ONE-POT SYNTHESES OF 2,3-DIHYDRO-2,2-DIMETHYLBENZOFURAN DERIVATIVES

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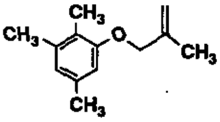
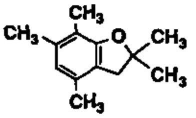
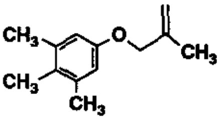
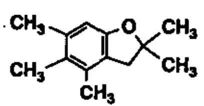
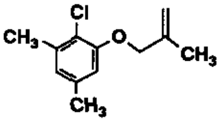
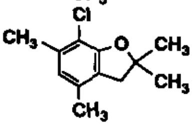
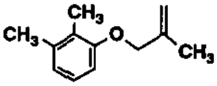
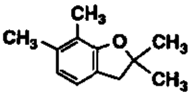
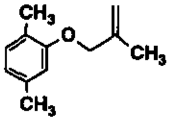
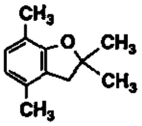
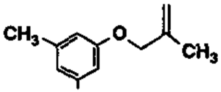
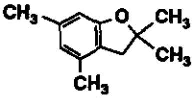
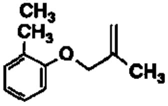
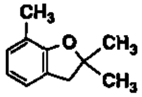
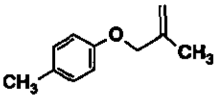
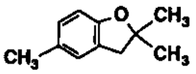
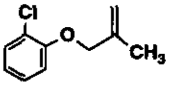
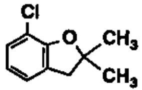
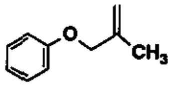
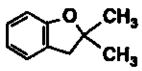
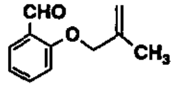
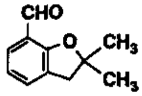
Abstract - A tandem Claisen rearrangement-cyclization reaction of aryl methallyl ethers afforded the corresponding 2,3-dihydro-2,2-dimethylbenzofuran derivatives at -70 °C with aluminium chloride.

2,3-Dihydrobenzofurans are known to be important intermediates in the natural product chemistry.[1] Though there are some reports that 2,3-dihydrobenzofurans were obtained as minor products during Claisen rearrangement,[2] they were generally synthesized by two steps from allyl aryl ethers by the Claisen rearrangement followed by cyclization of the resulting 2-allylphenols in the presence of strong acid catalysts.[3] These procedures resulted in low yields and required vigorous reaction conditions with tedious work-ups. Some other methods reported also required vigorous reaction conditions in several steps.[4] A tandem Claisen rearrangement-cyclization reaction was achieved by refluxing methallyl *p*-tollyl ether at 140 °C for 9 h in the presence of zinc chloride.[5] The reaction conditions, however, were still unsatisfactory with comparatively low yields. Recently, Saidi reported that the rearrangement of allyl naphthyl ethers promoted by titanium tetrachloride produced 2,3-dihydronaphthofurans.[6]

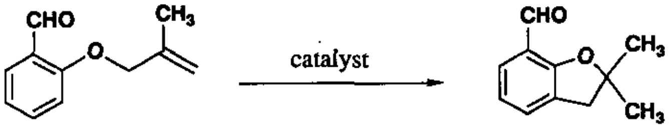
In this paper, we wish to report a facile procedure of the synthesis of 2,3-dihydro-2,2-dimethylbenzofurans from aryl methallyl ethers involving aluminium chloride under very mild conditions. Aryl methallyl ethers were prepared by refluxing substituted phenols with 3-chloro-2-methylpropene and potassium carbonate in a mixted solvent (acetone/DMF, 5/1). Addition of DMF to acetone promoted the reactions to afford better yields in a shorter time. The aryl methallyl ether was treated with 0.1 equiv. of aluminium chloride in dichloromethane at -70 °C and the reaction mixture was allowed to warm to room temperature. The results

Table 1. One-pot synthesis of 2,3-dihydro-2,2-dimethylbenzofuran derivatives from aryl methallyl ethers by using aluminium chloride (0.1 equiv.).

