Polar Effects in Free-Radical Reactions. A Novel Homolytic Acylation of Heteroaromatic Bases by Aerobic Oxidation of Aldehydes, Catalysed by *N*-Hydroxyphthalimide and Co Salts.

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Received July 12, 2002

A new process for the homolytic acylation of protonated heteroaromatic bases is described; an N-oxyl radical (PINO) generated from *N*-hydroxyphthalimide by air oxygen and Co(II) abstracts a hydrogen atom from an aldehyde. The resulting nucleophilic acyl radical adds to a heteroaromatic base, which is then rearomatised in a chain process. Quinazoline has an anomalous behaviour, giving 3*H*-quinazolin-4-one as the only reaction product.

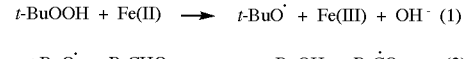
J. Heterocyclic Chem., **40**, 325 (2003).

The great synthetic interest of the substitution of protonated heteroaromatic bases by nucleophilic carbon-centred radicals results from the high regio- and chemoselectivity, due to polar effects, the large variety of inexpensive radical sources and the simple experimental conditions. The overall polar effect in these reactions is the result of the polarity and the polarisability of both the radicals and the substrates. While carbon-centred radicals usually do not show an extremely marked nucleophilic character, the electrophilic polarity of heteroaromatic bases is greatly increased by protonation. The strongly induced activation of heteroaromatic bases towards nucleophilic species, due to protonation, cannot be exploited with ionic nucleophiles, whose primary effect is deprotonation of the base. This problem is overcome by the use of free-radical nucleophiles, which react with protonated heteroaromatic bases in a large variety of substitutions characterised by high reactivity and selectivity. These reproduce most of the features of the Friedel-Crafts aromatic substitutions, but with opposite reactivity and selectivity, so as to represent one of the main general reactions of this class of aromatic compounds [1].

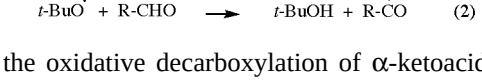
Because of their high reactivity (absolute rate constants in the range of 10^5-10^8 M^{-1} s^{-1} at r.t.) the most reactive bases are effective traps for revealing the presence of carbon-centred radicals in a reaction medium. Basically any carbonyl (acyl, carbamoyl, alkoxycarbonyl) or alkyl radical not bearing electron-withdrawing groups directly bonded to the radical centre can be successfully utilised to this purpose [1].

In previous works we have developed two general sources of acyl radicals, useful for the acylation of heteroaromatic bases:

1. the *t*-BuOOH/Fe(III) redox system in the presence of aldehydes [2] (eqs. 1, 2)

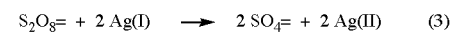


$$t\text{-BuOOH} + \text{Fe(II)} \longrightarrow t\text{-BuO}^{\cdot} + \text{Fe(III)} + \text{OH}^- \quad (1)$$

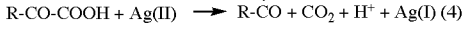


$$t\text{-BuO}^{\cdot} + \text{R-CHO} \longrightarrow t\text{-BuOH} + \text{R-}\dot{\text{C}}\text{O} \quad (2)$$

2. the oxidative decarboxylation of α-ketoacids by the $S_2O_8 = Ag^+$ redox system [3] (eqs.3, 4)

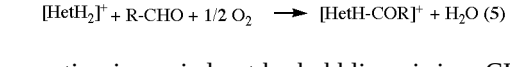


$$S_2O_8^{=} + 2\,\text{Ag(I)} \longrightarrow 2\,SO_4^{=} + 2\,\text{Ag(II)} \quad (3)$$



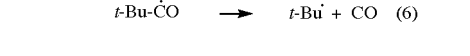
$$\text{R-CO-COOH} + \text{Ag(II)} \longrightarrow \text{R-}\dot{\text{C}}\text{O} + CO_2 + H^+ + \text{Ag(I)} \quad (4)$$

