Fries-type rearrangement of acylanilides in the presence of ytterbium triflate

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Ytterbium triflate has been used to catalyse the Fries-type rearrangement of various acylanilides with moderate yields when lithium perchlorate was used as co-catalyst.

Keywords: ytterbium triflate, Fries-type rearrangement, acylanilides, lithium perchlorate

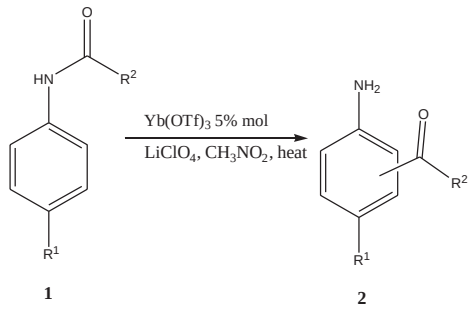
The Fries-rearrangement reaction[1] is very famous in organic chemistry. By this method, hydroxylaryl ketones can be obtained. The related reaction with aminoarylketones is more difficult to carry out. Dippy studied the rearrangement of *N*,*N*-diacylanilides[2] using freshly fused Zinc chloride. However, the yield was low. Thus, the migration in *N*,*N*-diacylanilides was slow and the rearrangement of *N*-monoacylanilides might be expected to be even more difficult to achieve. Thus, when *N*-monoacylanilides[3] were treated with anhydrous aluminium chloride at high temperature the *o*-amino-acylphenone or *p*-amino-acylphenone were obtained in low yields. In addition esters were obtained as by-products in this reaction.

In view of the difficulty in achieving the rearrangement of *N*-monoacylanilides, photochemical methods have been widely used.[4-11] Better results were obtained but there are also some by-products. Recently, Das *et al*. have developed a method to achieve the rapid rearrangement of sulfonanilides under the microwave irradiation in the presence of excess of aluminium chloride.[12]

Due to our interest in the catalytic activity of ytterbium triflate, we have reported the catalytic reactions of Friedel-Crafts acylation[13] and the cleavage of imines[14] with good results in which the catalytic ytterbium triflate had exhibited a high activity. To extend this work, we now report our study of the rearrangement of *N*-monoacylanilides catalysed by catalytic amounts of $Yb(OTf)_3$.

Results and discussion

Initial attempts using $Yb(OTf)_3$ as the only catalyst were unsuccessful. When the rearrangement reaction was attempted in low-boiling-point solvent, such as CH_2Cl_2, $CHCl_3$, CS_2 or C_6H_6, none of the expected products were detected even after refluxing for 8 h. Even when nitromethane, toluene or chlorobenzene were used only a trace of the desired rearrangement products was obtained after refluxing for 8 h.



1 **2**

Scheme 1

Although diphenylmethane or nitromethane was used, the yields did not increased significantly even at 190°C for 8h.

We tried our best to increase the yields and make the conditions less vigorous. Although the superacidic systems, which may be formed by mixing the appropriate Lewis acids (LA) and Bronsted acids have exhibited their excellent activity in both academic and industrial research,[15] and recently metal triflate/methanesulfonic acid has been used to promote the Fries-rearrangement of phenol esters with good yields,[16] the yields of rearrangement products of acylanilides in these superacidic systems were poor. When acetanilide was treated with 10% mol of $Yb(OTf)_3/CH_3COOH$ at 100°C in nitromethane for 8h, the yield was less than 5%. We postulate that the acid reacted with the amino product to form the amide at high temperature thereby losing its activity.

However, metal triflate/$LiClO_4$ systems have been used to catalyse some organic reactions and good yields have been obtained.[17,18] The improvement in these reactions is remarkable. Thus we attempted using a $Yb(OTf)_3$/ $LiClO_4$ system to improve the yields (Scheme 1). It is interesting and exciting that a clear increase in the yields was observed (Table 1).

Table 1 $Yb(OTf)_3/LiClO_4$ system catalysed Fries-type rearrangement of *N*-monoacylanilides in nitromethane