Entry	Starting Material	Product	Reaction Temp.	Yield(%)
1		 (1)	-70 °C → room temperature	98
2		 (2)	-70 °C → room temperature	84
3		 (3)	-70 °C → room temperature	88
4		 (4)	-70 °C → room temperature	67
5		 (5)	-70 °C → room temperature	61
6		 (6)	-70 °C → room temperature	83
7		 (7)	-70 °C → room temperature	44
8		 (8)	-70 °C → room temperature	58
9		 (9)	-70 °C → room temperature	30
10		 (10)	-70 °C → room temperature	37
11		 (11)	-70 °C → room temperature	43

are shown in Table 1. The structures of 2,3-dihydro-2,2-dimethylbenzofurans were easily confirmed with two typical singlets for 6 protons of 2,2-dimethyl group at around 1.5 ppm and for 2 protons of 3-methylene group at around 3.0 ppm, respectively in ^{1}H nmr spectra. The tandem Claisen rearrangement-cyclizations of various aryl methallyl ethers afforded the corresponding 2,3-dihydro-2,2-dimethylbenzofuran derivatives in moderate to good yields. The representative results are summarized in Table 1.

Table 2. Synthesis of 2,3-dihydro-2,2-dimethyl-7-formylbenzofuran from 2-formylphenyl methallyl ether with various catalysts.



Entry	Catalyst (equiv.)	Solvent	Reaction Temp./Reaction Time	yield[a] (%)
1	$AlCl_3$ (0.5)	CH_2Cl_2	-70 °C— room temperature / 1.5 h	42
2	$AlCl_3$ (0.1)	CH_2Cl_2	-70 °C— room temperature / 3 h	51
3	$ZnCl_2$ (0.5)	toluene	130 °C / 4 h	10
4	$ZnCl_2$ (0.1)	o-dichlorobenzene	135 °C / 2 h	33
5	$MgCl_2$ (0.1)	-	180 °C / 3 h	18
6	-	CF_3COOH	60 °C / 2 h	-
7	$BF_3 \cdot Et_2O$ (1.0)	ethyl ether	25 °C / 3 h	-

a. Yields were determined by gc.

The yield is increased as the aromatic ring is substituted by the electron donating groups such as increasing the number of methyl substituents (Entries 1-8 in Table 1). In the case of methallyl trimethylphenyl ethers we obtained the best results (Entries 1 and 2 in Table 1). Substitutions of electron withdrawing groups in aromatic ring gave comparatively low yields together with byproducts which could not be identified (Entries 9 and 11 in Table 1).

The tandem Claisen rearrangement-cyclization reaction was examined with 2-formylphenyl methallyl ether in the presence of various catalysts such as zinc chloride, magnesium chloride, trifluoroacetic acid, or boron trifluoride etherate, and the results are summarized in Table 2. The reaction using 0.1 equiv. of aluminium chloride gave the best yield under the mildest condition in a short time (Entry 2 in Table 2). When 0.5 equiv. of aluminium chloride was utilized, the reaction proceeded a little faster but a tar-like byproduct increased. The reactions using zinc chloride and magnesium chloride needed a higher reaction temperature and a longer reaction time than using aluminium chloride, and also afforded lower yields together with unknown byproducts (Entries 3, 4, and 5 in Table 2). Trifluoroacetic acid and boron trifluoride etherate failed to give the desired products at 60 °C and 25 °C, respectively (Entries 6 and 7 in Table 2).

As a conclusion, aluminium chloride is the best of the choice as catalyst for the tandem Claisen rearrangement-cyclization reaction under mild conditions in the synthesis of 2,3-dihydro-2,2-dimethylbenzofuran derivatives.

EXPERIMENTALS

Melting points were determined on a Unimelt capillary melting point apparatus and uncorrected. Ir spectra were recorded on a Shimadzu IR-435 spectrophotometer. ^{1}H Nmr spectra were obtained with a JEOL PMX-60SI and a Varian GEMINI-200 using $CDCl_3$ as a solvent. All chemical shifts are reported in ppm downfield from internal tetramethylsilane and coupling constants (J) are given in Hz. High resolution mass spectra (HRms) and mass spectra (ms) were obtained on a JEOL JMX-DX-303 mass spectrometer. Elememtal analyses were performed by the Korea Research Institute of Chemical Technology. Chromatographic separations were carried out on a silica gel column (Merck silica gel 60).

General Procedure in the preparation of aryl methallyl ether.

