Ring Transformation of 5-Amino (or Acylamino)-6-hydroxy (or Benzoyloxy)methylpyrimidin-4(3*H*)-ones into 1*H*-Imidazoles

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Treatment of 5-acylamino-6-hydroxy (or benzoyloxy)methyl-3-phenylpyrimidin-4(3*H*)-one **5,10** with 5% aqueous sodium hydroxide in ethanol gave 2-alkyl-5-hydroxymethyl-4-phenylcarbamoyl-1*H*-imidazoles **7,11**. Oxidation of 5-amino-6-benzoyloxymethyl-3-phenylpyrimidin-4(3*H*)-one **9** in the presence of copper(II) chloride in alcohol gave 2-alkoxy-5-alkoxymethyl-4-phenylcarbamoyl-1*H*-imidazoles **12a,b** accompanied by 5-amino-6-alkoxymethyl-3-phenylpyrimidin-4(3*H*)-ones **13a,b**.

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The previously reported ring transformation [1] of 5-acylamino-6-methyl-3-phenylpyrimidin-4(3*H*)-ones **1** into 2-alkyl (or aryl)-5-methyl-4-phenylcarbamoyl-1*H*-imidazoles **2** is one of the useful strategies for the preparation of 2-substituted 1*H*-imidazoles. We imagined that the replacement of the C6-methyl group of **1** with the more reactive hydroxy-methyl functionality would lead to the more useful 1*H*-imidazoles. Thus, we have examined the transformation of 5-amino (or acylamino-6-hydroxy (or benzoyloxy)methyl-3-phenylpyrimidin-4(3*H*)-ones **5,9,10** into 2-substituted 5-hydroxy (or alkoxy)-4-phenylcarbamoyl-1*H*-imidazoles **7,11,12a,12b**.

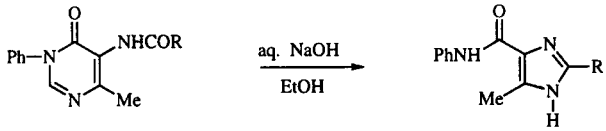
The starting compound 5-amino-6-formyl-3-phenylpyrimidin-4(3*H*)-one **3** [2] was reduced with sodium borohydride in methanol to give 5-amino-6-hydroxymethyl-3-phenylpyrimidin-4(3*H*)-one **4**, whose acylation with propionyl chloride in the presence of potassium carbonate at 0° gave 6-hydroxymethyl-5-propionamido-3-phenylpyrimidin-4(3*H*)-one **5** accompanied by 5-amino-6-propionyloxymethyl-3-phenylpyrimidin-4(3*H*)-one **6**. Transformation of **5** into 2-ethyl-5-hydroxymethyl-4-phenylcarbamoyl-1*H*-imidazole **7** was carried out in the presence of 5% aqueous sodium hydroxide in ethanol according to the previously reported procedure [1]. As for the synthesis of 2-methylimidazole, initially we planned its formation from 5-acetamido-6-hydroxy-3-phenylpyrimidin-4(3*H*)-one which was expected to be obtained by the reaction of **4** with acetyl chloride. However, the reaction of **4** with acetyl chloride gave resinous products which were probably mixtures of mono, di and tri acylated products of **4**. The attempted separation of the mixture was unsuccessful. Acetylation of **3** with acetic anhydride and pyridine also failed to provide the mono acetylated product. 5-*N,N*-Diacetylamino-6-formyl-3-phenylpyrimidin-4(3*H*)-one **8** was the only product prepared in 26% yield; **3** was recovered in 37% yield. We thought that if a bulky acyl chloride was used, only the mono substituted product might be obtained. Thus, the reaction of **4** with benzoyl chloride in dichloromethane in the presence of 5% aqueous sodium hydroxide [3] was carried out with cooling with ice to give the mono acylated product, which was identified as 5-amino-6-benzoyloxymethyl-3-phenylpyrimidin-4(3*H*)-one **9** by the infrared (ir) and proton magnetic resonance (^{1}H nmr) spectra. Another isomer 5-benzamido-6-hydroxymethyl-3-phenylpyrimidin-4(3*H*)-one was not obtained. In the ir spectrum absorptions due to the primary amine and ester carbonyl group were observed at 3420, 3315 and 1700 cm^{-1}. In the ^{1}H nmr spectrum, the signal due to the methylene protons, appeared downfield (δ 5.34 ppm) in comparison with that (δ 4.62 ppm) of **4**. We predicted acylation of **9** and its successive treatment in alkaline medium would give 1*H*-imdazoles. Thus, acylation of **9** with acetic anhydride in pyridine was carried out to give 5-acetamido-6-benzoyloxymethyl-3-phenylpyrimidin-4(3*H*)-one **10**, whose treatment with 5% aqueous sodium hydroxide in ethanol successfully afforded the objective imidazole **11**.

