51), 424 (M - 3 AcOH, 46), 364 (M - 4 AcOH, 56), 313 (48), 253 (100); ^{1}H NMR ($CDCl_3$) δ 0.85 (3 H, s, 18-H_3), 0.88 (6 H, d, J = 7 Hz, 26- and 27-H_3), 1.00 (3 H, s, 19-H_3), 2.04-2.05 (12 H, CH_3CO), 3.83 (1 H dd, J = 11.0, 7.0 Hz, 21-H), 3.97 (1 H dd, J = 11.0, 4.5 Hz, 21-H), 4.64 (1 H dd, J = 11.0, 5.0 Hz, 12-H), 4.90 (1 H, br s, $W_{1/2}$ = 11.0 Hz, 6α-H), 5.07 (1 H, br s, $W_{1/2}$ = 7 Hz, 3β-H).

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Registry No. 1, 99494-32-3; **1a**, 99458-05-6; **1b**, 99458-07-8; **1c**, 99458-08-9; **2**, 99458-04-5; **2a**, 99458-06-7; **3**, 99475-53-3.

A General, Selective, and Convenient Procedure of Homolytic Formylation of Heteroaromatic Bases

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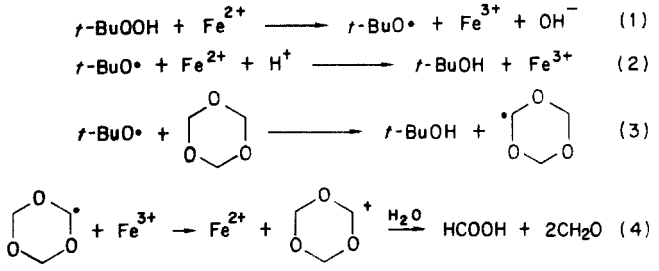
The substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals reproduces the numerous aspects of the aromatic Friedel-Crafts alkylation and acylation, formylation included, but with opposite reactivity and selectivity.[1]

The formylation by trioxane has till now given poor results;[1] the main reason is that the reaction has been carried out at room temperature, which requires almost stoichiometric amounts of Fe(II) salt. The relatively high concentration of Fe(III) salt formed according to eq 1 and 2 determines the fast oxidation[2] of the trioxanyl radical generated by hydrogen abstraction from trioxane (eq 3 and 4). The competition of the reactions 2 and 4 leads to poor



yields of attack of the trioxanyl radical to the protonated heteroaromatic base (eq 5). We have developed a new

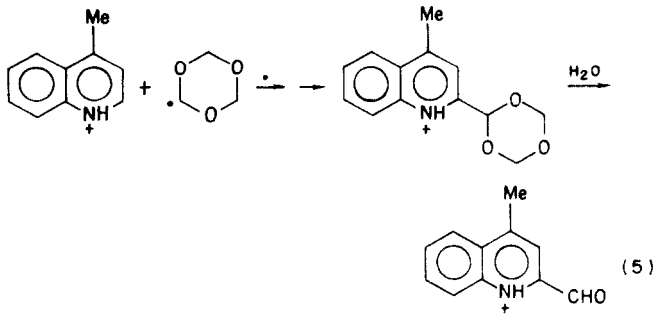


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Table I. Formylation of Heteroaromatic Bases

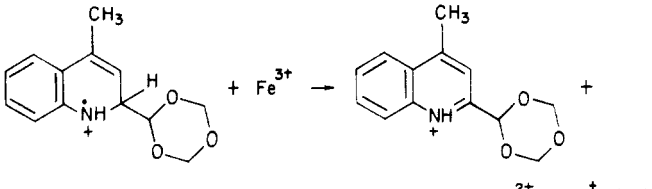
heteroaromatic base (mmol)	*t*-BuOOH, mmol	position of formylation	conversion, %	yield,[a] %
quinoline (16)	32	2 (58%) 4 (42%)	81	92
4-methylquinoline (14)	17	2	65	95
4-methylquinoline (14)	33	2	89	94
2-methylquinoline (14)	32	4	65	94
isoquinoline (14)	30	1	83	92
quinoxaline (14)	28	2	38	94
benzothiazole (14)	30	2	37	90

[a] GLC, based on converted heteroaromatic compound.

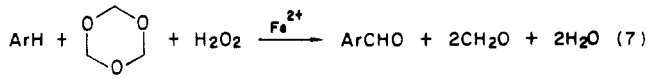
procedure[3] by combining the thermal effect and the redox catalysis which allows use of small amounts of Fe(II) salt (1%) to minimize therefore the competitive reactions 2 and 4 and to obtain much higher yields.