Entry	R^1	R^2	$LiClO_4$/ equiv	Time/h	Product **2**	Yield/%
1	H	CH_3	1	8	*p*-Aminoacetophenone	20
2	H	CH_3	4	8	*p*-Aminoacetophenone	44
3	H	CH_3	4	2	*p*-Aminoacetophenone	18
4	H	C_2H_5	4	8	*p*-Aminopropiophenone	43
5	H	C_3H_7	4	8	*p*-Aminobutyrophenone	39
6	CH_3	Ph	4	8	2-Amino-5-methyl-benzophenone	31
7	Cl	CH_3	4	8	2-Amino-5-chloro-acetophenone	32
8	OCH_3	CH_3	4	8	75/25[a]	51
9	CH_3COO	CH_3	4	8	3-Acetyl-4-hydroxy-acetanilide	65
10	H	Ph	4	8	*p*-Aminobenzophenone	22
11	NO_2	CH_3	4	12	-	Trace
12	CN	CH_3	4	12	-	Trace
13	CH_3CO	CH_3	4	12	-	Trace

a) the ratio of 2-amino-5-methoxyacetophenone/5-amino-2-methoxyacetophenone

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As can be seen from Table 1, the rearrangement proceeded at a lower temperature and the substrate was converted into aminoaryl ketones in moderate yields. The effect of the additive ($LiClO_4$) is clear; an excess of $LiClO_4$ increased the yield. Benzanilide also could be converted into aminobenzophenone (entry 10), but the yield is lower than with aliphatic acylanilides. In entries 1, 2, 3, 4 and 5 the main products were the *p*-amino products that could not be isolated by steam distillation, and the amounts of *o*-amino products formed were small. When there are strong electronic withdrawing groups on the aromatic ring, such as a nitro, nitrile or acyl group, only a trace of the desired products was detected (by TLC) (entries 11, 12, 13). And the presence of a methoxy or methyl group on the aromatic ring is beneficial to the rearrangement (entries 6, 8). It is interesting that when *p*-methoxylacetanilide is the substrate, there are two isomer products and the ratio is 75/25 (entry 8). However, the methoxyl group survived in the reaction, while usually presence of an excess of $AlCl_3$ leads to demethylation products. Thus we postulate the possible mechanism (Scheme 2). We suggest that the electronic attack could proceed in two ways to form different products.

Kobayashi attributed high reactivity to such a cationic species generated by $LiClO_4$ in the presence of $Ln(OTf)_3$.[17]

To test the difficulty of the rearrangement, 4-acetylaminophenyl acetate was used as the substrate and 0.5mol $Yb(OTf)_3$/(4 equiv)$LiClO_4$ was involved (entry 9). After heating at 100°C for 5h, hydroxyl compound [*N*-(3-Acetyl-4-hydroxyphenyl)-acetamide] was obtained, and no rearrangement to form an amino compound was detected. Thus, it is clear that the Fries-rearrangement of phenol esters is more facile than the rearrangement of acylanilides.

However, it is noteworthy that anhydrous conditions are needed to maximise the activity of $Yb(OTf)_3$ because of the presence of the amino group on the rearrangement products. In addition, toluene and chlorobenzene can be used as solvents, but nitromethane is the most efficient.

In conclusion, the rearrangement of acylanilides could be achieved in this catalytic system with moderate yields over some hours and this catalytic system is effective for this type of rearrangement.

CAUTION: Appropriate precautions should be taken when carrying out reactions involving perchlorates particularly in work up procedures with organic compounds because of the possibility of explosion.

Experimental

(ESI) Mass spectra were determined by a Thermo Finnagan LCQ Advantage instrument. ^1H NMR spectra were recorded on a Varian-400 MHz instrument using $CDCl_3$ as the solvent with TMS as an internal standard. IR spectra were recorded on a AVATAR-370 Infrared Spectrophotometer. Melting points were determined on a Digital Melting Point Apparatus WRS-1B and are uncorrected. $Yb(OTf)_3$ was prepared from ytterbium oxide and trifluoromethanesulfonic acid in water according to the literature.[19]

General procedure: A suspension containing acetanilide (3 mmol), $Yb(OTf)_3$ (0.15 mmol) and $LiClO_4$ (12 mmol) in nitromethane (10 ml) was stirred at room temperature until most had dissolved. Then the solution was heated to 100°C for 8 h. A red-dark solution was obtained and after cooling, the mixture was diluted with 20 ml CH_2Cl_2 and treated with 10 ml water. The isolated aqueous layer was extracted with 10 ml CH_2Cl_2 and combined the organic solution. After concentration, the residue was purified by recrystallisation from acetone–petroleum ether to obtain *p*-aminoacetophenone (**2a**).

p-Aminoacetophenone **2a**: M.p. 106–107°C (Lit.[4], 108–110°C); ν_{max}/cm^{-1}: 3310, 1668; δ_H: 7.58 (2H, d, *J*=8.2 Hz, ArH), 6.55 (2H, d, *J*=8.2 Hz, ArH), 4.14 (2H, s, NH_2), 2.54 (3H, s, CH_3).

p-Aminopropiophenone **2b**: M.p. 136–137°C (Lit.[4], 139–140°C); ν_{max}/cm^{-1}: 3315, 1665; δ_H: 7.60 (2H, d, *J*=8.2 Hz, ArH), 6.56 (2H, d, *J*=8.2 Hz, ArH), 4.10 (2H, s, NH_2), 2.46 (2H, m, CH_2), 1.23 (3H, m, CH_3).

