A New, Convenient, Highly Selective Free-Radical Hydroxymethylation of Heteroaromatic Bases by Persulfate Oxidation of Ethylene Glycol and Glycerol, Catalysed by $AgNO_3$

Francesco Minisci,*[a] Ombretta Porta,[a] Francesco Recupero,[a] Carlo Punta,[a] Cristian Gambarotti,[a] Barbara Pruna,[a] Monica Pierini,[a] Francesca Fontana[b]

[a] Dipartimento di Chimica, Materiali e Ingegneria Chimica G. Natta, Politecnico di Milano, via Mancinelli, 7, 20133 Milano, Italy
E-mail: francesco.minisci@polimi.it

[b] Dipartimento di Ingegneria Industriale, Università di Bergamo, viale Marconi 5, 24044 Dalmine BG, Italy

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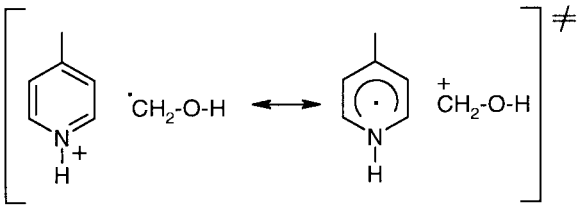
Abstract: A new, convenient and selective source of hydroxymethyl ($^{\bullet}CH_2OH$) radical has been developed by persulfate oxidation of ethylene glycol with $AgNO_3$ catalysis. The $^{\bullet}CH_2OH$ radical is selectively trapped by protonated heteroaromatic bases, providing a new, general process of hydroxymethylation; the importance of the β-scission of the alkoxyl radical intermediate is emphasised.

Key words: hydroxymethylation, heterocycles, free-radicals, diols, persulfate

Nucleophilic carbon-centred radicals selectively react with protonated heteroaromatic bases allowing the development of processes of great synthetic interest.[1–3] At the same time these very fast reactions provide quite useful traps for the elucidation of free-radical mechanisms.[4] Since the polar effect is the main factor determining reactivity and selectivity,[5] all alkyl radicals without electron-withdrawing groups directly bound to the radical centre are suitable for the selective substitution. Electron-releasing groups (-OR, -NHR) in the α-position to the radical centre increase the nucleophilic character, enhancing the reactivity towards protonated heteroaromatic bases. However, at the same time, radicals with a pronounced nucleophilic character show an increased tendency to undergo electron-transfer oxidation.

Hydroxymethyl radical, $^{\bullet}CH_2OH$, has a marked nucleophilic character, which can be qualitatively related to a partial charge development in the transition state (Equation.1),

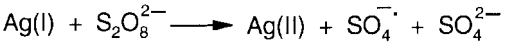


Equation 1

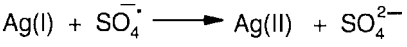
According to the FMO theory,[6] the LUMO of the pyridinium cation has the highest coefficients[7] at the carbon atoms 2 and 4 and the dominant interaction in the radical addition is the one between these LUMO and the nucleophilic $^{\bullet}CH_2OH$ radical SOMO. This radical can be generated by hydrogen abstraction from MeOH by oxygen- or nitrogen-centred radicals ($HO^{\bullet}$, *t*-$BuO^{\bullet}$, $PhCOO^{\bullet}$, $H_3N^{+\bullet}$) and it easily reacts with protonated heteroaromatic bases.[8] However, the drawback of this substitution is that the resulting hydroxymethyl derivatives, due to their benzylic structure, are much more reactive than MeOH towards hydrogen abstraction, because of the enthalpic effect, so that further oxidation occurs. The dissociation enthalpy of the C–H bond in MeOH is, in fact, about 10 kcalmol^{-1} higher than that of the C–H bonds in these hydroxymethyl groups.

Several years ago we suggested[9] that alkoxyl radicals may be formed from the corresponding alcohols by Ag(II) salt oxidation (Equation 2). The easy oxidation of Ag(I) by $S_2O_8^{2-}$ (Equations 3 and 4) would make Equation 2 a very convenient source of alkoxyl radicals in a catalytic cycle.

Equation 2



Equation 3



Equation 4

By oxidation of MeOH with $S_2O_8^{2-}$ and $AgNO_3$ catalysis in aqueous solution in the presence of protonated lepidine, hydroxymethylation of the protonated heteroaromatic base occurs, but the reaction is not clean since a significant amount of aldehyde is also formed, even by using a large excess of MeOH, e.g. a MeOH–lepidine ratio > 100 (Equation 5).

