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A NOVEL ELECTROPHILIC N-AMIDATION *VIA* ELECTRON DEFICIENT COMPLEXES : ACTION OF FERRIC CHLORIDE ON N-ACETYLOXYAMIDES

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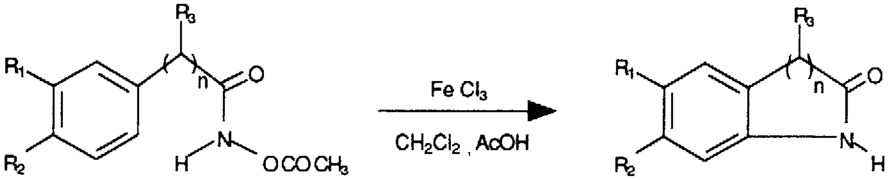
Summary : The action of $FeCl_3$ on N-acetyloxyamides leads to electron deficient species which can react intra or intermolecularly with an aromatic group to give oxindoles or analogues.

We have found a novel, high yield, reaction of N-acetyloxyamides bearing an aromatic group with ferric chloride, giving in particular oxindoles or analogues.



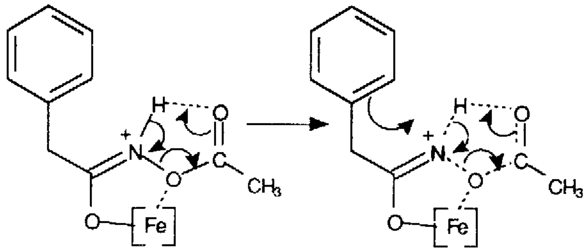
1 - 5 **6 - 9**

1 ,**6** ; n = 1 ; R_1 = $R_2 = R_3 = H$
2 ,**7** ; n = 1 ; R_1 = $R_2 = H$ $R_3 = Me$
3 ,**8** ; n = 2 ; R_1 = $R_2 = R_3 = H$
4 ,**9** ; n = 1 ; R_1 = OMe $R_2 = R_3 = H$
5 ,**10** ; n = 1 ; R_1 = $R_3 = H$ $R_2 = OMe$

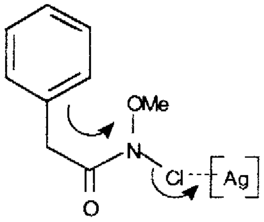
The substrates <u>1</u>-<u>5</u> are easily obtained by acetic anhydride acetylation of hydroxamic acids, themselves obtained from hydroxylamine and the required ester or acid chloride.

Treated at room temperature, in methylene chloride and in the presence of one mol. equiv. of acetic acid[1], and two mol. equiv. of anhydrous ferric chloride, the N-acetyloxyamides 1-5 are transformed in a few hours into the cyclic amides 6-9, easily isolated by washing with 10% HCl and filtration on silica gel (see Table). The reaction can be extended to the intermolecular N-amidation of anisole, to give in this case moderate yields of mixtures (see Table entry 9 and 10).

A plausible interpretation of these results can be given. It is well known that hydroxamic acids give stable and colored complexes with ferric salts ; this appears to occur also with their O-acetates such as 1, as the addition of this N-acetyloxyamide to a solution of ferric chloride in methylene chloride slightly modifies the UV spectrum, a broad band arising around 314 nm. We assume that a transition state such as 11 leads to the oxindole. The iron complexation through the enol form makes the amidic proton much more acidic, thus protonating intramolecularly the acetyloxy group, and making it a good leaving group. The remaining formal nitrenium ion is reminiscent of the formal intermediate from 12 in a related reaction described by Glower[3] and Kikugawa[4,5] and their coworkers, involving treatment of N-chloro N-alkoxyamides with silver or zinc salts.



1 1



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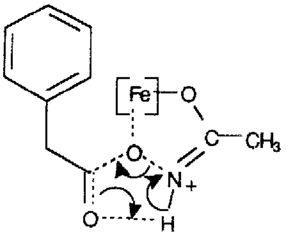

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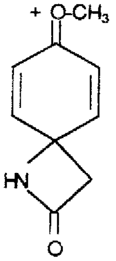

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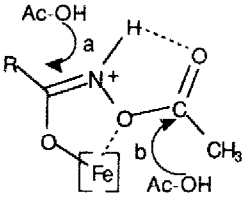
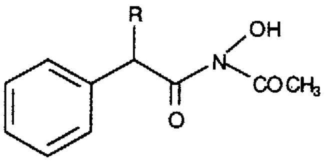


1 5

The electrophilic character of intermediates such as 11 is well illustrated by the products formed with anisole as well as from amide 4 and 5[6]. The methoxy group activating the para position, the amide 5 leads to the intermediate 14, as suggested by Glover[3] and Kikugawa[5], but in this reaction the exclusive migration of C-C bond gives the 5-methoxyoxindole 9 only.

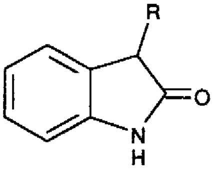
Our procedure is much simpler as it does not require prior halogenation ; its major limitation is that the presence of a hydrogen on the amide nitrogen is essential. The N-methyl derivative of 1 (entry 7) like N-acetyl N-acetyloxyphenethylamine (entry 8) have been recovered unchanged. It is of particular interest that N-phenylacetyloxy acetamide, as well as the corresponding N-phenylpropanoyloxy acetamide, give no intramolecular reaction, but after a few days, only the corresponding carboxylic acids in 54% and 39% yields respectively. The required transition state 13 shows that the intramolecular cyclisation is geometrically impossible as the aromatic ring stands far from the electrophilic nitrogen. This cleavage as well as the loss of material could be explained by acetic acid attack according to paths a or b on 15 : path a would lead to a mixed anhydride giving acid on hydrolysis, path b to a hydroxamic acid, part of which could complex the ferric chloride and be water soluble, giving the observed dark violet water coloration.