A mixture of the substituted phenol (0.5 mol), 3-chloro-2-methylpropene (54.9 g, 0.6 mol), and potassium carbonate (55.3 g, 0.4 mol) in acetone-DMF (acetone:DMF, 200 ml:40ml) was heated under reflux in the presence of a catalytic amount of potassium iodide (1 g, 0.006 mol) until the substituted phenol disappeared. The reaction mixture was poured into cold water (300 ml) and the organic layer was extracted with ether (300 ml). The ethreal layer was washed 10 % NaOH solution, water, and brine. The ethreal layer was dried over anhydrous $MgSO_4$ and concentrated to afford aryl methallyl ether as a pale yellow oil in good yield.

The oil was further purified by vacuum distillation to afford a colorless oil in good yields (> 80 %).

Methallyl 2,3,5-trimethylphenyl ether

A colorless oil after vacuum distillation (97 %). bp 61-62 °C / 0.05 mmHg; ^{1}H nmr ($CDCl_3$) δ 1.80 (s, 3H), 2.13 (s, 3H), 2.20 (s, 3H), 2.25 (s, 3H), 4.35 (s, 2H), 4.95 (s, 1H), 5.11 (s, 1H), 6.49 (s, 1H), 6.58 (s, 1H); ms (R. I.) 190 (M^+, 100), 175 (88); Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.37; H, 9.40.

Methallyl 3,4,5-trimethylphenyl ether

A colorless oil after vacuum distillation (85.6 %). bp 71 °C / 0.05 mmHg; ^{1}H nmr ($CDCl_3$) δ 1.80 (s, 3H), 2.17 (s, 3H), 2.24 (s, 6H), 4.35 (s, 2H), 4.96 (s, 1H), 5.09 (s, 1H), 5.21 (s, 1H), 6.60 (s, 1H); ir (cm^{-1}) 3008, 1599, 1501, 1443, 1306, 1197, 1139; ms (R. I.) 190 (M^+, 100), 175 (84); Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.25; H, 9.59.

2-Chloro-4,5-dimethylphenyl methallyl ether

A colorless oil after vacuum distillation (97 %). bp 81-82 °C / 0.01 mmHg; ^{1}H nmr ($CDCl_3$) δ 1.82 (s, 3H), 2.12 (s, 3H), 2.17 (s, 3H), 4.42 (s, 2H), 4.97 (s, 1H), 5.12 (s, 1H), 6.67 (s, 1H), 7.07 (s, 1H); ir (cm^{-1}) 2943, 1649, 1598, 1486, 1438, 1379, 1280, 1193, 1149, 1039; ms (R. I.) 212 (29), 210 (M^+, 100); Anal. Calcd for $C_{12}H_{15}OCl$: C, 68.41; H, 7.18. Found: C, 68.21; H, 7.23.

2,3-Dimethylphenyl methallyl ether

A colorless oil after vacuum distillation (86 %). bp 58 °C / 0.025 mmHg; ^{1}H nmr ($CDCl_3$) δ 1.83 (s, 3H), 2.18 (s, 3H), 2.25 (s, 3H), 4.37 (s, 2H), 4.96 (s, 1H), 5.10 (s, 1H), 6.64-6.77 (m, 2H), 6.97-7.05 (m, 1H); ms (R. I.) 176 (M^+, 100), 161 (99); Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.51; H, 9.02.

2,5-Dimethylphenyl methallyl ether [2c)]

A colorless oil after vacuum distillation (85 %). bp 53 °C / 0.05 mmHg; ^{1}H nmr ($CDCl_3$) δ 1.80 (s, 3H), 2.20 (s, 3H), 2.27 (s, 3H), 4.54 (s, 2H), 4.94 (s, 1H), 5.10 (s, 1H), 6.60 (s, 1H), 6.63 (d, J=7.2 Hz, 1H), 6.97 (d, J=7.2 Hz, 1H); ms (R. I.) 176 (M^+, 76), 161 (100).

3,5-Dimethylphenyl methallyl ether

A colorless oil after vacuum distillation (86 %). bp 56 °C / 0.05 mmHg; ^{1}H nmr ($CDCl_3$) δ 1.81 (s, 3H), 2.26 (s, 6H), 4.36 (s, 2H), 4.95 (s, 1H), 5.08 (s, 1H), 6.54 (s, 2H), 6.57 (s, 1H); ir (cm^{-1}) 2888, 1649, 1583, 1455, 1434, 1309, 1282, 1144; ms (R. I.) 176 (M^+, 74), 161 (100); Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.34; H, 9.08.

