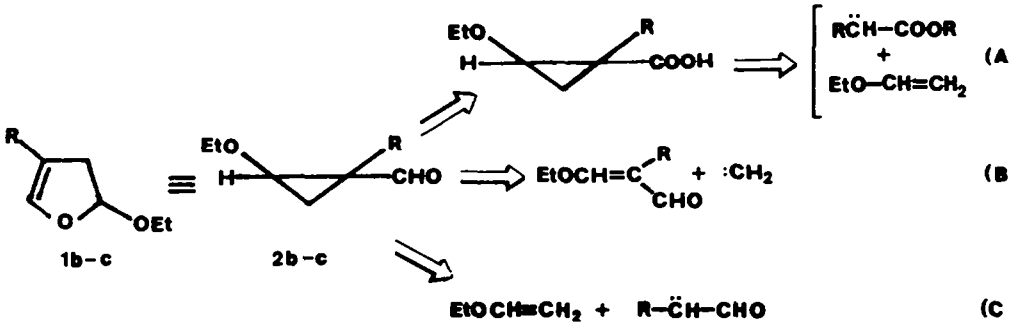
We have already reported the stereocontrolled reductive rearrangement of 2-ethoxy-5-alkyl-3,4-dihydro-2H-pyrans in the presence of $AlBu^i_3$.[2]

In order to establish whether the dynamic and stereochemical aspects of the reaction depend on the ring size, we decided to react 2-ethoxy-4-alkyl-2,3-dihydrofurans (**1**) with $AlBu^i_3$, too. Hence the problem of synthesizing such heterocyclic derivatives, the preparation of which has never been investigated: certain authors unexpectedly obtained samples of 2-alkoxy-3,4-dihydrofurans from the oxidation of cyclopropyl carbinols.[3]

Recently, we also found that mild oxidation of 2-ethoxycyclopropyl-1-methanol, as well as the selective reduction of ethyl 2-ethoxycyclopropylcarboxylate with DBAH, leads to 2-ethoxy-3,4-dihydrofuran (**1a**):[4] these findings showed us that the elusive 2-ethoxycyclopropyl-1-carbaldehyde (**2a**) must be considered as a formal equivalent of **1a**.[4]

In this connection, the synthesis of **2b,c** had to be planned, in order to obtain **1b,c**. In Scheme 1 some reasonable retrosynthetical approaches to **2** are described.

Scheme 1



R=Me(b), Et(c)

The synthetic approach suggested by sequence **A** has been already used to prepare **1a**:[4] to obtain **1b,c** by adopting the same strategy, the corresponding α-diazoesters have to be reacted with ethyl vinylether in the presence of $Rh_2(OCOMe)_4$[5] but, as is well known, in such reaction conditions, α-alkyl-α-diazoesters unfortunately give the corresponding α,β-unsaturated esters.[6]

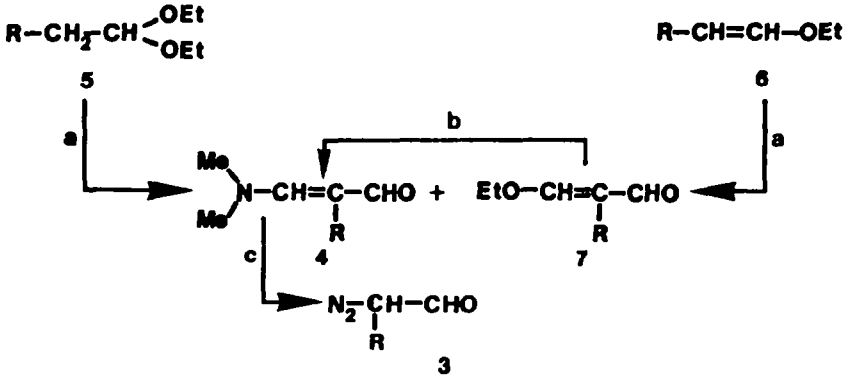
All attempts failed to react carbene with 2-methyl-3-ethoxypropenal (Scheme 1, seq. **B**) in the Simmons-Smith reaction conditions,[7]: the aldehyde was almost totally recovered from the reaction mixture.

