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HOMOLYTIC ALKOXYCARBONYLATION REACTIONS IN TWO-PHASE SYSTEMS, PART II[1]

STUDIES ON THE ETHOXYCARBONYLATION OF SOME SELECTED π-DEFICIENT N-HETEROAROMATIC SYSTEMS[2]

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Abstract - A systematic study on the homolytic substitution of pyridine, quinoline and pyrazine by ethoxycarbonyl radicals was performed. It is demonstrated that under appropriate conditions Minisci-type alkoxycarbonylation reactions can provide convenient access to heteroaromatic monocarboxylic acid esters, like alkyl 2-pyrazinecarboxylates and alkyl 4-alkyl-2-pyridinecarboxylates.

Recently it was reported that Minisci-type alkoxycarbonylation reactions under appropriate reaction conditions can be utilized for convenient high yield syntheses of pyridazine- and alkylpyridazinecarboxylic acid esters[1], despite the fact that so far this reaction principle in general was thought to be of only limited value from a preparative point-of-view[3,4] due to increased formation of polysubstitution products. Based on these findings, investigations employing some additional heteroaromatic systems (pyridine, quinoline and pyrazine) now have been carried out in order to study the influence of varying amounts of radical and the presence of an organic layer on conversion rates and product distributions.

RESULTS AND DISCUSSION

According to a report by Minisci and co-workers[5], polysubstitution of pyridine by alkoxycarbonyl radicals (generated by redox decomposition of oxyhydroperoxide of ethyl pyruvate) only can be minimized, when an excess of the heteroarene is applied. As shown in table 1, the extremly low conversion rate thus resulting, also cannot be increased by employing a base: peroxide ratio of 1:3. Running the reaction in presence of dichloromethane, we did succeed in rising the conversion rate up to 61%, applying a tenfold excess of radicals even up to 92%. However, there is no significant improvement with respect to suppression of di- and polysubstituted products.

TABLE 1. Reactions of Pyridine with Ethoxycarbonyl Radical
[% ratio of products (% yield based on converted base)]

mole ratio base:peroxide	3:1[a]	1:3	1:3	1:10
ml CH_2Cl_2 added	-	-	150	150
Pyridine	>75 /	>70 /	39 /	8 /
Ethyl 2-pyridine-carboxylate[6]	-- (63)	-- (29)	16 (26)	25 (28)
Ethyl 4-pyridine-carboxylate[7]	-- (18)	-- (14)	6 (10)	4 (4)
Diethyl 2,4-pyridine-dicarboxylate[8]	-- (10)	-- (14)	23 (38)	34 (37)
Σunidentified products	-- (10)	-- (43)	15 (25)	29 (31)

[a] Also compare refs.[5,18]

Similar results were obtained in experiments starting with quinoline (cf. table 2). Again, almost quantitative conversion of the heteroaromatic substrate could be achieved by application of a base:peroxide ratio of 1:10 and performing the reaction in presence of dichloromethane. However, also in this case the product distribution could not decisively be influenced in favour of monosubstituted compounds.

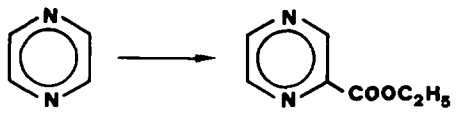
TABLE 2. Reactions of Quinoline with Ethoxycarbonyl Radical
[% ratio of products (% yield based on converted base)]

mole ratio base:peroxide	1:3[a]	1:3	1:10
ml CH_2Cl_2 added	-	150	150
Quinoline	13 /	5 /	- /
Ethyl 2-quinoline-carboxylate[9]	- (-)	26 (27)	28 (28)
Ethyl 4-quinoline-carboxylate[10]	6 (6)	22 (23)	8 (8)
Diethyl 2,4-quinolinedicarboxylate[11]	82 (94)	40 (42)	52 (52)
Σunidentified products	- (-)	7 (7)	11 (11)

[a] Also compare ref.[5]

In contrast, the concept of performing homolytic alkoxycarbonylation reactions in a two-phase system , recently developed considering that an alkoxycarbonylated heteroarene should exhibit increased lipophilicity and reduced basicity[1], proved to be of high synthetic utility in the case of pyrazine (1)[12]. Whereas 1 under usual conditions of Minisci-type reactions (base: peroxide ratio = 1:2[5] or 1:3) predominantly affords the three theoretically possible disubsti-

tuded products[13] (in 47%[5] and 69% yield, respectively), an experiment run in presence of dichloromethane, employing a threefold amount of ethoxycarbonyl radical yielded 83% of ethyl 2-pyrazinecarboxylate (2)[16]. Applying 150 ml of dichloromethane finally permits the facile one-step preparation of 2 in 89% yield.

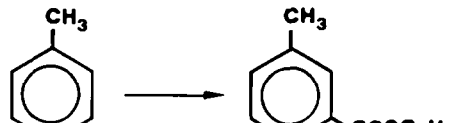


1 2

mole ratio base:peroxide	ml CH_2Cl_2 added	% yield[a] 2	∑disubst. products	∑unidentif. products
1:3	-	13	69	2
1:3	30	83	14	1
1:3	150	89	8	-

[a]based on starting 1

These encouraging results prompted us to investigate reactions also with 4-methylpyridine (3)[17], considering that also in a C-4 substituted pyridine system there is only one type of ring-carbon atoms attackable by nucleophilic radicals (i.e. C_α). Unlike an experiment, carried out in absence of an organic layer (base:peroxide ratio = 1:3; conversion rate <30%), reacting 3 with a tenfold amount of ethoxycarbonyl radical in presence of 150ml of dichloromethane actually afforded 53% of ethyl 4-methyl-2-pyridinecarboxylate (4)[8] (≈76% yield based on converted 3), easily separable from starting material and by-products by medium pressure liquid chromatography on silica gel. Although in this case the conversion rate does not exceed 70% - a fact which can be interpreted in terms of desactivation of the heteroaromatic system by the alkyl substituent - this method is superior to previously used procedures for preparing 4[8], which, similar to compound 2, seems to be of interest in syntheses of pharmacologically active compounds.