In this Note we report a new homolytic acylation of heteroaromatic bases by aerobic oxidation of aldehydes, catalysed by *N*-hydroxyphthalimide (NHPI) and Co salts. The overall stoichiometry is given by eq. 5, $[HetH_2]^+$ being the protonated base.



$$[HetH_2]^+ + \text{R-CHO} + 1/2\,O_2 \longrightarrow [\text{HetH-COR}]^+ + H_2O \quad (5)$$

The reaction is carried out by bubbling air in a CH_3CN or PhCN solution of the heteroaromatic base protonated by CF_3COOH, the aldehyde, NHPI and the Co(II) salt. In the absence of NHPI no reaction occurs under the same conditions. The reactivity of acyl radicals towards protonated heteroaromatic bases is so high that, even in the case of aldehydes R-CHO where R is a tertiary alkyl group, addition of the acyl radical to the heterocyclic ring competes with decarbonylation (eq. 6), which is a fast process [4].



$$t\text{-Bu-}\dot{\text{C}}\text{O} \longrightarrow t\text{-Bu}^{\cdot} + \text{CO} \quad (6)$$

The ratio between acylation and alkylation of the heterocyclic ring depends on the temperature: decarbonylation, being a unimolecular process, is more affected by temperature, so that alkylation increases at higher temperatures. When R in eq. 5 is an aryl or primary alkyl group no decarbonylation is observed, while with secondary alkyl groups only minor decarbonylation occurs. The results are reported in the Table. The selectivity of acylation in the α and γ positions of the heterocyclic ring (the positions of higher nucleophilic reactivity) is in all cases good, while conversions depend on the reactivity of the heterocyclic ring. Quinoxaline is more reactive than quinoline and gives better conversions under the same conditions.

These features, as well as the absence of acylation in experiments without NHPI, find a satisfactory explanation in the competition between oxygen and heteroaromatic base towards reaction with the acyl radical (eq. 7). They also suggest that the acyl radical is formed by hydrogen abstraction from the aldehyde by the phthalimido-N-oxyl radical (PINO, eq. 8) and not by the acylperoxyl radical (eq. 9).

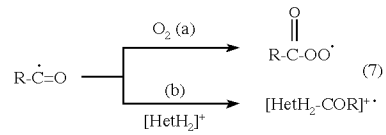
The importance of the polar effect in this new acylation method is particularly marked; this is shown by the quantitative conversion and complete selectivity in the acylation of 4-cyanopyridine as compared with the behaviour of pyridine, which reacts only in traces under the same conditions. With pyridine, reaction 7a is much faster than 7b and

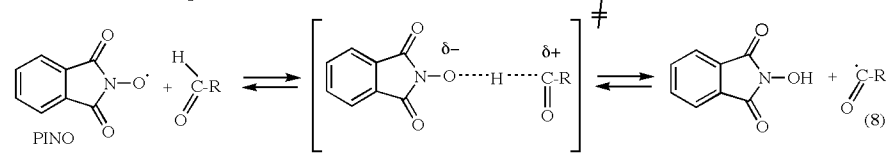
Table

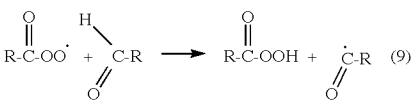
Acylation of Heteroaromatic Bases by Aerobic Oxidation of Aldehydes, R-CHO