On the other hand the reaction of α-alkyl-α-diazoaldehydes (**3b,c**) with ethyl vinylether, in the presence of $Rh_2(OCOMe)_4$, yielded (25-35%)[8] the expected 2-ethoxy-4-alkyl-2,3-dihydrofurans (Scheme 1, seq. **C**); in this context, it must be stressed however that, when α-i-propyl-α-diazoethanal (**3d**) was used, no trace of **1d** was detected: an appreciable amount of 3-methyl-2-butenal was present in the reaction mixture.[9]

The required aldehydes **3b-d** were prepared by reacting the corresponding 3-N,N-dimethylamino-2-alkylpropenals (**4b-d**) with an excess of p-toluensulphonylazide, according to a procedure[1] already described (CAUTION: as soon as the reagents are mixed, at 0° C, the reaction apparatus must be rapidly connected with an efficient mechanical pump in order to avoid explosion)(see Experimental).

Since the preparation of **4b-d**, in the experimental conditions described by Makin,[11] failed, the reaction between acetals (**5**) or ethyl 1-propenyl ether (**6b**) and dimethylformamide and different acid chlorides was reinvestigated (Scheme 2).

Scheme 2



5: R=Me(b),Et(c),Pr^i(d); **6**: R=Me(b)

[a] DMF, XCl [X= $POCl_3$, COCl, $(CO)_2Cl$], CH_2Cl_2; [b] aq.Me_2NH; [c] p.TsN_3, 0° C

The Table shows the main results obtained: in the reaction of diethyl acetals **5b-d** the corresponding **4b-d** are obtained only if a molar ratio [XCl]/[5]=2.1-2.5, is used; the yields are better when phosgene or oxalyl chloride are employed (the latter is easier to handle!).

Table

run	Substrate (A)	XCl	molar ratio [XCl]/[A]	**4** yield%[a]	7/4[b]
1	**5b**	$POCl_3$	2.3	55(66)[c]	0.20
2		$COCl_2$	2.5	70	0.01
3		$(COCl)_2$	2.4	80	0.09
4	**5c**	$POCl_3$	2.3	23	0.50
5		$(COCl)_2$	2.1	75	0.20
6	**5d**	$POCl_3$	2.3	1(27)[c]	30.0
7		$(COCl)_2$	2.1	60(72)[c]	0.2
8	**6b**	$POCl_3$	1.1	32(64)[c,d]	1[d]
9			1.2	75	0.06
10		$(COCl)_2$	1.2	50(66)[c,d]	0.32[d]
11			1.2	80	0.08

[a] Hydrolysis performed with a saturated solution of K_2CO_3; [b] Glc; [c] Mixture of **7** and **4**; [d] Hydrolysis performed with water followed by a saturated solution of K_2CO_3.

If **6b** is used, an almost equimolecular ratio of reagents is required and the overall yields are the same irrespectively of whether $POCl_3$ or $(COCl)_2$ is used.

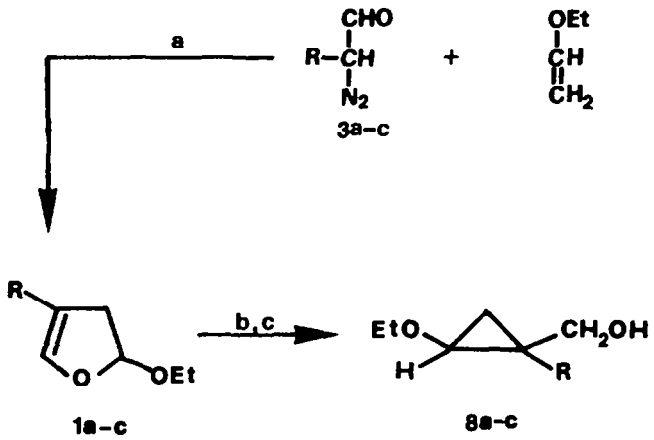
In all cases, the yield was observed to depend on the hydrolysis conditions: higher yields in **4** are obtained if a saturated solution of K_2CO_3 is used (Table). Finally, larger amounts of the side products **7** were observed when $POCl_3$ was used and the formation of **7** also depended on the nature of the precursors (Table); **7** can, however, been converted into **4** by treatment with an acqueous solution of dimethylamine.[12]

