SYNTHESIS OF ANILIDES BY REDUCTIVE N-ACYLATION OF NITROARENES MEDIATED BY METHYL FORMATE

E.M. NAHMED and G. JENNER*

Laboratoire de Piézochimie Organique, Chimie Organique Appliquée, associé au CNRS, Ecole Européenne des Hautes Etudes des Industries Chimiques, 1, rue Blaise Pascal, 67008 Strasbourg (France).

Summary : Anilides are synthesized from nitroarenes via sequential reductive N-acylation, catalyzed by ruthenium compounds in the presence of a carboxylic acid and methyl formate or formic acid. In the reduction step, hydrogen is supplied by the formic compound.

Anilides are compounds of current industrial interest as intermediates in the production of pharmaceuticals and dyes. For example, 4-hydroxy-acetanilide (paracetamol \bigcirc) is taken for headaches and acetophenetidin is used as an analgaesic; on the other hand, acetoacetanilide serves as dyestuff in the preparation of dry colors. As nitrobenzenes are readily available industrial chemicals, it is more efficient to start directly from the nitrocompound rather than from the corresponding amine or isocyanate, thereby bypassing the reduction step.

This procedure was previously examined by Ho^1 and Owsley^2 . In the first case, N-acylation of nitrobenzene was accomplished by acetic acid with excess Mo(CO)_6 and in the second case, N-acylation occurred in the presence of stoechiometric amounts of iron dissolved in acetic acid. Another approach has considered catalytic procedures via reductive carbonylation. Anilides have been obtained either via nickel³ or rhodium⁴ or platinum⁵-catalyzed carbonylation of nitroarenes. However, in each case, the reaction required 50 to 100 atm CO.

We have found interesting to report our own results using methyl formate as the source of either CO or H_2 , depending on the reductive route followed⁶.

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Mononitrobenzene is permitted to react in an autoclave with acetic acid and methyl formate in the presence of a catalytic amount of $Ru_3(CO)_{12}$, without initial hydrogen or carbon monoxide pressure. This reaction results in the formation of a gas mixture (CO, CO_2, H_2). The following liquid and solid products are derived from nitrobenzene : acetanilide, formanilide, aniline and usually minor amounts of N-methyl- and N,N-dimethylaniline. In addition to these products, the reaction yields methanol and methyl acetate⁷.

The effects of varying the relative concentrations of methyl formate and acetic acid are reported in Table 1.

Table 1

Methyl formate	Acetic acid	Conversion		Yields ^b %		
(mmol)	(mmol)	%	aniline	ма ^ь	FA ^b	AA ^b
0	35.3	0	0	0	0	0
16.2	35.3	62	5	1	0	56
32.4	35.3	100	30	3	5	62
48.6	35.3	100	35	3	20	40
32.4	35.3	100	30	3	5	62
32.4	52.9	100	15	2	0	83
32.4	70.6	100	8	ז	0	91

Synthesis of acetanilide^a.

 $^{a}C_{6}H_{5}NO_{2}$ (9.8 mmol), $Ru_{3}(CO)_{12}$ (7.5 x 10⁻³ mmol), 180°C, 5h

bChromatographic yields. MA(methylanilines), FA(formanilide), AA(acetanilide)

When the acid concentration remains constant, there is an optimum for the yield of acetanilide for a formate : acid molar ratio of I:1. A low concentration of methyl formate is unable to fully reduce nitrobenzene, whereas an excess leads to the production of mostly aniline and a substantial amount of formanilide.

Increasing the concentration of acid promotes the synthesis of acetanilide (91% yield for a formate : acid ratio of 1:2). This is easily

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understandable in the light of the sequential mechanism involved in the first step, i.e. reduction of the nitroarene to aniline, followed by acylation. Acetic acid must be present in sufficient amount since there is competitive esterification of methanol originating from methyl formate.

Generalization of the procedure leads to good yields of the corresponding anilides (Table 2).

Table 2

Synthesis of anilides via reductive N-acylation of nitroarenes^a

Nitroarene	Carboxylic acid	Yield of anilide ^b %	
nitrobenzene	propionic acid ^C	82 (73)	
nitrobenzene	butyric acid	70 (51)	
p-nitrotoluene	acetic acid	78 (66)	
p-nitroanisol	acetic acid	85 (72)	
p-nitrochlorobenzene	acetic acid	95 (80)	
p-nitrophenol	acetic acid	92	

[°]Chromatographic yields based on nitroarene. Isolated yields are shown in parentheses

^CReaction time (5h)

A possible reaction set is illustrated below :

нсоосн _з	\longrightarrow	CO + CH ₃ OH
сн _з соон + нсоосн _з	~`	нсоон + сн _а соосн _а
НСООН	>	$H_{2} + CO_{2}$
сн _з он + сн _з соон	\leftarrow	н ₂ 0 + сн ₃ соосн ₃
$C_{6}H_{5}NO_{2} + H_{2}$	\longrightarrow	$C_{6}H_{5}NH_{2} + H_{2}O$
с ₆ н ₅ мн ₂ + сн ₃ соон	>	C ₆ H ₅ NHCOCH ₃ + H ₂ O
с ₆ н ₅ мн ₂ + нсоосн ₃	\longrightarrow	с ₆ н ₅ мнсно + сн _з он
$C_6H_5NH_2 + CH_3COOCH_3$	>	с ₆ н ₅ мнсосн ₃ + сн ₃ он

As previously indicated, the source of CO and ${\rm H_2}$ is methyl formate via ruthenium catalyzed decomposition. Acetic acid could activate the process via

transesterification of methyl formate yielding formic acid which is easily decomposed into H₂ and CO₂. Nitrobenzene is readily reduced into aniline in the presence of minute quantities⁸ of $Ru_3(CO)_{12}$. In our scheme, acetanilide is presumed to originate from aniline via acylation either by acetic acid or by methyl acetate. We have demonstrated independently that both ways are operating. Considering the role of formic acid in the above scheme, we replaced methyl formate by formic acid. It was found that under conditions of Table 1, acetanilide could be synthesized in 93% yield by using formic acid (26-53 mmol) and either acetic acid (53 mmol) or acetic anhydride (22-38 mmol). This procedure avoided formation of methyl by-products, however needed separation of formanilide (3-5%) which systematically contaminated the acetanilide formed.

In conclusion, the present method of synthesizing anilides from nitroarenes, via reductive N-acylation in the presence of methyl formate or formic acid, is very simple and affords the targeted product in good yields. The main advantage of this procedure is that it circumvents the necessity of an initial hydrogen pressure.

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 The liquid phase was analyzed by GC (FID). Girdel 300, PPE 7% on Chr. Gaw. DMCS, 60-230°C, 10°C/min. The amides were isolated by recrystallization from methanol, analyzed by NMR and characterized by their melting points.
- 8. The concentration of the catalyst can even be reduced : 90% acetanilide are obtained under conditions of Table 1 with 0.003 mmol $Ru_3(CO)_{12}$.

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