Run	Heterocycle	R	Conv. (%)	Products (%)
1	Quinoline [a]	Ph	50	2-Acyl (**1**) (34), 4-Acyl (**2**) (41), 2,4-Diacyl (**3**) (22)
2	4-Methylquinoline	“	15	2-Acyl (**4**) (98)
3	Quinoxaline [b]	“	76	2-Acyl (**5**) (86), 2,3-Diacyl (**6**) (12)
4	Quinoxaline [c]	“	88	2-Acyl (**5**) (75), 2,3-Diacyl (**6**) (21)
5	Quinoxaline	“	86	2-Acyl (**5**) (85), 2,3-Diacyl (**6**) (14)
6	Quinoxaline [d]	“	0	—
7	Quinoxaline [e]	“	80	2-Acyl (**5**) (82), 2,3-Diacyl (**6**) (15)
8	Quinoxaline [f]	“	39	2-Acyl (**5**) (98)
9	Quinoxaline [e][f]	“	33	2-Acyl (**5**) (99)
10	Quinoxaline [f]	*t*-Bu	100	2-Acyl (**7**) (45), 2-*t*-Bu (**8**) (52)
11	Quinoxaline	“	100	2-Acyl (**7**) (26), 2-*t*-Bu (**8**) (72)
12	“	*s*-C_3H_7	51	2-Acyl (**9**) (78), 2-*i*-Pr (**10**) (16)
13	“	*n*-C_7H_{15}	91	2-Acyl (**11**) (77), 2,3-diacyl (**12**) (14)
14	“	Cyclohexyl	100	2-Acyl (**13**) (43), 2,3-diacyl (**14**) (32), 2-Acyl-3-cyclohexyl (**15**) (12)
15	Quinazoline	*n*-C_6H_{13}	100	3H-Quinazolin-4-one (**16**) (96)
16	“	Ph	100	3H-Quinazolin-4-one (**16**) (98)
17	Pyrazine	*n*-C_6H_{13}	85	2-Acyl (**17**) (96)
18	“	Ph	82	2-Acyl (**18**) (97)
19	4-Cyanopyridine [e]	“	100	2-Acyl (**19**) (96)
20	Pyrimidine	*n*-C_6H_{13}	14	4-Acyl (**20**) (98)
21	Pyridine	Ph	traces	—

[a] Reaction time 6 h, 9.1 mmol of PhCOOH are formed; [b] Reaction time 2 h, 2 mmol of PhCOOH are formed; [c] Oxygen instead of air, reaction time 0.7 h, 13.3 mmol of PhCOOH are formed; [d] Without NHPI; [e] CH_3CN instead of PhCN as solvent; [f] 20 °C instead of 70 °C.

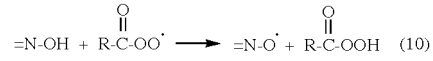






the only result is the oxidation of benzaldehyde to benzoic acid.

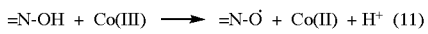
Recently, the Ishii group utilised the NHPI catalysis to perform a variety of aerobic oxidations of organic compounds [5], in all of which hydrogen abstraction by PINO radical from the C-H bonds plays a key role. The formation of acyl radicals from aldehydes according to eq. 8 has also been suggested by the same group for the catalytic free-radical addition of aldehydes to alkenes [6]. The presence of NHPI in this case somewhat improves the conversion and the selectivity of the addition; this, however, at variance with our process, must be carried out in the absence of oxygen, since the reaction of acyl radicals with O_2 (eq. 7a) is much faster than the addition of nucleophilic acyl radicals [1] to electron-rich alkenes. With electron-poor alkenes yields and selectivity are high regardless of the presence of NHPI. We have shown how hydrogen abstraction (eq. 8) is strongly affected by polar and enthalpic effects in the selective oxidation of alcohols [7], amines [8], amides [9] and silanes [10]. We have also evaluated [11] the bond dissociation energy (BDE) of the O-H bond in NHPI (88.1 kcal mol^{-1}) so that eq. 8, which is almost thermoneutral (BDE of the RCO-H bond is 87 kcal mol^{-1}), can be considered an equilibrium process. This is however shifted to the right by the subsequent fast reaction of the acyl radical with the heteroaromatic base or with oxygen (eq. 7). Moreover, we have evaluated [12] that hydrogen abstraction from the =N-OH group in NHPI by peroxyl radical ROO• , (7.2×10^3 M^{-1} s^{-1} at r.t.) is much faster than from C-H bonds (10^{-3} – 10^{-1} M^{-1} s^{-1}) and we can reasonably expect that hydrogen abstraction by the acylperoxyl radical, RCO-OO ·, should also be much faster from =N-OH (eq. 10) than from C-H bonds in aldehydes (eq. 9).



(10)

This should allow regeneration of the PINO radical in a chain process (in full agreement with the assumption that the acyl radical is formed according to eq. 8 and not to eq. 9).