Samples of chemically pure **1a-c** (Scheme 3, seq. **A**) were reacted with $AlBu^i_3$ (2 molar equivalents). After hydrolysis, 1/1 mixtures of cis- and trans-2-ethoxy-1-hydroxymethyl-1-alkylcyclopropanes **8a-c** (Scheme 3, seq. **B**) were recovered in good yields (75-90%).

The results obtained show that, once again, the hydride transfer from $AlBu^i_3$ to the C_5 of the heterocyclic ring occurs regioselectively and such a transfer results in contraction of the ring as also happens in the case of 2-ethoxy-5-alkyl-3,4-

dihydro-2H-pyrans[2] even though, in the present case, no stereochemical control occurs.

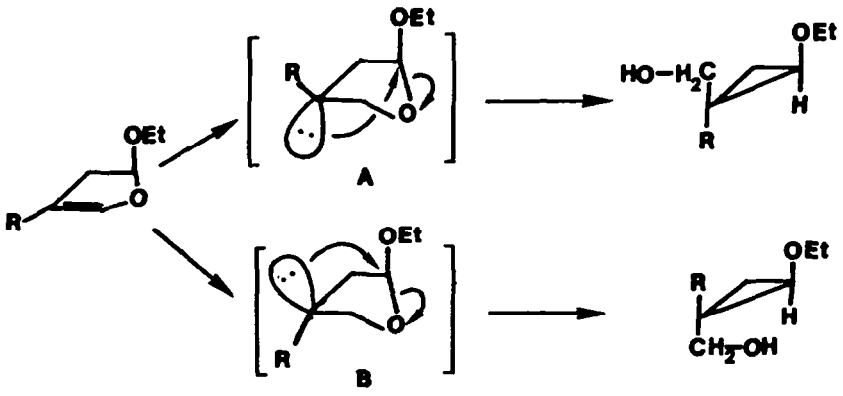
Scheme 3



[a] $Rh_2(OCOMe)_4$; [b] $AlBu^i_3$, n-hexane, 60°C, 20 h; [c] H_3O^+.

The lack of stereocontrol could be explained by assuming that the ring opens as a result of the coordination of $AlBu^i_3$ to the endocyclic oxygen[13] of 1, followed by an unstereocontrolled ring closure. Since the reductive rearrangements of 2-ethoxy-5-alkyl-3,4-dihydro-2H-pyrans[1] and 1 are unlikely to follow different

Scheme 4



mechanistic pathways, it seems more reasonable to suppose that the new C_4-C_2 bonds are formed, in energetically similar transition states, from both the

C_4-diastereomeric carbanions (Scheme 4, **A** and **B**) produced by the hydride transfer to the C_5 of **1**.

The pseudoaxial or pseudoequatorial situation of both substituents and of the C_4-electron pair makes **A** energetically equivalent to **B**.

On the other hand, in the case of dihydropyran derivatives, the analogous carbanionic intermediates are energetically different, owing to the conformational requirements of the 2-ethoxytetrahydropyran ring,[14] so their conversion into reaction products is a stereocontrolled process.

Experimental

All the bp are uncorrected. The IR and ^{1}H Nmr spectra were recorded with a Perkin Elmer 255 spectrophotometer and with a Varian T$_1$ 60 spectrometer, respectively. The IR absorptions are reported as ν_{max} in cm^{-1} and the chemical shifts are expressed in δ ppm with TMS as an internal standard. The MS were obtained with a Hewlett-Packard HP-5995 GC-MS spectrometer equipped with a Hewlett-Packard HP-9825A data station. Glc analyses were performed on a Perkin Elmer F-30 instrument equipped with 2mX0.29 cm columns packed with 8% Carbowax 20M + 2%KOH on 80-100 mesh Chromosorb W DMCS (CW 20 M); preparative glc purifications were carried out on a Perkin Elmer F-21 chromatograph equipped with 3mX0.95 cm columns filled with CW 20M. All the compounds described in this paper gave satisfactory elemental analyses.