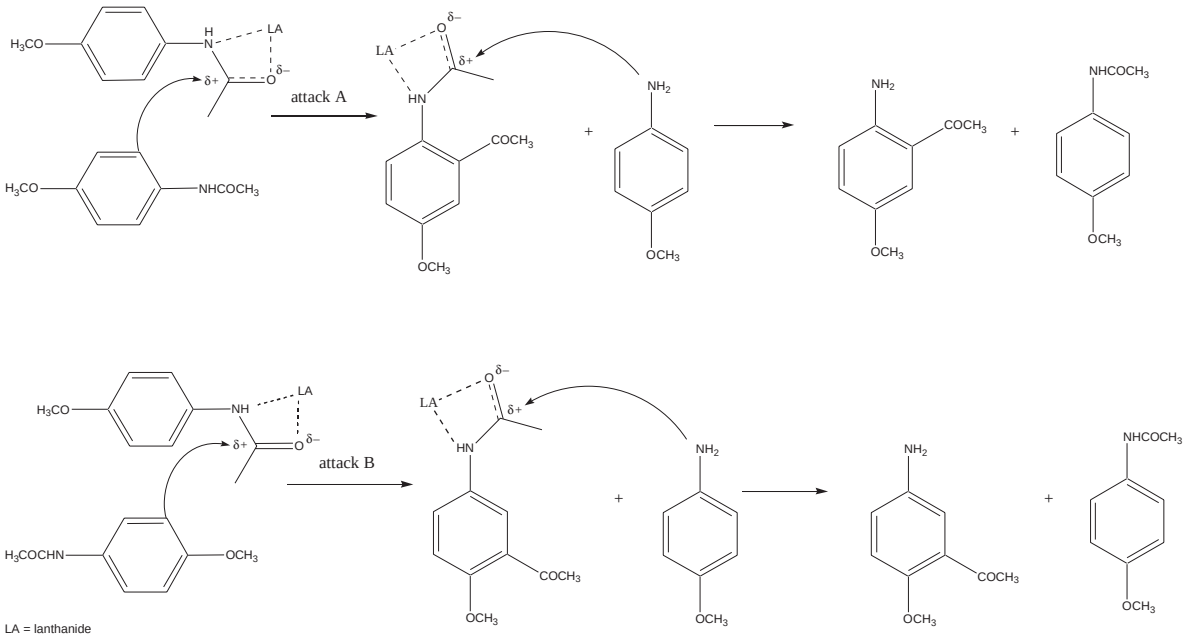
p-Aminobutyrophenone **2c**: M.p. 92–94°C (Lit.[4], 95–97°C); ν_{max}/cm^{-1}: 3285, 1658; δ_H: 7.61 (2H, d, *J*=8.2 Hz, ArH), 6.55 (2H, d, *J*=8.2 Hz, ArH), 4.02 (2H, s, NH_2), 2.44 (2H, m, CH_2), 1.72 (2H, m, CH_2), 1.01 (3H, m, CH_3).

2′-Amino-5′-methyl-benzophenone **2d**: M.p. 59°C (Lit.[2], 62°C); ν_{max}/cm^{-1}: 3305, 1661; δ_H: 7.71–7.74 (2H, m, ArH), 7.28–7.46 (4H, m, ArH), 7.08 (1H, d, *J*=8.4 Hz, ArH), 6.46 (1H, d, *J*=8.4 Hz, ArH), 4.23 (2H, s, NH_2), 2.38 (3H, s, CH_3).

2′-Amino-5′-chloro-acetophenone **2e**: M.p. 98°C (Lit.[2], 97°C); ν_{max}/cm^{-1}: 3265, 1669; δ_H: 7.64 (1H, s, ArH), 7.26 (1H, d, *J*=8.2 Hz, ArH), 6.48 (1H, d, *J*=8.2 Hz, ArH), 3.89 (2H, s, NH_2), 2.54 (3H, s, CH_3).