PINO radical can also be regenerated from NHPI by oxidation with Co(III) salt (eq. 11) formed by the peroxyl oxidation of Co(II) salt through a redox chain (eq. 12).



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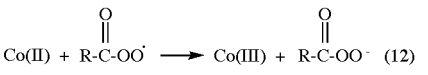
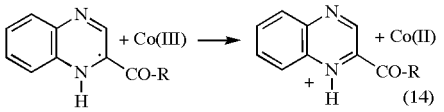


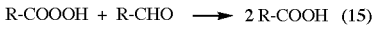
(12)

Co(III) may also play a significant role in the rearomatisation of the heterocyclic radical adduct (eqs.13, 14).



(14)

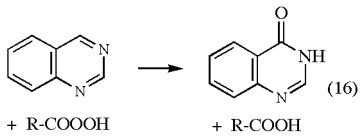
Carboxylic acids, R-COOH, from the aldehydes R-CHO are formed as by-products, deriving from the oxidation of aldehydes by peracids (eq. 15).



(15)

Since the ratio between acylation of the heterocycle and formation of the carboxylic acid depends on the competition represented in eq. 7, its value increases with increasing reactivity of the heteroaromatic base and with decreasing oxygen concentration. Thus, with quinoxaline a higher ratio has been obtained by working with air than with oxygen (entries 4 and 5 in the Table); moreover, more carboxylic acid is formed with quinoline (entry 1) than with the more reactive quinoxaline under the same conditions.

Quinazoline has an anomalous behaviour compared to the other heteroaromatic bases; no acylation occurs under the same conditions, while *3H*-quinazolin-4-one is the only reaction product. The formation of this latter compound by oxidation of quinazoline with H_2O_2 in acetic acid is well-known [13]; in this case we explain its formation by a similar oxidation of the heteroaromatic base by the peracid (eq. 16), formed in eqs. 10 and 12.



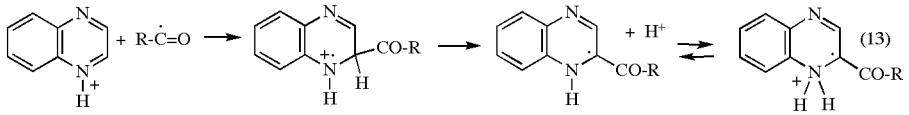
(16)

EXPERIMENTAL

The heteroaromatic bases and the aldehydes were commercial products. The reaction products were all known and prepared by the previously developed procedure of acylation and alkylation by aldehydes and the redox system *t*-BuOOH/Fe(II).

General Procedure.

Air was bubbled in a solution of the heteroaromatic base (3 mmol), CF_3COOH (0.23 mL, 3 mmol), aldehyde (15 mmol), NHPI (49 mg, 0.3 mmol), $Co(acac)_2$ (1.3 mg, 5×10^{-3} mmol) and $Co(acac)_3$ (3,6 mg, 10^{-2} mmol) in 8 mL of Ph-CN heated at 70 °C for 12h. Some experiments were carried out in CH_3CN solution, at 20 °C and for shorter reaction times. The solution was diluted with 30 mL of 5% H_2SO_4 aqueous solution and extracted by



(13)

ethyl acetate to separate the excess aldehyde and the formed carboxylic acid. 10% NaOH (15 mL) were then added to the aqueous solution and the basic products were extracted with ethyl acetate. The reaction products were identified by gc-ms analysis and comparison with authentic samples prepared according to known procedures [2-4], [12] and analysed by gc with internal standard. Compound **4** was utilised as internal standard for reaction products **1**-**3** and **5**-**20**, while compound **5** was used as internal standard for compound **4**. The results of the gc analyses are reported in the Table.

The reaction products were isolated by flash chromatography on silica gel (*n*-hexane-ethyl acetate 5:1), obtaining the following acylation products (yields % of acylation are based on converted heterocyclic substrates).

Quinoline with Benzaldehyde.

