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MOM-protected 3-Hydroxy-5-phenyl-isoxazole: Regioselective Preparation and Synthetic Application

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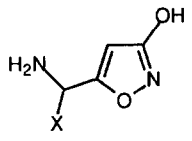
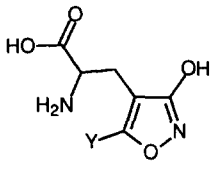
Abstract: Highly regioselective (>90%) MOM-protection of 3-hydroxy-5-phenyl-isoxazole, followed by elaboration in 4-position via directed ortho-metalation and mild deprotection with cold methanolic HCl provided ready access to a series of zwitterionic isoxazole derivatives.

The 3-hydroxy-isoxazole unit is a structural feature encountered in ibotenic acid (**1**)[1] and muscimol (**2**)[2], both constituents of a mushroom called fly agaric (*Amanita muscarina*). Ibotenic acid (**1**) has fly-killing activity and is a potent agonist of the human GABA-receptors[3]. Muscimol (**2**) arises *via* decarboxylation of **1** and represents the main poisonous principle of *Amanita muscarina*[4].

3-Hydroxy-isoxazoles have been exploited for a number of purposes[5], and particularly for the design of CNS drugs[6] like AMPA (**3**) and APPA (**4**), where the 3-hydroxy-isoxazole unit acts as an effective bioisosteric and conformationally restricted substitute for the γ -carboxylic group of glutamate, the major excitatory amino acid neurotransmitter.



1 X = COOH
2 X = H

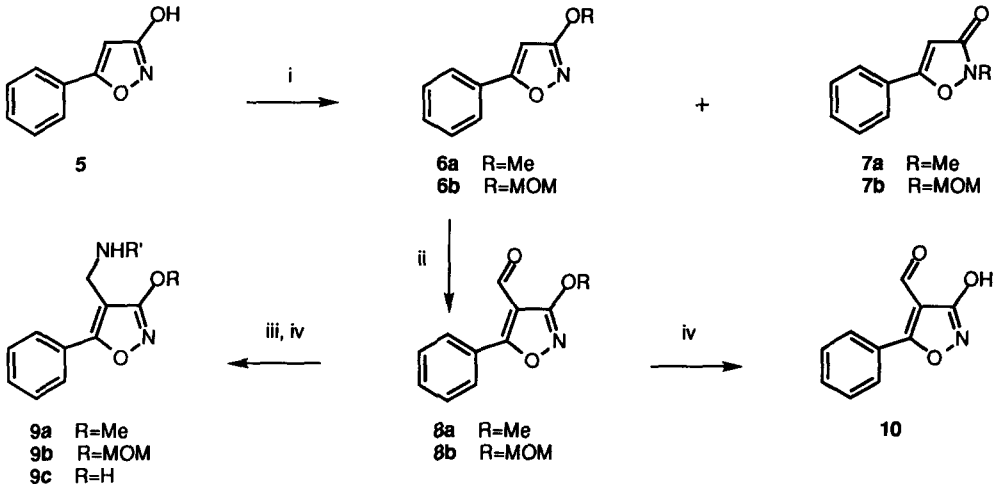


3 Y= Me
4 Y = Ph

We became interested in 3-hydroxy-isoxazoles in connection with a medicinal chemistry program aiming at the discovery of novel inhibitors of the heme polymerization process operating in *Plasmodium falciparum* species during hemoglobin degradation[7].

We planned to synthesize a series of zwitterionic isoxazoles **9c**, by reductive amination and deprotection of the methoxyaldehyde **8a** (Scheme 1). We met with difficulties in the deprotection (48% HBr in refluxing AcOH)[8] of the O-methyl protected isoxazoles **9a** and in the purification of the resulting zwitterionic isoxazoles **9c**. Moreover, the formation of the required 3-methoxy-5-phenyl-isoxazole (**6a**) from 3-hydroxy-5-phenyl-isoxazole (**5**)[9] is accompanied by predominant N-methylation leading to the 5-phenyl-isoxazol-3-one (**7a**), while displacement of the bromo substituent of 3-bromo-5-phenyl-isoxazole[10] by methoxide[11] is sluggish. Deprotection of the methoxyaldehyde **8a** to **10** failed under a variety of conditions (TMS-I/$ClCH_2CH_2Cl$, TMSOTf/Ac_2O, TMSOTf/quinoline, HBr/AcOH, BBr_3/CH_2Cl_2, pyridine.HCl).