Previously we reported the transformation of 5-amino-6-methyl-3-phenylpyrimidin-4(3*H*)-one to 2-alkoxy-5-methyl-4-phenylcarbamoyl-1*H*-imidazoles in the presence of copper(II) chloride in alcohols [4]. We thought it might be interesting to investigate the reaction of **9** with copper(II) chloride in methanol or ethanol, because the reaction seemed to afford imidazoles with more active functional groups. The reaction of **9** with copper(II) chloride in methanol gave 2-methoxymethyl-4-phenylcarbamoyl-1*H*-imidazole **12a** and 5-amino-6-methoxymethyl-3-phenylpyrimidin-4(3*H*)-one **13a**. The benzoyloxy group was replaced by a methoxy group. The structural confirmation was carried out by ^{1}H nmr, ms and ir spectra. Similarly the reaction of **9** with copper(II) chloride in ethanol afforded 2-ethoxy-5-ethoxymethyl-4-phenylcarbamoyl-1*H*-imidazole **12b** and 5-amino-6-ethoxymethyl-3-phenylpyrimidin-4(3*H*)-one **13b**.

A possible reaction mechanism of the formation of **13** is shown in Scheme 4. Nucleophilic attack of the alcohol

on the methylene carbon of **9** aided by chelation of copper(II) chloride to the oxygen atom of the benzoyl ester should form **13**. Transformation of **13** to **12** is expected to proceed by the same mechanism reported earlier [4].