3 4

mole ratio base:peroxide	ml CH_2Cl_2 added	%yield[a]
1:3	-	< 22
1:10	150	53

[a]based on starting 3

Application of homolytic alkoxycarbonylation reactions in two-phase systems, with respect to the introduction of a single alkoxycarbonyl group into N-heteroaromatics bearing electron withdrawing substituents is under investigation, the results will be reported elsewhere.

EXPERIMENTAL

Melting points (uncorrected) were determined with a Kofler apparatus. Ir spectra were recorded on a Jasco IRA-1 spectrometer (KBr disks, $\tilde{\nu}$ in cm^{-1}). ^{1}H-nmr spectra were recorded on a Varian EM 390 (90MHz), using $CDCl_3$ as solvent; chemical shifts (J in Hz) are reported in ppm downfield from internal TMS. Mass spectra were obtained on a Varian MAT CH-7. Glc analyses were carried out with an Erba Fractovap 2351 AC, using a 25m x 0.22mm OV 17 WCOT-FS column, N_2, split vent 150ml/min, FID. Medium pressure liquid chromatography (mplc) was carried out in Lobar® glass columns, filled with LiChroprep® Si 60, 40-63μm (Merck), flow rate 4-6ml/min. Preparative thin layer chromatography (prep.tlc) was carried out on silica gel 60 F_{254} (Merck). All reagents were commercial products and were reacted without further purification. The yields were determined by glc analyses, the reaction products were identified by comparison with authentic samples.

General Procedure for the Reaction of Pyridine, Quinoline, Pyrazine and 4-Methylpyridine with Ethoxycarbonyl Radical. (For amounts of reagents also see table 3).

30% H_2O_2 was added with stirring to ethyl pyruvate at -10° to 0°. This solution was then added with stirring and cooling (-5° to 0°) to a mixture of the heteroaromatic base (10mmol), conc. H_2SO_4 (3g), H_2O (8g), $FeSO_4.7H_2O$ (and CH_2Cl_2). After 15min of further stirring, the resulting mixture was poured into ice water and the aqueous phase was exhaustively extracted with CH_2Cl_2. After drying the combined organic layers over anhydrous Na_2SO_4, the solvent and excess ethyl pyruvate was removed in vacuo.
[For quantitative analyses, unconverted heteroaromatic bases were recovered after addition of 5g citric acid (15g when a base:peroxide ratio of 1:10 was applied) and basification of the reaction mixture with conc. NH_4OH, by exhaustive extraction with CH_2Cl_2.]

TABLE 3. Amounts of Reagents Employed in the Reactions of Pyridine, Quinoline and 4-Methylpyridine with Ethoxycarbonyl Radical.

	mole ratio base:peroxide			
	3:1	1:3	1:3	1:10
30% H_2O_2	0.34g (3mmol)	3.4g (30mmol)	3.4g (30mmol)	11.3g (100mmol)
ethyl pyruvate	0.52g (4.5mmol)	5.2g (45mmol)	5.2g (45mmol)	17.3g (150mmol)
$FeSO_4.7H_2O$	0.83g (3mmol)	8.3g (30mmol)	8.3g (30mmol)	28.0g (100mmol)
CH_2Cl_2	-	-	150ml	150ml

Separation of Reaction Products:

Resulting from pyridine: mplc (dichloromethane/ethyl acetate 8/1);
fraction I: diethyl 2,4-pyridinedicarboxylate[8]
fraction II: ethyl 4-pyridinecarboxylate[7]
fraction III: ethyl 2-pyridinecarboxylate[6]

Resulting from quinoline: mplc (dichloromethane/ethyl acetate 8/1);
fraction I: diethyl 2,4-quinolinedicarboxylate[11]
fraction II: ethyl 2-quinolinecarboxylate[9]
fraction III: ethyl 4-quinolinecarboxylate[10]

Resulting from pyrazine (1) [Reactions carried out in presence of 30ml CH_2Cl_2 (or 150ml CH_2Cl_2, resp.)]; Spontaneously crystallizing pale yellow needles, mp=49°-51° (diethyl ether)(ref.[16]: 52°-53°); yield 1.2g (80%) [or 1.3g (85%)] of ethyl 2-pyrazinecarboxylate (2)[16].

Resulting from 4-methylpyridine (3): mplc (dichloromethane/ethyl acetate 4/1);
0.8g (49%) of a pale yellow oil: ethyl 4-methyl-2-pyridinecarboxylate (4)[8]. Ms: M^+ at m/z 165; ir: 1720 ($\nu_{C=O}$); nmr: 8.63 (d,J=5,1H,H-6), 8.00 (d,J=2,1H,H-3), 7.30 (dd,J=5,J=2,1H,H-5), 4.49 (q,J=7,2H,CH_2), 2.41 (s,3H,CH_3), 1.45 (t,J=7,3H,CH_2-CH_3).

ACKNOWLEDGEMENT

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