Methallyl 2-methylphenyl ether [2c)]

A colorless oil after vacuum distillation (97 %). bp 41 °C / 0.05 mmHg; ^{1}H nmr ($CDCl_3$) δ 1.83 (s, 3H), 2.25 (s, 3H), 4.41 (s, 2H), 4.94-4.95 (m, 1H), 5.08-5.09 (m, 1H), 6.72-6.83 (m, 2H), 7.07-7.17 (m, 2H); ms (R. I.) 162 (M^+, 100), 147 (99).

Methallyl 4-methylphenyl ether[2c)]

A colorless oil after vacuum distillation (87 %). bp 47 °C / 0.1 mmHg; ^{1}H nmr ($CDCl_3$) δ 1.80 (s, 3H), 2.16 (s, 3H), 4.27 (s, 2H), 4.95 (d, J=0.8 Hz, 1H), 5.07 (d, J=0.8 Hz, 1H), 6.79-6.85 (m, 2H), 7.02-7.08 (m, 2H); ms (R. I.) 162 (M^+, 100), 147 (75).

2-Chlorophenyl methallyl ether

A colorless oil after vacuum distillation (98 %). bp 59 °C / 0.025 mmHg; ^{1}H nmr ($CDCl_3$) δ 1.90 (s, 3H), 4.52 (s, 2H), 5.05 (s, 1H), 5.20 (s, 1H), 6.85-6.95 (m, 2H), 7.17-7.21 (m, 1H), 7.38-7.42 (m, 1H); ir (cm^{-1}) 2891, 1650, 1579, 1471, 1444, 1369, 1265, 1236, 1055, 1034; ms (R. I.) 184 (28), 182 (M^+, 88), 147 (46), 55 (100); Anal. Calcd for $C_{10}H_{11}OCl$: C, 65.76; H, 6.07. Found: C, 65.53; H, 6.11.

Methallyl phenyl ether[2c)]

A colorless oil after vacuum distillation (92 %). bp 35 °C / 0.05 mmHg; ^{1}H nmr ($CDCl_3$) δ 1.80 (s, 3H), 4.38 (s, 2H), 4.95 (d, J=1.6 Hz, 1H), 5.07 (d, J=1.6 Hz, 1H), 6.87-6.95 (m, 3H), 7.20-7.28 (m, 2H); ms (R. I.) 148 (M^+, 77), 133 (100).

2-Formylphenyl methallyl ether

A colorless oil after vacuum distillation (90 %). bp 84 °C / 0.05 mmHg; ^{1}H nmr ($CDCl_3$) δ 1.80 (s, 3H), 4.32 (s, 2H), 4.97 (d, 2H), 6.7-7.2 (m, 4H), 11.5 (s, 1H); ir (cm^{-1}) 2850, 1680, 1592, 1465, 1230, 1005, 750; ms (R. I.) 176 (M^+, 10), 175 (33, M-1), 121 (100); Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.73; H, 6.72.

2,3-Dihydro-2,2,4,6,7-pentamethylbenzofuran (1).

Methallyl 2,3,5-trimethylphenyl ether (38.3 g, 0.2 mol) in anhydrous dichloromethane (150 ml) was cooled at -70 °C under nitrogen atmosphere. To this mixture was added slowly aluminium chloride (2.7 g, 0.02 mol, 0.1 equiv.) over 15 min and the mixture was stirred at that temperature for 30 min, then slowly warmed up to room temperature. The brown reaction mixture was poured in several portions into an ice-cold water with stirring. The organic layer was separated, washed with brine twice, dried over $MgSO_4$, and concentrated to give a brown solid. The solid was purified on a short silica gel column (n-hexane) to give 2,3-dihydro-2,2,4,6,7-pentamethylbenzofuran (1) as a white crystalline solid (37.7 g, 98.6 %), mp 47 °C; bp 65 °C / 0.05 mmHg; ^{1}H nmr ($CDCl_3$) δ 1.47 (s, 6H), 2.08 (s, 3H), 2.15 (s, 3H), 2.20 (s, 3H), 2.90 (s, 2H), 6.49 (s, 1H); ir (cm^{-1}) 1506, 1453, 1401, 1276, 1144, 1080, 833; HRms calcd. for $C_{13}H_{18}O$: 190.1358, found: 190.1375; Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.89; H, 9.47.