Scheme 1



1 **2**

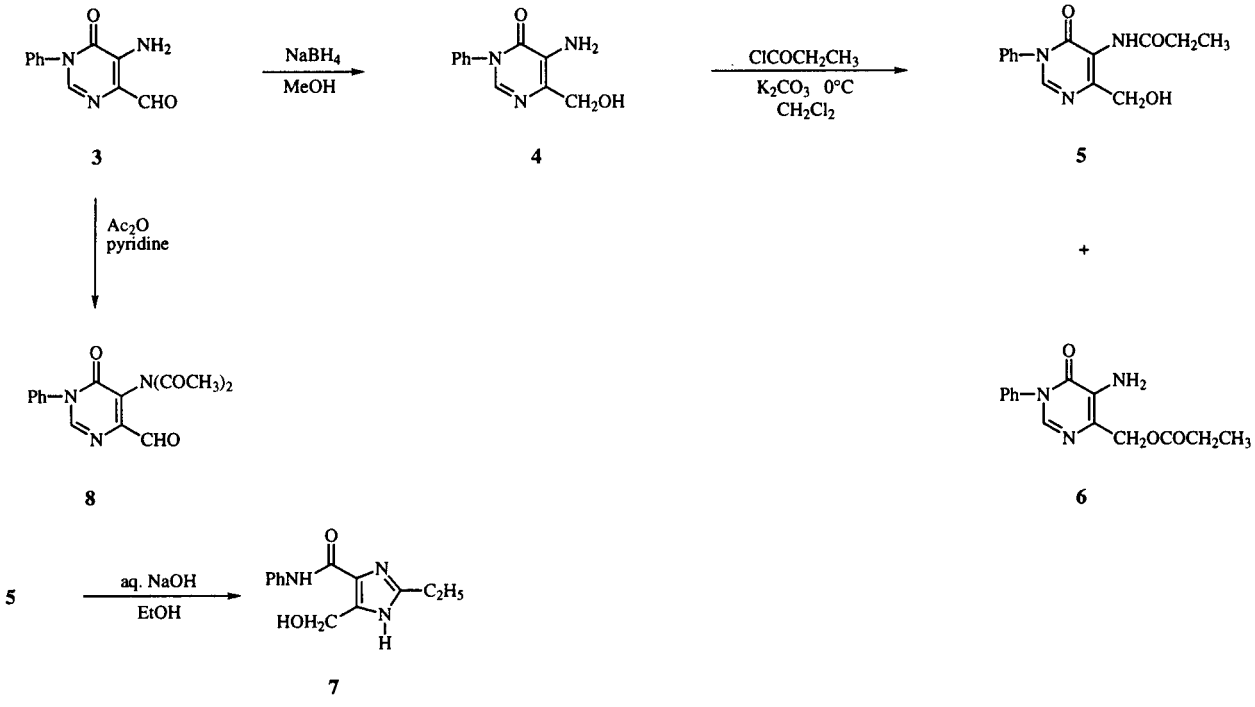
EXPERIMENTAL

All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. The infrared spectra were measured with a JASCO IR-180 spectro photometer. Mass spectra were measured with a JEOL JMS-DX 300 mass spectrometer. Proton nuclear magnetic resonance spectra were recorded with a JEOL JNM-FX-100 spectrometer using tetramethylsilane as internal standard. Abbreviations are as follows: s, singlet; d, doublet; q, quartet; br, broad; m, multiplet.

5-Amino-6-hydroxymethyl-3-phenylpyrimidin-4(3*H*)-one (**4**).

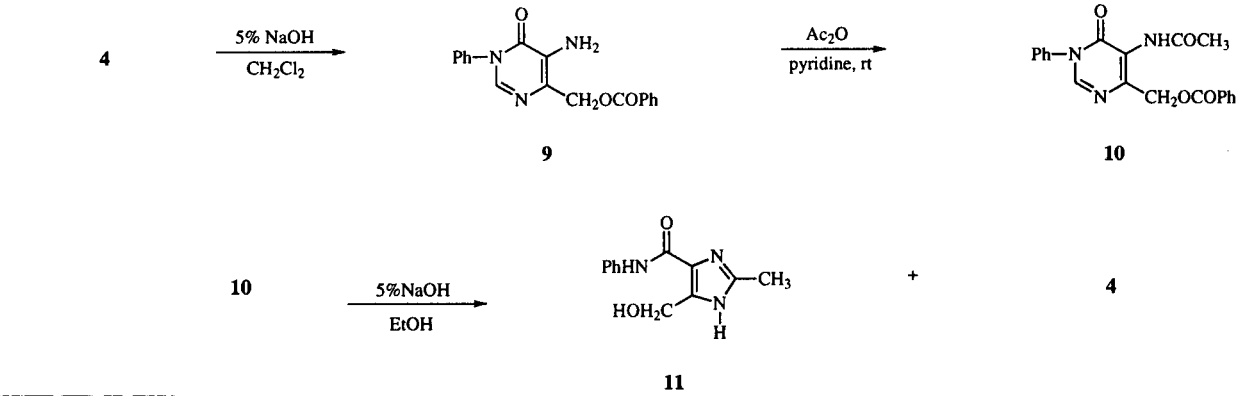
Sodium borohydride (106 mg, 2.79 mmoles) was added to a stirred solution of **3** (400 mg, 1.86 mmoles) in 500 ml of methanol. Stirring was continued for 4 hours at room temperature.