Moreover the new procedure is much simpler because the small amount of catalyst does not interfere during the isolation of the reaction products, whereas with stoichiometric iron salt considerable amount of Fe(III) hydroxide precipitates during the separation of the reaction products (sometimes complexing the heterocyclic compounds) and heavily affects the overall process.

The reaction is very selective and only the positions α and γ of the heterocyclic ring are substituted. The results are reported in Table I; the conversions can be further increased by increasing the amount of *t*-BuOOH. No reaction takes place in the absence of iron salt at the temperature used in the table, and only traces of substitution products are formed at room temperature in the presence of the catalytic amounts of employed Fe(II) salt, thus clearly indicating that the combination of the thermal effect and the redox catalysis is necessary for the success of the reaction. The Fe(II) salt consumed in eq 1 is regenerated in the oxidation of the heteroaromatic radical adduct (eq 6).



Hydrogen peroxide can be used instead of *t*-BuOOH; the stoichiometry is shown by the eq 7. The difference between *t*-BuOOH and aqueous H_2O_2 is that *t*-BuOOH leads to 97-98% of trioxanyl derivatives and only to 2-3% of the aldehyde generated by hydrolysis. The trioxanyl



derivative can be useful, as a masked aldehyde, for further transformations, and the hydrolysis can be accomplished at the right step. H_2O_2 always leads to mixtures of comparable amounts of trioxanyl derivatives and aldehyde due to the presence of more water; it is convenient in this case to transform all the reaction products to the aldehyde by complete hydrolysis.

1,3-Dioxolane can also be utilized by a similar procedure for the synthesis of heteroaromatic aldehydes, but the

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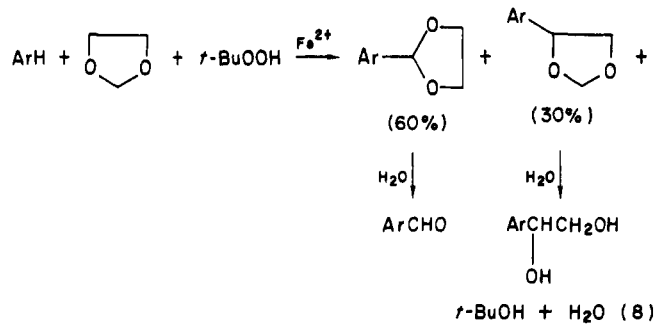

process is not selective (eq 8).

Experimental Section

Formylation Using *t*-BuOOH—General Procedure. A solution of the heteroaromatic base, CF_3COOH (equimolecular with the base), and *t*-BuOOH in the amounts reported in the table and 0.7% of ferrous sulfate (based on the hydroperoxide) were refluxed for 5 h with 120 g of trioxane and 200 mL of acetonitrile. The solution was concentrated by distilling the solvent, basified with 5% NaOH solution (50 mL, and extracted with ether (3 × 50). GLC and TLC analyses reveal only the presence of the starting base and of the trioxanyl derivative and small amounts (2–3%) of aldehyde. The solvent was distilled and the residue refluxed with 50 mL of 10% H_2SO_4, made basic with 5% NaOH, extracted with ether, and analyzed by GLC (with internal standard, 2- or 4-methylquinoline). The results are reported in the table. All the aldehydes were isolated as pure samples by silica gel chromatography (1:1 hexane–ethyl acetate under pressure) and identified by comparison with authentic compounds (mp, IR, NMR, MS).[1]

Formylation of 4-Methylquinoline Using H_2O_2. The procedure is identical with that used with *t*-BuOOH with the only difference being that 1 mol of 30% H_2O_2 per mol of lepidine is used. GLC and TLC show that the reaction product is a mixture of unreacted lepidine and 2-trioxanyl- and 2-formyllepidine. The hydrolysis by 10% H_2SO_4 leads to a mixture of lepidine and 2-formyllepidine. GLC analysis (2-methylquinoline as internal standard) indicates a conversion of 38% and a yield of 93% based on converted lepidine. The 2-formyllepidine (mp 76–77 °C) has been isolated by silica gel chromatography and identified by comparison (IR, NMR, MS) with an authentic sample.

Reaction of Lepidine with 1,3-Dioxolane. Lepidine (14 mmol), 16 mmol of CF_3COOH, 24 mmol of *t*-BuOOH, and 0.1 mmol of ferrous sulfate in 100 mL of 1,3-dioxolane were warmed under stirring for 5 h at 78 °C. The solution was then concentrated by distilling the dioxolane, made basic by 5% NaOH solution, extracted with ether, and analyzed by GLC (2-methylquinoline as internal standard). The conversion of lepidine was 93%; the yields of 2-dioxolan-2-yl-4-methylquinoline and 2-dioxolan-4-yl-4-methylquinoline were 61% and 30%, respectively. The products were isolated by silica gel chromatography.