2-Benzoylquinoline (**1**) was obtained in 29% yield; MS (m/z): 233 (M^+), 216, 176, 156, 128, 105, 77, 51. 4-Benzoylquinoline (**2**) was obtained in36% yield; MS (m/z): 233 (M^+), 204, 176, 151, 128, 105, 77, 51. 2,4-Dibenzoylquinoline (**3**) was obtained in18% yield; MS (m/z): 337 (M^+), 308, 280, 232, 176, 155, 127, 105, 77, 51.

4-Methylquinoline with Benzaldehyde.

2-Benzoyl-4-methylquinoline (**4**) was obtained in 91% yield; MS (m/z): 247 (M^+), 218, 140, 115, 105, 77, 51.

Quinoxaline with Benzaldehyde.

In run 3, 2-benzoylquinoxaline (**5**) was obtained in 79% yield; MS (m/z): 234 (M^+), 206, 129, 105, 77, 51; 2,3-dibenzoylquinoxaline (**6**) was obtained in 7% yield; MS (m/z): 338 (M^+), 310, 233, 105, 77, 51. In run 8, 2-benzoylquinoxaline (**5**) was obtained in 93% yield.

Quinoxaline with Pivalaldehyde.

In run 10, 2-pivaloylquinoxaline (**7**) was obtained in 41% yield; MS (m/z): 214 (M^+), 186, 171, 158, 144, 130, 102, 76, 50, 41; 2-*t*-butylquinoxaline (**8**) was obtained in 46% yield; MS (m/z): 186 (M^+), 171, 144, 129, 102, 76, 50, 41.

Quinoxaline with 2-Butanal.

2-Butanoylquinoxaline (**9**) was obtained in 71% yield; MS (m/z): 234 (M^+), 200, 185, 159, 111, 71, 56, 43; 2-isopropylquinoxaline (**10**) was obtained in 9% yield; MS (m/z): 172 (M^+), 185, 157, 129, 102, 76, 41.

Quinoxaline with *n*-Octanal.

2-Octanoylquinoxaline (**11**) was obtained in 72% yield; MS (m/z): 256 (M^+), 229, 185, 157, 144, 129, 102, 76, 57, 41; 2,3-dioctanoylquinoxaline (**12**) was obtained in 8% yield; MS (m/z): 382 (M^+), 354, 312, 270, 228, 185, 144, 129, 102, 57.

Quinoxaline with Cyclohexancarboxaldehyde.

Cyclohexyl-quinoxalin-2-yl methanone (**13**) was obtained in 36% yield; MS (m/z): 240 (M^+), 212, 144, 130, 102, 76, 55, 41; (3-cyclohexanecarbonyl-quinoxalin-2-yl)-cyclohexyl-methanone (**14**) was obtained in 26% yield; MS (m/z): 350 (M^+), 322, 240, 129, 102, 85, 55; cyclohexyl-(3-cyclohexyl-quinoxalin-2-yl)-methanone (**15**) was obtained in 7% yield; MS (m/z): 322 (M^+), 240, 129, 102, 83, 55, 41.

Quinazoline with *n*-Heptanal.

3*H*-Quinazolin-4-one (**16**) was obtained in 91% yield; MS (m/z): 146 (M^+), 118, 90, 76, 63, 50.

Quinazoline with Benzaldehyde.

3*H*-Quinazolin-4-one (**16**) was obtained in 91% yield.

Pyrazine with *n*-Heptanal.

2-Heptanoylpyrazine (**17**) was obtained in 90% yield; MS (m/z): 192 (M^+), 182, 167, 122, 104, 80, 44.

Pyrazine with bBnzaldehyde.

2-Benzoylpyrazine (**18**) was obtained in 92% yield; MS (m/z): 184 (M^+), 156, 105, 77, 51.

4-Cyanopyridine with Benzaldehyde.

2-Benzoyl-4-cyanopyridine (**19**) was obtained in 93% yield; MS (m/z): 208 (M^+), 180, 153, 105, 77, 51.

Pyrimidine with *n*-Heptanal.

4-Heptanoylpyrimidine (**20**) was obtained in 91% yield; MS (m/z): 192 (M^+), 149, 135, 107, 94, 80, 52, 43.

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