Scheme 1



i) $TMSCHN_2$, MeOH or see Table 1; ii) BuLi, THF, -70° ; DMF iii) $R'NH_2$, EtOH, 80° ; $NaBH_4$, EtOH, 0-20° ; iv) HCl, MeOH

We therefore envisaged to proceed, as depicted in Scheme 1, *via* the methoxymethyl(MOM) protected aldehyde **8b**, speculating that the MOM group would favor the ortho-metalation[8d] and finally be removed conveniently with methanolic HCl to afford directly the hydrochlorides of the target compounds **9c**.

Obviously, the regioselective introduction of the MOM group presented a challenge because the phenyl group at C-5 of the isoxazole **5** renders the heterocycle vulnerable to electrophilic attack, a problem which, as reported elsewhere[12], does not arise with the deactivated 3-hydroxy-isoxazole-5-carboxylic acid methyl ester.

We have undertaken a systematic investigation of reaction conditions for the regioselective introduction of the MOM group into isoxazole **5**. Our results are summarized in Table 1.

The previously reported conditions[12] employing Hünig's base in THF (entry 1) gave an approximate a 2:1-ratio of **6b**:**7b**. Similar results were obtained by replacing Hünig's base with triethylamine (entry 2). Sodium hydride in THF (entry 3) afforded predominantly the undesired regioisomer **7b** in a sluggish reaction and with incomplete conversion, whereas DBU in THF (entry 4) shifted the ratio substantially (5:1) in favor of the desired regioisomer **6b**. Since the unwanted regioisomer **6b** is considerably more polar and thus readily

removed by flash chromatography, entry 4 already specifies viable conditions for the preparation of **6a**. Upon switching the solvent to dichloromethane (entry 5), which dissolved isoxazole **5** only partially, the ratio worsened again.

We then turned to using the so far tested nitrogen bases in large excess and with different cosolvents (entry 6-9). To our surprise, the conditions specified in entry 9 yielded the desired O-protected isoxazole **6b** with over 90% regioselectivity and in 80% yield, while acidic conditions led exclusively[13] to the isoxazolone **7b** (entry 10).

Table 1. methoxymethylation of the 3-hydroxy-isoxazole **5** under various reaction conditions

entry	reagent (equiv)	base or acid (equiv)	solvent	T [°C]	time	HPLC ratio[%] **5 : 6b : 7b**
1	MOM-Cl (1.2)	EtN^iPr_2 (1.2)	THF	20	2h	0 : 66 : 34
2	MOM-Cl (1.5)	TEA (1.5)	THF	0	45min	0 : 68 : 32
3	MOM-Cl (1.5)	NaH (1.5)	THF	20	12h	23 : 12 : 65
4	MOM-Cl (1.5)	DBU (1.5)	THF	0	10min	1 : 82 : 17
5	MOM-Cl (1.0)	DBU (1.0)	CH_2Cl_2	0	10min	9 : 57 : 32
6	MOM-Cl (1.5)	EtN^iPr_2 excess	EtN^iPr_2/ CH_2Cl_2 1:1	20	5min	0 : 70 : 30
7	MOM-Cl (1.5)	DBU excess	DBU/ CH_2Cl_2 1:1	20	2h	64 : 32 : 4
8	MOM-Cl (1.5)	TEA excess	TEA/THF 10:1	0	45min	2 : 74 : 24
9	MOM-Cl (1.5)	TEA excess	TEA/DMSO 10:1	0	10min	1 : 91 : 8
10	$CH_2(OMe)_2$ excess	P_2O_5 excess	CH_2Cl_2/ $CH_2(OMe)_2$ 10:1	20	2h	0 : 0 : 100

The optimized procedure for the preparation of **6b** is as follows: Chloromethyl methyl ether (1.28 mmol, 0.1 ml) was added dropwise to a stirred suspension of **5** (139 mg, 0.86 mmol) in triethylamine/methyl sulfoxide 10:1 (1.1 ml) at 0°C under argon. The mixture was stirred for 10 min. at 0°C, treated with hexane (1 ml), and allowed to warm to r.t. while stirring for further 20 min. The white precipitate was removed by filtration through Celite and washed with ethyl acetate (3 ml). Concentration *in vacuo* followed directly by silica gel chromatogaphy in hexane/ethyl acetate 7:1 afforded **6b** (141 mg, 80%) as white solid.

