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Fries Rearrangement of Anilides in the Presence of Phosphorus Pentoxide in Methanesulfonic Acid

Babak Kaboudin and Yaghoub Abedi

Department of Chemistry, Institute for Advanced Studies in Basic Sciences Gava Zang, Zanjan, Iran

Aminoaryl ketones are an important class of compounds that exhibit a variety of interesting and useful properties.[1–3] Some aminoaryl ketones are useful intermediates for the synthesis of benzodiazepines exhibiting activity as peptide antagonists, antivirals, antimalarials, and inhibitors of DNA interactions.[4–7] Moreover, *p*-aminoaryl ketones are useful intermediates in the synthesis of other compounds that are used as sunscreens, anti-inflammatory agents, dyes, and inhibitors of MAP kinases.[8–11] The Fries reaction of aryl esters is an important rearrangement in aromatic chemistry.[12–14] In contrast to the widely studied Fries rearrangement of phenolic esters, relatively few papers have been reported on the Fries rearrangement of anilides[12] to *o*- and *p*-aminoaryl ketones, by photolysis or thermolysis (above 200–350°C) with various Lewis acids such as $ZnCl_2$, $SnCl_4$, $TiCl_4$, $ThCl_4$ and $BiCl_3$.[15–18] The Fries rearrangement of acetanilide has been also reported over zeolite catalysts at 280°C with 50% conversion.[19] Recently a Fries-type rearrangement of anilides has been reported by using strong bases *via* an anionic rearrangement.[20]

Methanesulfonic acid is a Brönsted acid that is used as catalyst and solvent for condensation or rearrangement reactions.[21–23] Its use as catalyst in the Fries rearrangement of phenolic esters is already known.[24–26] Addition of P_2O_5 increased the solubility of organic compounds in methanesulfonic acid that has been used extensively in organic synthesis.[27] As a part of our effort to explore methodologies for organic transformations,[28–45] we described a new method for the Fries rearrangement of phenolic esters for the synthesis of acylaryl methane sulfonates in the presence of $POCl_3$ in methanesulfonic acid.[46] Herein, we report the Fries rearrangement of anilides in the presence of a mixture of P_2O_5 in methanesulfonic acid (1:7) as an efficient reagent for the selective synthesis of *p*-aminoaryl ketones.

The Fries rearrangement of benzanilide (**1a**), chosen as a model compound, was studied in the presence of P_2O_5 in methanesulfonic acid, and the progress of the reaction monitored by TLC (*Scheme 1* and *Table 1*). Treatment of **1a** with a mixture of P_2O_5 in methanesulfonic

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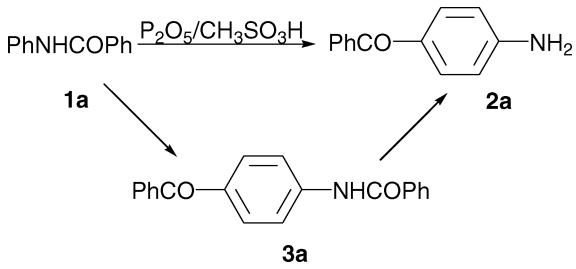
Address correspondence to Babak Kaboudin, Department of Chemistry, Institute for Advanced Studies in Basic Sciences, Gava Zang, Zanjan 45195-1159, Iran. E-mail: kaboudin@iasbs.ac.ir



Scheme 1

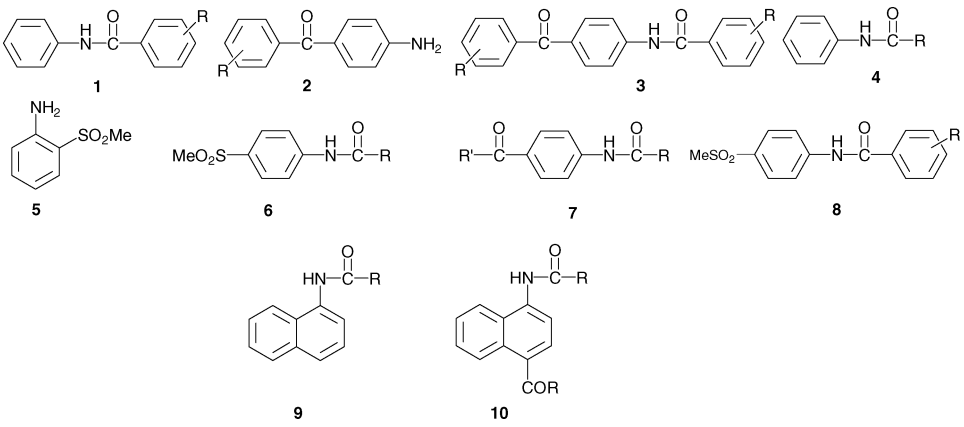
acid (1:12) gave 4-aminobenzophenone (**2a**) in 8% yield after 48 h at 100°C (*Table 1, Entry 2*). Surprisingly, we found that increasing the amount of P_2O_5 led to acceleration of the reaction rate and an increase in the yield of **2a** (*Entries 3–6*). We obtained the best results with 1:7 ratio of P_2O_5 in methanesulfonic acid (*Entry 6*). The yield of the reaction did not change with increasing amounts of P_2O_5. Increasing the reaction temperature to 110°C also let to an increase in yield (*Entry 9*). Decomposition occurred when the reaction temperature was raised to 120°C. ^{1}H NMR studies on the Fries rearrangement of **1a** at different temperatures showed that at the beginning of the reaction, *p*-benzoyl- benzanilide (**3a**) is the major product. Sulfonated products **5** and **8a** (*Table 2*) were detected in low yields (<10%) in the reaction mixture after 48 h. In a separate experiment, when compound