3-N,N-Dimethylamino-2-methylpropenal (**4b**):[11] Procedure A

Oxalyl chloride (31.2 g, 0.245 mol) dissolved in 30 ml of 1,2-dichloroethane was slowly (30 min) added to a cooled (-10° C) solution of N,N-dimethylformamide (18.2 g, 0.245 mol) in the same solvent (30 ml) in a 750 ml three-necked flask equipped with a condenser, a mechanical stirrer and a dropping funnel. The mixture was stirred for 15 min at room temperature and then a solution of 1,1-diethoxypropane (**5b**)[15a,b] (13.6 g, 0.103 mol) in 1,2-dichloroethane (25 ml) was also slowly added (30 min) at 0° C.

The reaction mixture was heated at 70° C (4 h) and then hydrolyzed at 0° C with 80 ml of a saturated K_2CO_3 solution, followed by 100 ml of water. Most of the solvent was removed by distillation and the residue, stirred at 90° C for 15 min, was extracted in chloroform (500 ml), after cooling. The organic phase was washed with a saturated solution of K_2CO_3 and dried (K_2CO_3). The excess of N,N-dimethylformamide was removed at reduced pressure (120 mmHg) and distillation of the residual oil gave chemically pure (CW 20M) **4b** (9.3 g, 78%); Bp: 142° C /20mmHg; ^{1}H Nmr: 8.80(1H,s), 6.47(1H,s), 3.18(6H,s), 1.85(3H,s); IR(neat): 3040, 2920, 2870, 2810, 2720, 1600, 1490, 1440, 1395, 1360, 1290, 1195, 1125, 1070, 1015, 870, 725; MS: m/e(I%) 41(100), 96(87.4), 113(M$^+$,85.2), 44(57.9), 45(54,2), 38(41.3), 40(28.0), 39(24.4), 68(23.0), 84(21.1), 69(20.3), 112(20.0), 98(19.8), 43(15.5), 82(14.9), 81(13.1), 70(11.9).

3-N,N-Dimethylamino-2-ethylpropenal (**4c**)[16]

Following procedure A, N,N-dimethylformamide (27.5 g, 0.377 mol) in methylene chloride (45 ml) was treated with oxalyl chloride (47.8 g, 0.376 mol) in 30 ml of the same solvent. The suspension was then reacted with 1,1-diethoxybutane (**5c**)[17] (6.5 g, 0.182 mol) in methylene chloride (30 ml).

After the usual workup, distillation of the crude reaction mixture gave 97% chemically pure **4c** (17.0 g, 72%); Bp 145°C/20 mmHg; ^{1}H Nmr: 8.65(1H,s), 6.36(1H,s), 3.12(6H,s), 2.30(2H,q), 0.95(3h,t); IR(CCl_4): 3040, 2960, 2920, 2870, 2810, 2715, 1595, 1485, 1440, 1395, 1380, 1320, 1300, 1250, 1190, 1120, 1060, 980, 860, 815, 790, 700.

3-N,N-Dimethylamino-2-i.propilpropenal (**4d**)[11]

Using procedure A and starting from N,N-dimethylformamide (21.5 g, 0.294 mol) in methylene chloride (40 ml) and 1,1-diethoxy-3-methylbutane (**5d**)[17] (21.9 g, 0.137 mol) dissolved in the same solvent (30 ml), 97% chemically pure (CW 20M) **4d** (7.70 g) and a 1/1.4 mixture of **4d** and **7d** (4.3 g) were recovered after distillation. This mixture, when reacted with an acqueous 33% solution of Me_2NH,[12] provided a further drop of **4d**. Altogether, a 62% yield was obtained. Bp: 137° C/20 mmHg; ^{1}H Nmr: 8.65(1H,d), 6.30(1H,s), 3.08(6H,s), 3.30-2.70(1H,m), 1.20(6H,d); IR(CCl_4): 3030, 2980, 2950, 2920, 2870, 2815, 2685, 1650, 1600, 1480, 1450, 1380, 1330, 1270, 1200,

1110, 1060, 860, 770.