With compound **6b** in hand, ortho- metalation[8d] with n-BuLi in THF at -70°C and quenching with DMF gave rise to the MOM-protected aldehyde **8b** in 85% yield. This transformation corroborated the assignments of structures **6b** and **7b** which was far from unequivocal, based on mere spectroscopic evidence (^{1}H- and ^{13}C-NMR, NOE, IR). Reductive amination with primary amines $R'NH_2$[14] in ethanol at reflux and *in situ* reduction with $NaBH_4$ at 0-20°C afforded, generally uneventfully and in fair yield, the secondary amines **9b**, which were cleanly deprotected with cold methanolic HCl to furnish directly the readily precipitating hydrochlorides of the desired amines **9c**.[15]

The ease in which the MOM-group is removed in this system is further illustrated by the clean deprotection of the aldehyde **8b** to **10** which we had failed to obtain by the above mentioned route *via* aldehyde **8a**.

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14. E.g. 5-diethylamino-2-pentylamine, 2-(2-aminomethyl)pyridine, (1S,2S)-1,2-diaminocyclohexane etc.
15. Analytical data of the new compounds:

6b: m.p. 38°C.^{1}H-NMR ($CDCl_3$, 400MHz) δ = 3.58 (s,3H,OCH_3), 5.37(s,2H,OCH_2O), 6.23(s,1H,ArH), 7.43(m,3H,Ph), 7.73(m,2H,Ph). MS(EI) m/z (%): 205(M^+,12), 174(M^+-OCH_3,16), 147(M^+-OCH_3-HCN,100), 105(PhCHO$^+$,16), 45($CH_2O^+CH_3$, 32)

7b: m.p. 60°C.^{1}H-NMR ($CDCl_3$, 400MHz) δ = 3.47 (s,3H,OCH_3), 5.26(s,2H,OCH_2O), 6.02(s,1H,ArH), 7.51(m,3H,Ph), 7.70(m,2H,Ph). MS(EI) m/z (%): 205(M^+,12), 174(M^+-OCH_3,16), 147(M^+-OCH_3-HCN,100), 105(PhCHO$^+$,24), 45($CH_2O^+CH_3$, 76)

8b: m.p. 51°C.^{1}H-NMR ($CDCl_3$, 250MHz) δ = 3.64 (s,3H,OCH_3), 5.53(s,2H,OCH_2O) 7.56(m,3H,Ph), 8.10(m,2H,Ph), 9.97(s1H,CHO). MS(EI) m/z (%): 233 (M^+,4), 201(M^+-CH_3OH,12), 173 (M^+-CH_3OH-CO,12), 105(PhCHO$^+$,64), 45($CH_2O^+CH_3$, 100)

9b (R'NH_2 = 2-(2-aminomethyl)pyridine): colorless oil (46% yield). ^{1}H-NMR ($CDCl_3$, 250MHz) δ = 3.01(m,2H,CH_2CH_2), 3.08(m,2H,CH_2CH_2), 3.55(s,3H,OCH_3), 3.76(s,2H,CH_2N), 5.42(s,2H,OCH_2O), 7.25(m,2H,β+δ-H-py), 7.44(m,3H,Ph), 7.58(dt,1H,γ-H-py), 7.77(m,2H,Ph), 8.50(d,1H,α-H-py),. MS(ISP) m/z (%): 340.2 (M+H$^+$,100)

9c (R'NH_2 = 2-(2-aminomethyl)pyridine): yield 90%; m.p. 208-210°C. ^{1}H-NMR (d_6-DMSO, 250MHz) δ = 3.29(m,2H,CH_2CH_2), 3.45(m,2H,CH_2CH_2), 4.21(s,2H, CH_2N), 5.42(s,2H,7.50(m,2H,β+δ-H-py), 7.59(m,3H,Ph), 7.83(m,2H,Ph), 8.04(m,1H,γ-H-py), 8.58(d,1H,α-H-py), 9.5(br,2H,NH_2^+), 12.0(br,1H,OH). MS(ISP) m/z (%): 296.2 (M+H$^+$,100)

10: m.p. 150°C.^{1}H-NMR ($CDCl_3$, 250MHz) δ = 7.60(m,3H,Ph), 7.88(m,2H,Ph), 9.00(br,1H,OH) 10.16(s,1H,CHO). MS(EI) m/z (%): 189 (M^+,100), 105(PhCHO$^+$,56), 77(36)

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