Table 1
Fries Rearrangement of **1a** in the Presence of Phosphorus Pentoxide in Methanesulfonic Acid

Entry	P_2O_5:CH_3SO_3H (w:w)	Solvent	Temperature (° C)	Yield[a,b] (%) **2a**
1	0:1	—	100	—
2	1:12	—	100	8
3	1:10	—	100	20
4	1:9	—	100	28
5	1:8	—	100	35
6	1:7	—	100	43
7	1:7	—	80	8
8	1:7	—	90	15
9	1:7	—	110[c]	46
10	1:7	$ClCH_2CH_2Cl$	reflux	—
11	1:7	$C_6H_5NO_2$	100	—
12	1:7	C_6H_5Cl	100	—

a) Isolated yields.
b) Reactions carried out for 48 h.
c) Reaction mixture decomposed at 120° C

Table 2
The Fries Rearrangement of Anilides in a Mixture of Methanesulfonic Acid/Phosphorus Pentoxide (7:1) for 48 h



Substrate	R	Product	Temperature (°C)	Yield (%)[a]	Ratio[b]
1a	H	**2a + 3a**	110	51	9:1 (**2a:3a**)
1b	*m*-Cl	**2b + 3b**	110	61	3:1 (**2b:3b**)
1c	*o*-Cl	**2c**	100	45	—
1d	*p*-CH_3	**2d + 3d**	100	45	3:2 (**2d:3d**)
1e	*m*-CH_3	**2e + 3e**	100	56	3:1 (**2e:3e**)
1f	*p*-NO_2	**8f**	110	65	—
4a	CH_3	**—**	110	—	—
4a	CH_3	**5 + 6a + 7a**	115	50	1:1:1 (**5:6a:7a**)
9a	Ph	**10a**	85	32	—

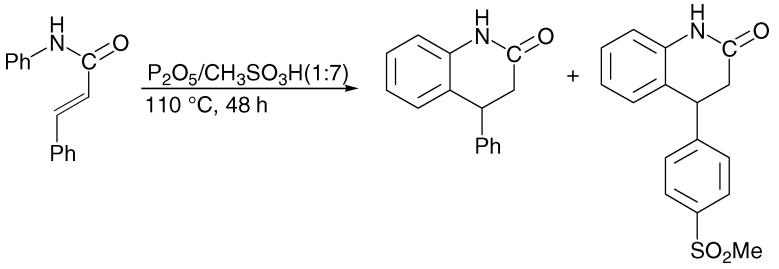
a) Yield refers to isolated yield by column chromatography.
b) Ratio of products was calculated after separation by column chromatography.

3a was added to a mixture of P_2O_5/methanesulfonic acid (1:7) and stirred for 48 h at 100°C, compound **2a** was formed in 90% yield.

These results may be explained by considering the initial formation of **3a** which undergoes decomposition to **2a**. The Fries rearrangement of benzanilide (**1a**) failed with a mixture of P_2O_5/methanesulfonic acid (1:7) in 1,2-dichloroethane, nitrobenzene, and chlorobenzene respectively at 100°C for 48 h.

The process was successfully extended to other anilides as summarized in *Table 2*. The Fries rearrangement of benzanilides (**1b-e**) with P_2O_5/methanesulfonic acid (1:7) afforded the desired products in 45–61% yields (*Table 2*). The reaction of *p*-nitrobezoyl benzanilide (**1f**) in the presence of this reagent led only to sulfonated product (**8f**) as the major product. Treatment of acetanilide (**4a**) in the presence of P_2O_5 in methanesulfonic acid failed for 48 h at 110°C failed. However at 115°C this reaction gave three products: **5**, **6a**, and **7a** in 1:1:1 ratio in 50% total yield. With this reagent, *N*-benzoyl-1-naphthylamine (**9a**) gave **10a**

in 32% yield after 48 h at 85°C, decomposition occurred after 48 h at 110 °C. In the case of *N*-phenylcinnamamide (**4b**), the cyclization product **11** was obtained as major product in 68% yield (*Scheme 2*). A sulfonated product **12** was also detected as a side- product in the reaction mixture (20% yield).