The $^{\bullet}CH_2OH$ radical can be generated by hydrogen abstraction from MeOH either by the $CH_3O^{\bullet}$ radical formed in Equation 2 or by the $SO_4^{-\bullet}$ radical of Equation 3. On the

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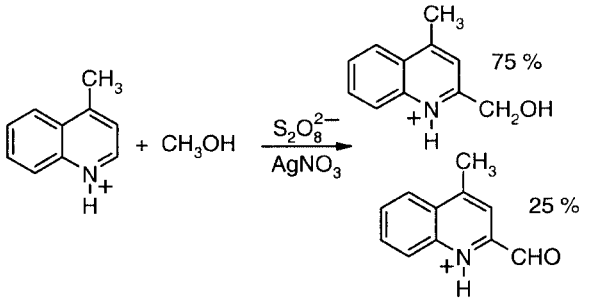
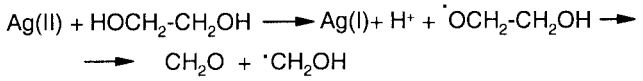


Equation 5

other hand, alkoxyl radicals can undergo a fast β-scission; for instance, the rate constant value for the β-scission of *t*-BuO$^{\bullet}$ radical to acetone and methyl radical is about 10^6 s^{-1} at 30 °C; three factors may contribute to increase in the rate of β-scission of alkoxyl radicals compared to hydrogen abstraction:[10] (i) the stability of the resulting radical; (ii) polar solvents; (iii) high temperature, β-scission being a unimolecular process.

Thus, we have developed a different synthetic strategy based on the oxidation of ethylene glycol by persulfate and Ag(I) catalysis, considering that $^{\bullet}CH_2OH$ is more likely to be formed from MeOH and $CH_3O^{\bullet}$. Since $^{\bullet}CH_2OH$ radical is more stable than $CH_3^{\bullet}$, β-scission should be faster for the alkoxyl radical formed from glycol (Equation 6) than for *t*-BuO$^{\bullet}$. The formation of the hydroxymethyl radical is also favoured by the polar solvent (H_2O–$OHCH_2CH_2OH$, 1:1) and the high temperature (reflux).



Equation 6

Actually, a very selective and clean hydroxymethylation of the heterocyclic rings, with formation of traces of aldehydes, occurs by persulfate oxidation of ethylene glycol in the presence of protonated heteroaromatic bases in aqueous solution.

In addition to their synthetic interest, the results reported in the Table 1 clarify the reaction mechanism, which in turn can explain the high selectivity. The alkoxyl radical of Equation 6 undergoes β-scission faster than hydrogen abstraction from C–H bonds, leading to $^{\bullet}CH_2OH$ and subsequent hydroxymethylation. Equation 6 being an electron-transfer process, the enthalpic effect is of very minor significance, and the β-fragmentation of the alkoxyl radical is so fast that the intermolecular hydrogen abstraction from the reaction products is minimised.

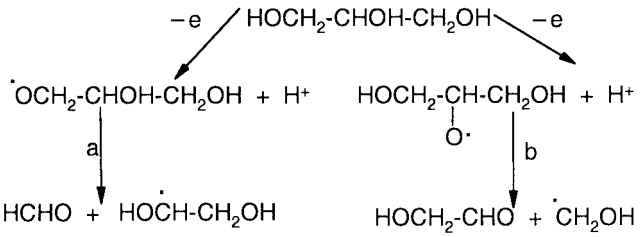
Recently, Steckam[12] has reported a mild, selective method for the formal generation of $^{\bullet}CH_2OH$ by photoinduced radical electron-transfer of α-silyl ethers; this method can be used for the hydroxymethylation of heteroaromatic bases, even if it is somewhat more complex compared to the methodology described in this paper.

Table 1 Hydroxymethylation of Heteroaromatic Bases by Persulfate Oxidation of Ethylene Glycol (A), Glycerol (B) or MeOH (C)[13,]

Heteroaromatic base	Radical source	Yields (%)	Selectivity (Isomer) %
Lepidine	A	92	(2) 100
Lepidine	B	15	(2) 100
Lepidine	C	98	(2) 75 CH_2OH; (2) 25 CHO
Quinoline	A	76	(2) 61; (4) 39
Quinoline	B	12	(2) 63; (4) 37
Quinaldine[(a)]	A	98	(4) 85
Isoquinoline	A	58	(1) 100

[a] H_2SO_4 (0.5 mmol) was used instead of CF_3COOH.

With glycerol a similar clean and selective hydroxymethylation also occurs, but conversions based on $S_2O_8^{2-}$ are lower, due to competitive oxidation of all the –OH groups (Equation 7).



Equation 7

No substitution takes place with the secondary ketyl radical formed according to Equation 7a, for two main reasons: it is more oxidisable than $^{\bullet}CH_2OH$ and its addition to the heterocyclic ring is more reversible,[11] so that it is further oxidised, with $S_2O_8^{2-}$ consumption.

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(13) Typical Experimental Procedure: Lepidine (20 mmol), CF_3COOH (20 mmol), $(NH_4)_2S_2O_8$ (80 mmol) and $AgNO_3$ (2 mmol) were refluxed in H_2O (75 mL) and ethylene glycol (75 mL) for 3 h. The solution was made basic by NaOH and extracted with CH_2Cl_2. GC analysis (quinoline as internal standard) revealed the presence of 2-hydroxymethyllepidine (18.5 mmol) and lepidine (1.3 mmol). The CH_2Cl_2 solution was evaporated and the residue gave, by flash chromatography (hexane–EtOAc, 2:1) pure 2-hydroxymethyllepidine (17.1 mmol), identified by comparison with an authentic sample. The results in the Table 1 refer to GC analyses.