Scheme 2

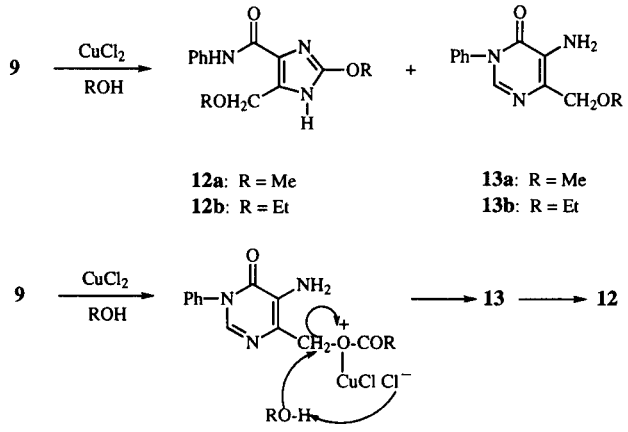


3 **4** **5** **8** **6** **7**

Scheme 3



Scheme 4



The solvent was removed by distillation. Water was added to the residue and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate. The solvent was distilled and the residue was purified by column chromatography on silica gel eluting with a mixture of chloroform-methanol (15:1), mp 163-164° (from ethanol), yield 364 mg (90%); ^{1}H nmr (deuteriochloroform): δ 3.20 (1H, br, -OH), 4.41 (2H, br s, $-NH_2$), 4.62 (2H, s, $-CH_2OH$), 7.20-7.60 (5H, m, -Ph), 7.68 (1H, s, -N-CH=N-); ir (potassium bromide): ν max 3460-3350 cm^{-1} (OH, NH_2), 1660 (C=O) cm^{-1}; ms: m/z 217 (M^+).

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.56; H, 5.10; N, 19.09.

6-Hydroxymethyl-5-propionamido-3-phenylpyrimidin-4(3*H*)-one (**5**) and 5-Amino-6-propionyloxymethyl-3-phenylpyrimidin-4(3*H*)-one (**6**).

A solution of propionyl chloride (101 mg, 1.1 mmoles) in 10 ml of dichloromethane was added to a solution of **4** (204 mg, 1 mmole) in 20 ml of dichloromethane with stirring at 0° in the presence of potassium carbonate (100 mg). The stirring was continued for 4 hours. The solvent was removed by distillation and the residue was subjected to column chromatography on silica gel to give **5** and **6**.

Compound **5** had mp 164-166° (from ethanol), yield 197 (72%); ^{1}H nmr (deuteriochloroform): δ 1.25 (3H, t, J = 7 Hz, $-CH_2CH_3$), 2.42 (2H, q, J = 7 Hz,$-CH_2CH_3$), 3.70 (1H, bs, $-CH_2OH$), 4.42 (2H, s, $-CH_2OH$), 4.66 (1H, s, -NH-), 7.20-7.80 (5H, m, aromatic protons), 8.12 (1H, s, -N=CH-N); ir (potassium bromide): ν max 3460 cm^{-1} (OH), 3260 cm^{-1} (NH), 1660 cm^{-1} (C=O); ms: m/z 273 (M^+).

Anal. Calcd. for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.14; H, 5.20; N, 15.66.

Compound **6** had mp 90-92° (from ethanol), yield 46 mg (17%); ^{1}H nmr (deuteriochloroform): δ 1.20 (3H, t, J = 7 Hz, $-CH_2CH_3$), 2.48 (2H, q, J = 7 Hz, $-CH_2CH_3$), 4.85 (2H, br s, NH_2, deuterium oxide exchangeable), 5.12 (2H, s, $-CH_2O-$), 7.50-8.10 (6H, aromatic protons and N-CH=N); ms: m/z 273 (M^+).

Anal. Calcd. for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.67; H, 5.81; N, 15.59.

2-Ethyl-5-hydroxymethyl-4-phenylcarbamoyl-1*H*-imidazole (**7**).

A mixture of **5** (270 mg), 5% aqueous sodium hydroxide (3 ml) and ethanol (20 ml) was refluxed for 3 hours. After cooling the reaction mixture was neutalized with 5% aqueous hydrochloric acid and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was crystallized from ethanol to give colorless prisms, mp 189-190°, yield 94 mg (38%); ^{1}H nmr (deuteriochloroform): δ 1.37 (3H, t, J = 7 Hz, $-CH_2CH_3$), 2.75 (2H, q, J = 7 Hz, $-CH_2CH_3$), 4.82 (2H, s, CH_2OH), 7.10-7.70 (5H, m, aromatic protons); ir (potassium bromide): ν max 3210 cm^{-1} (NH), 3000 cm^{-1} (OH), 1650 cm^{-1} (C=O); ms: m/z 245 (M^+).

