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A Novel Convenient and Selective Alkoxycarbonylation of Heteroaromatic Bases by Oxalic Acid Monoesters

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Abstract - Methoxy- and ethoxycarbonyl radicals were easily produced by silver-catalyzed decarboxylation of methyl and ethyl esters of oxalic acid by $S_2O_8^{=}$. They were utilized for the alkoxycarbonylation of heteroaromatic bases with high yield and selectivity in a two-phase system, suitable for practical applications.

The homolytic alkylation and carbonylation of protonated heteroaromatic bases reproduces most of the numerous aspects of the Friedel-Crafts aromatic substitution, but with opposite reactivity and selectivity[1]. All carbonyl radicals have a clear-cut nucleophilic character, but, being σ-radicals, this character decreases in the series[2] $R\text{-}\dot{C}O > R_2N\text{-}\dot{C}O > RO\text{-}\dot{C}O$, whereas with π-alkyl radicals the sequence of nucleophilic character is[2] $R_2N\text{-}\dot{C}R_2 > RO\text{-}\dot{C}R_2 > \dot{C}R_3$.

The direct, selective introduction of a carboxylic group in heteroaromatic rings is an important general aspect of organic synthesis. The only radical source used until now for this purpose has been developed several years ago[3] in this laboratory and involves the peroxides of pyruvate esters. The reaction has been widely utilized for the alkoxycarbonylation of heteroaromatic bases[2,3,4], but it has some limitations concerning large-scale applications. Now we report a much more convenient, cheap and simple reaction, in which alkoxycarbonyl radicals are generated by oxydative decarboxylation of oxalic acid monoesters by $S_2O_8^{=}$ (eq.1)

$$\text{Het-H} + \text{ROCO-COOH} + S_2O_8^{=} \xrightarrow{Ag^+} \text{Het-COOR} + CO_2 + 2\,HSO_4^- \quad (1)$$

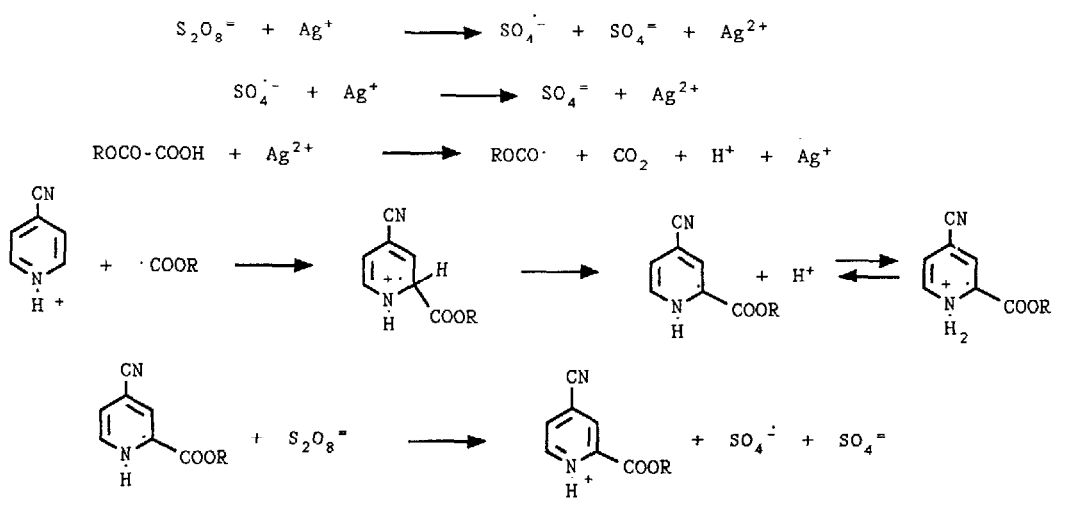
Monoesters of oxalic acid were easily prepared from oxalyl dichloride and alcohols or by partial hydrolysis of diesters. The reaction is carried out in a two-phase system: an organic phase containing the monoester and an aqueous phase in which the protonated heteroaromatic base, $S_2O_8^{=}$ and catalytic amounts of $AgNO_3$ are dissolved. A general experimental procedure is given: the solution of 12 mmol of methyl or ethyl monooxalate in 20 ml of CH_2Cl_2 was added to 20 ml of an aqueous solution containing 5 mmol of heteroaromatic base, 2.5 mmol of H_2SO_4, 10 mmol of $Na_2S_2O_8$ and 0.5 mmol of $AgNO_3$. The mixture was refluxed under stirring for 1.5 hrs, then made basic; the organic layer was separated and analyzed by GC-MS. The reaction products were isolated by flash-chromatography and identified by comparison with authentic samples, prepared according to the previously developed procedure[2-4]. The results are reported in the Table.