3-N,N-Dimethylamino-2-methylpropenal (**4b**): Procedure B

$POCl_3$ (20.96 g, 0.137 mol) in 40 ml of 1,2-dichloroethane was added to a solution of N,N-dimethylformamide (10.0 g, 0.137 mol) in the same solvent (40 ml), under nitrogen and at -10° C. A solution of ethyl, prop-1-enylether (**6b**) (10.22 g, 0.119 mol) in 20 ml of 1,2-dichloroethane was added to the suspension, stirred at room temperature for 15 min and then cooled at 0°C. The mixture was heated at 70°C for 40 min. and then hydrolyzed,using the procedure described above. After distillation, chemically pure (CW 20M) **4b** (10.16 g, 72 %) was recovered.

3-N,N-Dimethylamino-2-methylpropenal (**4b**): Procedure C

A large excess of dried $COCl_2$ was bubbled into a cooled (0° C) solution of N,N-dimethylformamide (37.0 g, 0.507 mol) in 80 ml of 1,2-dichloroethane in a three-necked flask equipped with a mechanical stirrer and a condenser. 1,1-Diethoxypropane (**5b**)(26.4 g, 0.200 mol) was slowly added to the white suspension obtained; stirring was continued and then the mixture was heated at 70° C (20 min). Hydrolysis was performed at room temperature with 80 g of brine followed by 160 ml of a saturated Na_2CO_3 solution.

Most of the solvent was azeotropically distilled and, after being heated at 90° C for 30 min, the residue was cooled at room temperature and extracted in a benzene-ethanol mixture (1/1). The organic phase was dried (Na_2CO_3), the solvent removed at reduced pressure and the residue distilled to give chemically pure (CW 20M) **4b** (16.70 g, 70%).

2-Diazopropanal (**3b**)[10a]

p.Toluensulphonylazide (60 g, 0.306 mol) was mixed, under nitrogen, with **4b** (10.0 g, 0.088 mol) in an Erlenmeier flask, cooled at 0°C and connected by means of a glass joint to a trap cooled at -78° C. The trap was rapidly joined to a mechanical pump (0.01mmHg) (CAUTION). The solid mixture was magnetically stirred at 0° C (3h) and then at room temperature (4h). Most of the product was collected in the trap. After restoring the atmospheric pressure with nitrogen, the mixture was warmed at 40° C (2h) and then a further drop of the product was recovered at reduced pressure. Altogether, 6.05 g (78%) of 78% (^{1}H Nmr) chemically pure **3b** were recovered. ^{1}H Nmr: 9.53(1H,s), 1.93(3H,s); IR(Film): 2920, 2870, 2740, 2080, 1630, 1320, 1260, 1245, 980, 820, 800.

2-Diazobutanal (**3c**)[10a]

Using the procedure described above, starting from p.toluensulphonylazide (30.0 g, 0.156 mol) and **4c** (5.61 g, 0.044 mol), 94% chemically pure (^{1}H Nmr) **3c** (2.82 g, 60%) was recovered. ^{1}H Nmr: 9.57(1H,s), 2.40(2H,q), 1.20(3H,t); IR(Film): 2970, 2930, 2870, 2830, 2750, 2070, 1630, 1455, 1330, 1300, 1210, 1050, 820, 790.

2-Diazo-3-methylbutanal (**3d**)

Using the procedure described above for **3b** and starting from p.toluensulphonylazide (30.0 g, 0.156 mol) and **4d** (6.20 g, 0.044 mol), 94% chemically pure (^{1}H Nmr) **3d** (2.84 g, 44%) was recovered. ^{1}H Nmr: 9.46(1H,s), 3.08-2.52(1H,m), 1.23(6H,d); IR(Film): 2960, 2930, 2870, 2750, 2070, 1675, 1635, 1460, 1340, 1330, 12250, 1215, 1060, 820, 710, 625.