This electrophilic reaction explains also one remarkable result reported by Royer and coll.[7]. These authors report a reaction between β-nitrostyrene and acetyl chloride in the presence of Friedel-Crafts catalysts ; they stress the particular case of $FeCl_3$, which gives either a hydroxamic acid described as acetylated on the nitrogen, 16, or a chloro-oxindole 18, depending on the reaction time. We have shown that compound 17,



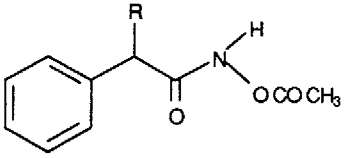
16 R = Cl

17 R = H



18 R = Cl

19 R = H



20 R = Cl

21 R = H

Table - Electrophilic Aromatic Substitution by N-acetyloxyamides promoted by $FeCl_3$.

Entry	Starting compounds[a]	Products	Isolated yield %
1	1	6	75
2	2	7	72
3	3 (mp : 103-104°)	8	90
4	4 (mp : 75-76°)	9	72
5	5 (mp : 152-153°)	9	50
6	$CH_3CONHOCOCH_3$ + anisole[b]	$CH_3OC_6H_4NHAc$ para	18
		$CH_3OC_6H_4NHAc$ ortho	14
		+ $pCH_3OC_6H_4COCH_3$[c]	15
7	$PhCH_2CON(CH_3)OCOCH_3$	-	-
8	$PhCH_2CH_2N(COCH_3)OCOCH_3$	-	-
9	$CH_3CON(CH_3)OCOCH_3$ + anisole[b]	$pCH_3OC_6H_4COCH_3$[c]	49
10	$PhCONHOCOCH_3$ + anisole[b]	$pCH_3OC_6H_4NHCOPh$	11
		$pCH_3OC_6H_4COCH_3$[c]	57

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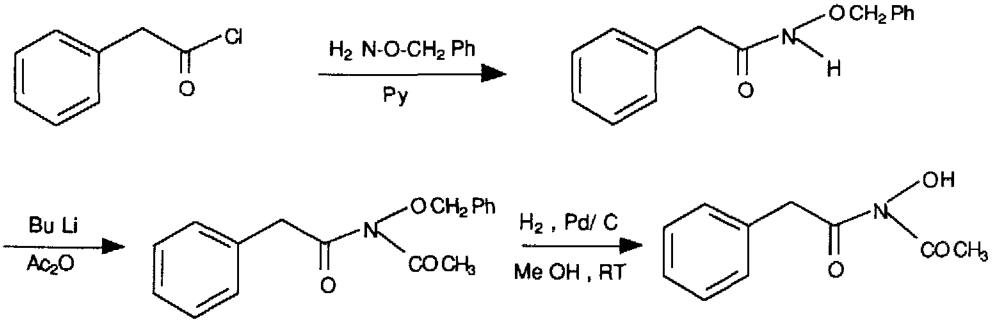
a) All compounds, when not yet known, gave correct analysis and spectroscopic data. b) Anisole was used in large excess. c) This ketone must be formed via path b on 15.

synthesized as shown below, is different from the substance obtained by Royer and coll. by hydrogenolysis of C-Cl bond of their product[8]. In fact, the product they obtained was identical to the derivative produced by O-acetylation of the corresponding hydroxamic acid[9]. So, the primary product obtained from β-nitrostyrene with $FeCl_3$ as catalyst was in reality 20, which underwent a subsequent cyclisation. These results are in accordance at the same time with our view on the reactivity of nitronate[10] and with the conclusions of the present communication.



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REFERENCES

1 Stricly anhydrous $FeCl_3$ was inert and insoluble. Addition of 1 mol. equiv. of water allows complexation, but leads to hydrolysis of the substrate. Acetic acid is adequate for $FeCl_3$ dedimerization, it participates in side reaction only when the cyclization is slow or inefficient. $AlCl_3$ and $TiCl_4$ were inefficient. For analogous observations, see ref. 2.

2 Jones T.K. and Denmark S.E., Helv. Chim. Acta, 1983, 66, 2377.

3 Glover S.A., Goosen A., McCleland C.W., Schoonrad J.L., J. Chem. Soc. Perkin Trans. I, 1984, 2255 and Tetrahedron, 1987, 43, 2577.

4 Kikugawa Y. and Kawase M., J. Amer. Chem. Soc., 1984, 106, 5728.

5 Kikugawa Y. and Shimada M., Chem. Letters, 1987, 1771.

6 Beside C-N bond formation, some primary amide is sometimes observed. See L. Demuynck and al., Tetrahedron Letters, next paper.

7 Guillaumel J., Demerseman P., Clavel J.M., Royer R., Platzer N., Brevard C., Tetrahedron, 1980, 36, 2459.

8 N-hydroxy N-acetyl phenylacetamide 17 : ^1H nmr in $CDCl_3$: CH_3 s at 2.47ppm, CH_2 s at 4.13ppm. ^{13}C nmr in DMSO d_6 : CH_3 at 24.69ppm, CH_2 at 42.06ppm.
N-acetyloxy phenylacetamide 21 : ^1H nmr in $CDCl_3$: CH_3 s at 2.14ppm, CH_2 s at 3.59ppm ; ^{13}C nmr in DMSO d_6 : CH_3 at 17.89ppm ; CH_2 at 38.64ppm.

9 Baur L. and Exner O. Angew. Chem. Internat. Edit., 1974, 13, 376.

10 Cherest M. and Lusinchi X., Tetrahedron, 1986, 42, 3825.

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