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.90; H, 6.00; N, 17.25.

5-Diacetylamino-6-formyl-3-phenylpyrimidin-4(3*H*)-one (**8**).

A mixture of **3** (54 mg), acetic anhydride (2 ml), and pyridine (2 ml) was heated 100° for 5 hours. Excess acetic anhydride and pyridine were distilled off and the residue was subjected to preparative thin layer chromatography to separate starting material **3** (20 mg, 37%) and **8** (18 mg, 26%). Compound **8** had colorless prisms of mp 151-152° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 2.15 (3H, s, $-COCH_3$), 2.40 (3H, s, $-COCH_3$), 7.25-7.55 (6H, m, aromatic protons and -N=CH-N), 8.28 (1H, s, -CHO); ir (potassium bromide): ν max 1770, 1740 cm^{-1} (C=O), 1680 cm^{-1} (N-C=O); ms: 299 (M^+).

Anal. Calcd. for $C_{15}H_{13}N_3O_4$: C, 60.19; H, 4.38; N, 14.04. Found: C, 60.41; H, 4.75; N, 14.42.

5-Amino-6-benzoyloxymethyl-3-phenylpyrimidin-4(3*H*)-one (**9**).

A solution of benzoyl chloride (178 mg, 1.27 mmoles) in 2 ml of dichloromethane was added to a stirred solution of **4** (250 mg, 1.15 mmoles) in 35 ml of dichloromethane and 25 ml of 5% aqueous sodium hydroxide with ice cooling. Water was added to the reaction mixture, which was extracted with chloroform. The extract was dried and the solvent was removed by distillation. The residue was subjected to preparative thin layer chromatography to give colorless prisms of mp 143-145° (from ethanol), yield 239 mg (65%); ^{1}H nmr (deuteriochloroform): δ 4.95 (2H, s, erased on deuterium oxide addition, NH_2), 5.34 (2H, s, $-CH_2O-$), 7.69 (1H, s, N-CH=N-), 7.35-8.10 (10H, m, aromatic protons); ir (potassium bromide): ν max 3420, 3315 cm^{-1} (NH_2), 1700 cm^{-1} (-O-C=O); ms: m/z 321 (M^+), 216 (M^+-PhCO).

Anal. Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.56; H, 4.92; N, 13.41.

5-Actamido-6-benzoyloxymethyl-3-phenylpyrimidin-4(3*H*)-one (**10**).

A mixture of **8** (100 mg, 0.31 mmole), pyridine (3 ml) and acetic anhydride (3 ml) was stood overnight at room temperature. The mixture was poured into water and extracted with chloroform. The extract was washed with water and dried over anhydrous magnesium sulfate. Chloroform was distilled off to give colorless prisms of mp 84-86° (from ethanol), yield 110 mg (97%); ms: m/z 363 (M^+).

Anal. Calcd. for $C_{20}H_{17}N_3O_4$: C, 66.11; H, 4.72; N, 11.57. Found: C, 66.25; H, 4.91; N, 11.82.

2-Methyl-5-hydroxymethyl-4-phenylcarbamoyl-1*H*-imidazole (**11**).

A mixture of **9** (36 mg), 5% aqueous sodium hydroxide (1 ml) and ethanol (5 ml) was refluxed for 3 hours. After cooling the raction mixture was neutralized with 5% hydrochloric acid and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and the solvent was distilled off. The residue was purified by preparative thin layer chromatography to give colorless prisms of mp 164-165° (from ethanol), yield 12 mg (52%); ^{1}H nmr (deuteriochloroform): δ 2.40 (3H, s, CH_3), 4.40 (1H, br, erased on deuterium oxide addition, OH), 4.85 (2H, s, -CH_2O-), 7.10-7.75 (5H, m, Ph), 9.00 (1H, br, deuterium oxide exchangeable, NH), 9.35 (1H, br, erased on deuterium oxide addition, NHCO); ms: m/z 231 (M^+).