2-Ethoxy-4-methyl-2,3-dihydrofuran (**1b**)

A solution of **3b** (6.0 g,[18] 0.069 mol) in 20 ml of ethyl vinyl ether was slowly (1.5 μ.l/s)[19] added to a suspension of $Rh_2(OCOMe)_4$ (0.0564 g, 0.13 mmol) in 40 ml of the same solvent, in a two-necked flask equipped with a condenser and a magnetic stirrer. The reaction mixture was stirred for 12 h and then filtered off through a short column filled with alumina.[20] The solvent was removed and, by careful distillation, 80% chemically pure **1b** (3.77g) was recovered; a sample of chemically pure **1b** (2.70, 30%) was obtained by means of preparative glc (CW 20M). Bp: 124° C; ^{1}H Nmr: 6.06(1H,m), 5.47(1H,dd), 3.83(1H,dq), 3.53(1H,dq), 2.73(1H,m), 2.31(1H,m), 1.67(3H,dt), 1.23(3H,t); IR(Film): 3090, 2980, 2920, 1670, 1440, 1370, 1340, 1300, 1190, 1110, 1065, 1005, 930, 870, 840, 760; MS: m/e(I%) 71(100), 128(M^+,56.5), 84(51.6), 28(46.7), 43(30.4), 29(22.8), 41(20.7), 99(20.7), 39(15.3), 55(15.2), 32(12.1), 53(12.0), 82(8.9), 100(8.7), 31(6.6), 54(6.5), 81(5.4).

2-Ethoxy-4-ethyl-2,3-dihydrofuran (**1c**)

Chemically pure **1c** (3.05g, 25%) was[22] recovered using the same procedure described above, starting from **3c** (7.34 g, 0.084 mol) in ethyl vinyl ether (30 ml) and $Rh_2(OCOMe)_4$ (0.0651 g, 0.15 mmol) in 45 ml of the same solvent, after purification by preparative glc (CW 20M). Bp: 65° C/20 mmHg; ^{1}H Nmr: 6.04(1H,m), 5.47(1H,dd), 3.83(1H,dq), 3.53(1H,dq), 2.74(1H,m), 2.32(1H,m), 2.06(2H,m), 1.22(3H,t), 1.04(3H,t); IR(Film): 3090, 2960, 2920, 2880, 2860, 2840, 1660, 1460,

1440, 1370, 1340, 1300, 1280, 1190, 1110, 1075, 1060, 1045, 940, 870, 835, 755; MS: m/e(I%) 85(100), 142(M^+,88.1), 41(66.7), 97(64.3), 43(57.1), 29(54.8), 32(38.1), 67(28.6), 71(28.3), 39(21.4), 55(19.6), 81(19.4), 99(19.1), 113(18.9), 57(16.7), 83(16.6), 53(14.3), 95(14.2), 31(8.5).

Rection of **1a-c** with $AlBu^i_3$: General procedure

0.5 Molar equivalents of **1a-c** in n.hexane were added to a solution of $AlBu^i_3$ in the same solvent, under Argon and at -5°C. After 15 min the reaction mixture was heated at 80° C for 21 h. Hydrolysis was carried out with water and the products were continuously extracted with ether; the solvent was removed and distillation of the residue gave a chemically pure (CW 20M) diastereoisomeric mixture of the corresponding **8a-c**.

For **8a**: Bp: 77° C/20 mmHg; ^{1}H Nmr(CCl_4): 3.80-3.30(4H,m), 3.50(1H,s, broad), 3.40-2.90(1H,m), 1.40-1.00(3H,2t), 1.00-0.20(3H,m); IR(Film): 3400, 3080, 2980, 2930, 2880, 1450, 1380, 1350, 1300, 1210, 1140, 1085, 1065, 1030, 980, 890.