2′-Amino-5′-methoxyacetophenone **2f**: M.p. 52°C (Lit.[20] 55°C) ν_{max}/cm^{-1}: 3318, 1662. δ_H: 7.13 (1H, s, ArH) 6.75 (1H, d, *J*=8.4 Hz, ArH), 6.50 (1H, d, *J*=8.4 Hz, ArH), 3.46 (2H, s, NH_2), 3.71 (3H, s, CH_3), 2.49 (3H, s, CH_3).

5′-Amino-2′-methoxyacetophenone **2f′**: M.P. 91°C, (Lit.[21] b.p. 125–127°C /0.25mmHg) ν_{max}/cm^{-1}: 3312, 1658. δ_H: 7.08 (1H, s,



Scheme 2

ArH) 6.68 (1H, d, *J*=8.2 Hz, ArH), 6.59 (1H, d, *J*=8.2 Hz, ArH), 4.18 (2H, s, NH_2), 3.69 (3H, s, CH_3), 2.51 (3H, s, CH_3).

3'-Acetyl-4'-hydroxy-acetanilide **2g**: M.P. 163–164°C (Lit.[21] 165°C). ν_{max}/cm^{-1}: 3418, 3302, 1668, 1647. δ_H: 12.08 (1H, s, ArOH), 8.18 (1H, s, NH), 8.08 (1H, s, ArH) 7.42 (1H, d, *J*=8.4 Hz, ArH), 6.97 (1H, d, *J*=8.4 Hz, ArH), 2.62 (3H, s, CH_3), 2.17 (3H, s, CH_3). (ESI)MS (*m/z*): 194.1 $(M+1)^+$, 166.1, 124.1; 192.2 $(M-1)^-$, 150.1.

p-Aminobenzophenone **2h:** M.p. 120–122°C (Lit.[4], 123–124°C); ν_{max}/cm^{-1}: 3234, 1671; δ_H: 7.75–7.79 (2H, m, ArH), 7.38–7.46 (5H, m, ArH), 6.60 (2H, d, *J*=8.2 Hz, ArH), 4.07 (2H, s, NH_2).

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Reference

1 K. Fries and G. Fink, *Ber.*, 1908, **41**, 4271.
2 J.F.J. Dippy and V. Moss, *J. Chem. Soc.*, 1952, 2205
3 J.F.J. Dippy and J.H. Wood, *J. Chem. Soc.*, 1949, 2719.
4 D. Elad, D.V. Rao and V.I. Stenberg, *J. Org. Chem.*, 1965, **30**, 3252.
5 J. Stumpe, A. Mehlhorn and K. Schwetlick, *J. Photochem.*, 1978, **8**, 1.
6 A.K. Singh and T.S. Raghuraman, *Synth. Commun.*, 1986, **16**, 485.
7 K.K. Park, J.J. Lee and J. Ryu, *Tetrahedron*, 2003, **59**, 7651.
8 D. Hellwinkel and R. Lenz, *Chem. Ber.*, 1985, **118**, 66.
9 H. Nozaki, T. Okada, R. Noyori and M. Kawanisi, *Tetrahedron*, 1966, **22**, 2177.
10 B. Weiss, H. Durr and H.J. Haas, *Angew. Chem. Int. Ed. Engl.*, 1980, **19**, 648.
11 K. Pitchumani, M.C.D. Manickam and C. Srinivasan, *Tetrahedron Lett.*, 1991, **32**, 2975.
12 B. Das, P. Madhusudhan and B. Venkataiah, *J. Chem. Res. (S)*, 2000, 200.
13 W.K. Su and C. Jin, *J. Chem. Res. (S)*, 2003, 694.
14 W.K. Su and C. Jin, *J. Chem. Res. (S)*, 2004, 188.
15 G.A. Olah, G.K.S. Prahash and J. Sommer, *Superacids*, Wiley: New York, 1985.
16 O. Mouhtady, H.G. Lloughmane, N. Roques and C.L. Roux, *Tetrahedron Lett.*, 2003, **44**, 6379.
17 A. Kawada, S. Mitamura and S. Kobayashi, *Chem. Commun.*, 1996, 183.
18 S. Kobayashi and I. Komoto, *Tetrahedron*, 2000, **56**, 6463.
19 J.H. Forsberg, V.T. Spaziano, T.M. Balasubramanian, G.K. Liu, S.A. Kinsley, C.A. Duckworth, J.J. Poteruca, P.S. Brown and J.L. Miller, *J. Org. Chem.*, 1987, **52**, 1017.
20 A.R. Osborn and K. Schofield, *J. Chem. Soc.* 1955, 2100.
21 D.W. Mathieson, G. Newbery, *J. Chem. Soc.* 1949, 1133.