The following 2,3-dihydro-2,2-dimethylbenzofuran derivatives were prepared in an analogous manner.

2,3-Dihydro-2,2,4,5,6-pentamethylbenzofuran (**2**).

A colorless oil after vacuum distillation (84 %). bp 59 °C / 0.025 mmHg; ^1H nmr ($CDCl_3$) δ 1.42 (s, 6H), 2.05 (s, 3H), 2.10 (s, 3H), 2.19 (s, 3H), 2.90 (s, 2H), 6.42 (s, 1H); ir (cm^{-1}) 1591, 1469, 1433, 1259, 1060, 1034, 875, 835, 780; HRms calcd. for $C_{13}H_{18}O$: 190.1358, found: 190.1398; Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.92; H, 9.46.

7-Chloro-2,3-dihydro-2,2,4,6-tetramethylbenzofuran (**3**).

A pale yellow crystalline solid (88 %). mp 41 °C; ^1H nmr ($CDCl_3$) δ 1.51 (s, 6H), 2.10 (s, 3H), 2.18 (s, 3H), 3.10 (s, 2H), 6.90 (s, 1H); ir (cm^{-1}) 1593, 1469, 1442, 1258, 1142, 1036, 870; HRms calcd. for $C_{12}H_{15}OCl$: 210.0811, found: 210.0972; Anal. Calcd for $C_{12}H_{15}OCl$: C, 68.41; H, 7.18. Found: C, 68.16; H, 7.11.

2,3-Dihydro-2,2,6,7-tetramethylbenzofuran (**4**).

A colorless oil after vacuum distillation (67 %). bp 45 °C / 0.05 mmHg; ^1H nmr ($CDCl_3$) δ 1.44 (s, 6H), 2.10 (s, 3H), 2.21 (s, 3H), 2.95 (s, 2H), 6.61 (d, J=7.2 Hz, 1H), 6.84 (d, J=7.2 Hz, 1H); ir (cm^{-1}) 1587, 1436, 1270, 1075, 907, 789; HRms calcd. for $C_{12}H_{16}O$: 176.1201, found: 176.1231; Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.54; H, 9.03.

2,3-Dihydro-2,2,4,7-tetramethylbenzofuran (**5**).4b)

A colorless oil after vacuum distillation (61 %). bp 48 °C / 0.03 mmHg; ^1H nmr ($CDCl_3$) δ 1.45 (s, 6H), 2.15 (s, 6H), 2.90 (s, 2H), 6.53 (d, J=7.6 Hz, 1H), 6.82 (d, J=7.6 Hz, 1H); ir (cm^{-1}) 1587, 1433, 1407, 1255, 1137, 1065, 871, 785; HRms calcd. for $C_{12}H_{16}O$: 176.1201, found: 176.1236.

2,3-Dihydro-2,2,4,6-tetramethylbenzofuran (**6**).

A colorless oil after vacuum distillation (83 %). bp 43 °C / 0.025 mmHg; ^1H nmr ($CDCl_3$) δ 1.45 (s, 6H), 2.17 (s, 3H), 2.25 (s, 3H), 2.85 (s, 2H), 6.40 (s, 1H), 6.45 (s, 1H); ir (cm^{-1}) 1600, 1483, 1445, 1407, 1275, 1112, 1044, 950, 867, 826, 776; HRms calcd. for $C_{12}H_{16}O$: 176.1201, found: 176.1227; Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.48; H, 9.21.

2,3-Dihydro-2,2,7-trimethylbenzofuran (**7**).2c), 4a)

A colorless oil after vacuum distillation (44 %). bp 32 °C / 0.1 mmHg; ^1H nmr ($CDCl_3$) δ 1.47 (s, 6H), 2.60 (s, 3H), 3.00 (s, 2H), 6.75-7.20 (m, 3H); ir (cm^{-1}) 1592, 1455, 1433, 1251, 1238, 1126, 873, 753; ms (R. I.) 162 (100, M^+), 147 (91).

2,3-Dihydro-2,2,5-trimethylbenzofuran (**8**).2c), 4a)

A colorless oil after vacuum distillation (58 %). bp 32 °C / 0.1 mmHg; ^{1}H nmr ($CDCl_3$) δ 1.47 (s, 6H), 2.38 (s, 3H), 3.00 (s, 2H), 6.80-7.20 (m, 3H); ir (cm^{-1}) 1607, 1474, 1437, 1243, 870, 802; ms (R. I.) 162 (100, M$^+$), 147 (75.7).