2-Dioxolan-4-yl-4-methylquinoline: liquid; NMR ($CDCl_3$) δ 2.7 (s, 3 H, Me-4), 4–4.5 (m, 2 H, $OCHCH_2O$), 5.1–5.3 (m, 3 H, CHO, OCH_2O), 7.4–8.1 (m, 5 H, Ar); MS, *m/e* 215 ($M^{+\cdot}$), 201, 185, 184, 170, 157, 143, 115.

2-Dioxolan-2-yl-4-methylquinoline, liquid, was identified by comparison (IR, NMR, MS) with an authentic sample prepared by ethylene glycol ketalization of 2-formyl-4-methylquinoline. By hydrolysis with 10% H_2SO_4 it is transformed in 2-formyl-4-methylquinoline.

Acknowledgment. This work was supported by Progetto Finalizzato Chimica Fine e Secondaria, CNR.

Registry No. *t*-BuO_2H, 75-91-2; H_2O_2, 7722-84-1; quinoline, 91-22-5; 4-methylquinoline, 491-35-0; 2-methylquinoline, 91-63-4; isoquinoline, 119-65-3; quinoxaline, 91-19-0; benzothiazole, 95-16-9; 2-formylquinoline, 5470-96-2; 4-formylquinoline, 4363-93-3; 2-formyl-4-methylquinoline, 40105-30-4; 2-methyl-4-formylquinoline, 6760-22-1; 1-formylisoquinoline, 4494-18-2; 2-formylquinoxaline, 1593-08-4; 2-formylbenzothiazole, 6639-57-2; trioxane, 110-88-3; 2-(dioxolan-4-yl)-4-methylquinoline, 99687-43-1; 2-(dioxolan-2-yl)-4-methylquinoline, 99687-44-2; 1,3-dioxolane, 646-06-0; 2-trioxanyllepidine, 40105-26-8.

Methylcopper(I)-Catalyzed Selective Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds by Diisobutylaluminum Hydride in the Presence of Hexamethylphosphoric Triamide

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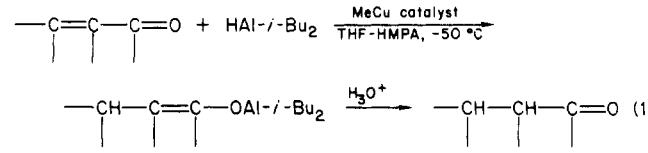
Selective conjugate reduction (1,4-reduction) of α,β-unsaturated carbonyl compounds is an important transformation in organic synthesis. Especially, the selective conjugate reduction on highly functionalized molecules is a recent subject of considerable interest. Several transition-metal hydride reagents including those produced in situ from transition-metal compounds and conventional reducing reagents have been developed.[1] Previously we reported that cuprous iodide catalyzes conjugate reduction of α,β-unsaturated carbonyl compounds by lithium aluminum hydride (LAH) in the presence of hexamethylphosphoric triamide (HMPA).[2] However, the efficiency and selectivity of the reduction were not very high. Diisobutylaluminum hydride (DIBAH) is a widely employed reducing reagent in organic synthesis, and it is interesting to exploit novel reducing reactivity of DIBAH modified by a transition-metal compound. Herein is reported methylcopper(I)-catalyzed highly efficient and selective conjugate reduction of α,β-unsaturated carbonyl compounds by DIBAH in the presence of HMPA (eq 1).



Reduction of α,β-unsaturated carbonyl compounds by DIBAH generally takes place at the carbonyl group (1,2-reduction) to produce allylic alcohols. It has been now found that a remarkable change of reducing reactivity of DIBAH is brought about by addition of HMPA. As is shown in Table I, conjugate reduction of *trans*-2-hexenal, 2-cyclohexen-1-one, and mesityl oxide by DIBAH was effectuated in a mixed solvent of HMPA–THF (v/v, 1:5) at 0 °C–room temperature in a good yield of ca. 90% without any 1,2-reduction. The DIBAH–HMPA system as a reagent of conjugate reduction, however, lacks generality, owing to limitation of applicable substrates. Conjugate reduction of 3-methyl-2-cyclopenten-1-one and α,β-unsaturated esters such as methyl crotonate and methyl cinnamate by DIBAH–HMPA did not proceed effectively.

Addition of a catalytic amount of MeCu which was prepared in situ from an equimolar reaction of methyllithium and CuI to the DIBAH–HMPA system produced a dramatic effect to cause at −50 °C selective and quantitative conjugate reduction of a variety of α,β-unsaturated carbonyl compounds including α,β-unsaturated esters and β,β-dialkyl-substituted α,β-enones without any 1,2-reduction. The results are summarized in Table I. A role of MeCu is crucial. Addition of an equimolar amount of

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