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.67; N, 18.17. Found: C, 62.61; H, 5.92; N, 18.44.

Reaction of **8** with Copper(II) Chloride in Methanol: Synthesis of 2-Methoxy-5-methoxymethyl-3-phenylcarbamoyl-1*H*-imidazole (**12a**) and 5-Amino-6-methoxymethyl-3-phenylpyrimidin-4(3*H*)-one (**13a**).

A mixture of **8** (100 mg, 0.13 mmole), copper(II) chloride (84 mg, 0.62 mmole), and methanol (25 ml) was refluxed for 7 hours. The solvent was removed by distillation. Water was added to the residue, which was extracted with chloroform. The extract was dried over anhydrous magnesium sulfate. Chloroform was removed by distillation and the residue was subjected to preparative thin layer chromatography (chloroform-methanol, 50:1) to give **12a** and **13a**.

Compound **12a** had mp 104-106° (from methanol), yield 7 mg (9%); ^{1}H nmr (deuteriochloroform): δ 3.43 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 4.90 (2H, s, -CH_2-), 7.10-7.71 (5H, m, aromatic protons), 8.12 (1H, br, -NH-), 10.13 (1H, br, -NH-); ir (potassium bromide): ν max 3450, 3200 cm^{-1} (NH), 1650 cm^{-1} (C=O); ms: m/z 261 (M^+).

Anal. Calcd. for $C_{13}H_{15}N_3O_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 59.52; H, 5.93; N, 16.40.

Compound **13a** had mp 78-80° (from methanol), yield 19 mg (26%); ^{1}H nmr (deuteriochloroform): δ 4.70 (2H, br, NH_2), 3.45 (3H, s, OCH_3), 4.54 (2H, s, -CH_2-), 7.60-7.42 (6H, m, phenyl protons and -CH= of pyrimidine ring); ir (potassium bromide): 3440, 3310 cm^{-1} (NH_2), 1660 cm^{-1} (C=O); ms: m/z 231 (M^+).

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.67; N, 18.17. Found: C, 62.03; H, 5.88; N, 18.41.

Reaction of **9** with Copper(II) Chloride in Ethanol: Synthesis of 2-Ethoxy-5-ethoxymethyl-4-phenylcarbamoyl-1*H*-imidazole (**12b**) and 5-Amino-6-ethoxymethyl-3-phenylpyrimidin-4(3*H*)-one (**13b**).

Compound **9** (100 mg) was treated in ethanol by a similar method described for **12a** and **13a**.

Compound **12b** was obtained as colorless glutinous oil, yield 20 mg (22%); ^{1}H nmr (deuteriochloroform): δ 1.00-1.50 (6H, OCH_2CH_3 x 2), 3.60 (2H, q, J = 7 Hz, OCH_2CH_3), 4.40 (2H, q, J = 7 Hz, CH_2CH_3), 4.94 (2H, s, -CH_2O-), 7.70-6.80 (5H, m, aromatic protons) 8.80 (1H, br, -NH-); ir (film): ν max 3170 cm^{-1} (NH), 1660 cm^{-1} (C=O); ms: m/z 289 (M^+), 260 (M^+-CH_2CH_3), 196 (M^+-C_6H_5NH).

Compound **13b** was a colorless glutinous oil, yield 46 mg (6%); ms: m/z 245 (M^+).

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REFERENCES AND NOTES

[1] T. Ueda, I. Matsuura, N. Murakami, S. Nagai, J. Sakakibara and M. Goto, *Tetrahedron Letters*, **29**, 4607 (1988).

[2] T. Ueda, S. Kawai and J. Sakakibara, *Chem. Pharm. Bull.*, **35**, 398 (1987).

[3a] C. Schotten, *Chem. Ber.*, **17**, 2544 (1884); [b] E. Baumann, *Chem. Ber.*, **19**, 3218 (1886).

[4] I. Matsuura, T. Ueda, N. Murakami, S. Nagai and J. Sakakibara, *J. Chem. Soc., Chem. Commun.*, 1688 (1991).