7-Chloro-2,3-dihydro-2,2-dimethylbenzofuran (9).

A colorless oil after vacuum distillation (30 %). bp 34 °C / 0.1 mmHg; ^{1}H nmr ($CDCl_3$) δ 1.48 (s, 6H), 3.00 (s, 2H), 6.80-7.40 (m, 3H); ir (cm^{-1}) 1577, 1468, 1436, 1239, 1190, 745; Anal. Calcd for $C_{10}H_{11}OCl$: C, 65.76; H, 6.07. Found: C, 65.61; H, 6.13.

2,3-Dihydro-2,2,-dimethylbenzofuran (10).[2c), 4a)]

A colorless oil after vacuum distillation (37 %). bp 31 °C / 0.1 mmHg; ^{1}H nmr ($CDCl_3$) δ 1.46 (s, 6H), 3.00 (s, 2H), 6.80-7.30 (m, 4H); ir (cm^{-1}) 1590, 1469, 1244, 1120, 875, 744; ms (R. I.) 148 (100, M$^+$), 133 (86.8), 105 (28.4), 94 (25.4).

7-Formyl-2,3-dihydro-2,2,-dimethylbenzofuran (11).

A colorless oil (43 %) after purification by a silica gel column (n-hexane / EtOAc, 10 / 1). mp 81-82 °C; ^{1}H nmr ($CDCl_3$) δ 1.49 (s, 6H), 2.99 (s, 2H), 6.60-7.55 (m, 3H), 10.05 (s, 1H); ir (cm^{-1}) 1660.3, 1594.1, 1379.9, 1278.3, 1239.4, 1192.4, 1123.7, 870.6, 786.4, 726.7; ms (R. I.) 177 (80.6, M+1), 176 (100, M$^+$); Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.69; H, 6.66.

REFERENCES

1. a) F. M. Dean, 'Naturally Occurring Oxygen Ring Compounds,' Butterworth, London, 1963, p. 135 ; b) P. Cagniant, D. Cagniant, 'Advanced Heterocyclic Chemistry,' Vol. 18, ed. by A. R. Katritzky and A. J. Boulton, Academic Press, New York, 1975, p. 358 ; c) A. Mustafa, 'The Chemistry of Heterocyclic Compounds, ed. by A. Weisenberg and E. C. Taylor, John Wiley & Sons, 1974, Chapt. IV.
2. a) L. Claisen and O. Eisleb, *Ann.*, 1913, **401**, 79 ; b) L. Claisen and E. Tietze, *Ber.*, 1926, **59**, 2344 ; c) Q. R. Bartz, R. F. Miller, and R. Adams, *J. Am. Chem. Soc.*, 1935, **57**, 371 ; d) R. T. Arnold and J. C. McCool, *J. Am. Chem. Soc.*, 1942, **64**, 1315 ; e) H. M. Okely and M. F. Grundon, *J. Chem. Soc., Perkin Trans. I*, **1981**, 897 ; f) V. Speziale, H. G. Dao, and A. Lattes, *J. Heterocycl. Chem.*, 1978, **15**, 225.
3. a) A. T. Shulgin and A. W. Baker, *J. Org. Chem.*, 1963, **28**, 2468 ; b) L. M. Harwood, *J. Chem. Soc., Chem. Commun.*, **1982**, 1120 ; c) L. M. Harwood, *J. Chem. Soc., Chem. Commun.*, **1983**, 530 ; d)

U. Widmer, H. Hansen, and H. Schmid, *Helv. Chim. Acta*, 1973, **56**, 2644 ; e) D. E. Nichols, A. J. Hoffman, R. A. Oberlender, and R. A. Riggs, *J. Med. Chem.*, **1986**, 302.

4. a) J. C. Martini, N. W. Franke, and G. M. Singerman, *J. Org. Chem.*, 1970, **35**, 2904 ; b) A. Arduini, A. Pochini, and R. Ungaro, *Synthesis*, **1984**, 950.
5. V. M. Feoktistov, L. I. Bunina-Krivorukova, and Kh. V. Bal'yan, *Zh. Org. Khim.*, **1978**, **14** , 807. (*Chem. Abstr.*, 1978, **89**, 59734h).
6. M. R. Saidi, *Heterocycles*, 1982, **19**, 1473.

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