The two-phase system is much more convenient than an aqueous solution mainly for two reasons: i) spontaneous conversion of oxalic acid monoesters into a mixture of oxalic acid and oxalic diesters is faster in acidic aqueous solution than in CH_2Cl_2; ii) the introduction of an alkoxycarbonyl group activates the heterocyclic ring towards further carboxylation, which leads to polysubstitution when several activated (α and γ) positions are available in the heterocyclic ring (e.g. in quinoline, 4-cyanopyridine, pyrazine etc.); in a two-phase system, the organic solvent continuously extracts the less basic, hence less protonated, reaction products from the aqueous phase, thus minimizing polysubstitution.

The mechanism of the reaction is shown by the Scheme .

The substitution mainly takes place at α and γ positions on the heterocyclic ring, but small amounts of other isomers were revealed by GC-MS analysis; this is in agreement with the lower nucleophilic character of alkoxycarbonyl radicals compared with acyl radicals (eq.2)

This latter process is by far prevailing with monoesters of tertiary



SCHEME

alcohols, leading to selective alkylation of heteroaromatic bases; with monoesters of secondary alcohols both carboxylation and alkylation take place in the range of temperatures 30-100°C, the amount of alkylation increasing with temperature.

$$\cdot COOR \longrightarrow CO_2 + R\cdot \qquad (2)$$

The determination of the absolute rate constants for the addition of ·COOR radicals to heteroaromatic bases is in progress; a preliminary evaluation obtained by competition from an eq.2-type decarboxylation of known rate indicates a range of 10^5-10^6 $M^{-1}s^{-1}$ for the reaction with quinoline.

The high yields and selectivities, the inexpensive reagents, the simple experimental conditions contribute to make this reaction[6] the method of choice for the direct carboxylation of heteroaromatic bases, suitable for practical applications, considering the commercial relevance of carboxylic derivatives of heteroaromatic bases.

Table-Alkoxycarbonylation of Heteroaromatic Bases by Monoesters of Oxalic Acid

Heteroaromatic base	Alkoxycarbonyl group	Orientation (%)	Conversion (%)	Yields[a] (%)
Pyrazine	MeOCO	2	70	93
Pyrazine	EtOCO	2	96	86
Quinoline	MeOCO	2(58); 4(27); 2,4(4)	47	89
Quinoline	EtOCO	2(48); 4(26); 2,4(9)	84	83
Quinoline[b]	i-PrOCO	2(39); 4(15); 2,4(3)	80	58
Benzothiazole[c]	MeOCO	2	50	70
Benzothiazole[d]	EtOCO	2	70	24
Lepidine	EtOCO	2	75	83
4-CN-Pyridine	EtOCO	2(61); 3(13); 2,6(9)	100	82
4-CN-Pyridine	MeOCO	2(65); 3(18)	55	86
3-Methyl-Pyrimidine	EtOCO	2(56); 6(27)	94	83
Isoquinoline	EtOCO	1(86); 1,3(10)	80	96
Isoquinoline[e]	EtOCO	1(34); 1,3(48)	100	82

a) Yields based on converted heteroaromatic base.
b) The following derivatives of quinoline are also formed: 2-isopropyl (8%), 4-isopropyl (9%), 2,4-isopropyl (11%).
c) 20% of 2-methylbenzothiazole is also formed.
d) 60% of 2-ethylbenzothiazole is also formed.
e) A twofold amount of $Na_2S_2O_8$ was utilized.

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