For **8b**: Bp: 85° C/20 mmHg; ^{1}H Nmr(CCl_4): 3.80-3.20(4H,m), 3.20-2.30(1H,m), 2.40(1H,s), 1.40-1.00(3H,2t), 1.20(3H,s), 0.80-0.20(2H,m); IR(Film): 3410, 3070, 2980, 2930, 2870, 1465, 1455, 1370, 1350, 1170, 1130, 1040, 960, 890.

For **8c**: Bp: 90° C/20mm Hg; ^{1}H Nmr(CCl_4): 3.80-2.80(5H,m), 2.90(1H,s), 2.00-1.10(2H,m), 1.20-1.10(3H,2t), 1.15-0.70(3H,2t), 0.70-0.10(2H,m); IR(Film): 3420, 3070, 2970, 2940, 2880, 1450, 1375, 1355, 1300, 1170, 1135, 1070, 1040, 690.

References and Notes

1. Thesis by M.G.(1984).
2. R.Menicagli, C.Malanga and L.Lardicci, J.Org.Chem., **47**, 288(1982).
3. a)E.Wenkert, M.E.Alonso, B.L.Buckwalter and K.J.Chou, J.Am.Chem.Soc., 99, 4778(1977); b) E.Wenkert, M.E.Alonso, B.L.Buckwalter and L.Sanches, ibidem, **105**, 2011(1983).
4. R.Menicagli, C.Malanga and L.Lardicci, J.Chem.Res., (S),20(1985).
5. M.P.Doyle, D.van Leusen and W.H.Tamblyn, Synthesis, 787(1981).
6. a)N.Ikota, N.Takamura, S.D.Yung and B.Ganem, Tetrahedron Lett., 4163(1981); b)D.Whittaker " The Chemistry of Diazonium and Diazo-groups" in "The Chemistry of "Functional Groups", S.Patai Ed.; J.Wiley and Sons: N.York, Vol.1, p. 404 (1978).
7. H.E.Simmons, T.L.Cairns, S.A.Vladirchick and C.M.Hoiness, Org.Reactions, **20**, 1(1973).
8. In the reaction mixtures, recovered by bulb-to-bulb distillation, no apprecia ble amount of by-products was present (glc). The purification of **3b-c** from the solvent, by preparative glc, caused the drop in the yields.
9. ^{1}H Nmr: 10.01(1H,d), 5.83(1H,ds), 2.15(3H,d), 1.82(3H,d); MS: m/e(I%) 31(100), 55(47.3), 84(M^+,40.2), 83(20.9), 41(10.2).
10. a)J.Kucera, Z.Janousek and Z.Arnold, Collection Czeck.Chem.Commun., **35**, 3818(1970); b) Z.Arnold, J.Chem.Soc.Chem.Commun., 299(1967).
11. S.M.Makin, O.A.Shravrygina, M.I.Berezhnaya and T.P.Koblova, J.Org.Chem.URSS(Engl.Transl.) **8**, 1415(1972).
12. Z.Arnold, F.Sorm,Collection Czech.Chem.Commun., **23**, 45(1958).
13. C.Malanga, G.Ceccarelli, R.Menicagli and L.Lardicci, work in progress.
14. a)W.L.F.Armarego and M.J.Gallager "Stereochemistry of Eterocyclic Compounds"; J.Wiley & Sons: N.York, 1977, Part II, p 80-90; b) C.B.Anderson and D.T.Sepp, Tetrahedron, **24**, 1707(1968) and literature cited therein.
15. a)A.L.Kranzfelder, R.R.Vogt, J.Am.Chem.Soc., **60**, 1714(1938);b)T.Curtis, G.Kraemer, J.Prakt.Chem., **125**, 303(1930).
16. M.Regitz, J.Hocker, A.Liechegener, Org.Synth.Coll., **V**, 179(1973).
17. S.M.McElvain, R.L.Clarke, C.D.Jones, J.Am.Chem.Soc., **64**, 1166(1942).
18. Chemical purity 74%.
19. A programmable Microprocessor Controlled Diluter/Dispenser (Micro Labm Hamilton) was used.
20. The main impurity was the solvent.
21. Chemical purity 94%.