4b **11** **12**

Scheme 2

In summary, P_2O_5/methanesulfonic acid (1:7) was shown as an efficient reagent in the Fries rearrangement of anilides to *p*-aminoaryl ketones. Studies on the reaction mixture showed that the reaction proceeded *via* the formation of *p*-acylated anilide (**3**). Some of the major advantages of this protocol are simple procedure, easy work-up, good yields, inexpensive and non-toxic catalyst, mild reaction conditions relative to other current methodologies, a lower reaction temperature than other methodologies and reactions with high selectivity for providing *p*-aminoaryl ketones. All reported methods to give a mixtiure of two products *p*- and *o*-aminoaryl ketones including other unknown mixture products. All NMR data could be assigned and are in good agreement with the product structures (*Tables 3* and *4*).

Experimental Section

All chemicals were commercial products and distilled or recrystallized before use. All melting points were obtained on a Buchi 510 apparatus and are uncorrected. Infrared (IR) spectra were determined using a FT-IR Brucker-Vector 22. NMR spectra were obtained on a DMX-250 Bruker Avance spectrometer in $CDCl_3$. Silica gel column chromatography was carried out on Silica gel 100 (Merck No. 10184). Merck Silica-gel 60 F254 plates were used for preparative TLC.

General Procedure for the Preparation of Anilides (1, 4, and 9)

Acid chloride or anhydride (10 mmol) was added to a stirred solution of anilide (10 mmol) in THF (50 mL). The mixture was stirred for 2 h at room temperature. A white solid precipitated which was filtered and washed with H_2O (5 × 20 mL). Pure anilide was obtained after recrystallization from AcOEt.

Table 3
^{1}H NMR and ^{13}C NMR of **2a-e**, **3a-d**, **5**, **6a**, **7a**, **8f**, and **10a**[a]

Cmpd	^{1}H NMR (δ)	^{13}C NMR (δ)
2a	4.46 (s, 2H, NH_2), 6.67 (d, 2H, $J = 8.5$ Hz), 7.41–7.60 (m, 3H), 7.68–7.78 (m, 4H)	113.6, 127.3, 128.1, 129.5, 131.4, 132.9, 138.9, 151.0, 195.4
2b	6.25 (s, 2H, NH_2), 6.58 (d, 2H, $J =$ 8.5 Hz), 7.45–7.65 (m, 6H)	113.1, 123.5, 127.8, 128.6, 130.6, 131.2, 133.1, 133.5, 141.6, 154.6, 192.2
2c	4.37 (s, 2H, NH_2), 6.58 (d, 2H, $J =$ 8.0 Hz), 7.25–7.65 (m, 4H), 7.71 (d, 2H, $J = 8.0$ Hz)	113.7, 126.4, 126.6, 128.7, 129.7, 130.5, 130.9, 139.4, 152.2, 193.5
2d	2.43 (s, 3H), 4.15 (s, 2H, NH_2), 6.67 (d, 2H, $J = 8.5$ Hz), 7.25 (d, 2H, $J = 8.0$ Hz), 7.65 (d, 2H, $J = 8.0$ Hz), 7.71 (d, 2H, $J = 8.5$ Hz)	21.6, 113.6, 127.7, 128.8, 129.8, 132.8, 135.9, 142.1, 150.7, 195.3
2e	2.37 (s, 3H), 4.35 (s, 2H, NH_2), 6.61 (d, 2H, $J = 8.5$ Hz), 7.25–7.55 (m, 4H), 7.67 (d, 2H, $J = 8.5$ Hz)	21.4, 113.6, 126.7, 127.5, 127.9, 130.0, 132.2, 132.9, 137.9, 139.2 150.9, 161.7
3a	7.45–8.10 (m, 14H), 8.24 (s, 1H, NH)	119.2, 127.2, 128.3, 128.9, 129.9, 131.7, 132.3, 133.2, 134.4, 137.7, 141.9, 166.0, 195.8
3b	7.45–8.05 (m, 12H), 10.72 (s, 1H, NH)	120.1, 127.1, 128.0, 128.5, 129.2, 131.0, 131.6, 131.8, 132.4, 133.8, 136.9, 140.0, 165.1, 193.7
3d	2.40 (s, 3H), 2.44 (s, 3H), 7.15–7.30 (m, 4H), 7.60–7.90 (m, 8H), 8.43 (s, 1H, NH)	21.6, 21.7, 119.2, 127.2, 129.0, 129.5, 130.2, 131.5, 133.2, 135.0, 142.0, 142.8, 143.1, 166.0, 195.7
3e	2.34 (s, 3H), 2.42 (s, 3H), 7.20–7.90 (m, 14H), 8.80 (s, 1H, NH)	21.3, 21.4, 119.4, 124.3, 127.2, 128.0, 128.1, 128.5, 130.3, 131.6, 132.8, 133.0, 133.1, 134.5, 137.8, 138.1, 138.6, 142.4, 166.6, 196.2
5	3.21 (s, 3H), 5.01 (s, 2H, NH_2), 6.75 (d, 1H, $J = 8.0$ Hz), 6.83 (t, 1H, $J = 8.0$ Hz), 7.39 (t, 1H, $J = 8.0$ Hz), 7.24 (d, 1H, $J = 8.0$ Hz)	42.2, 117.6, 118.0, 129.4, 135.1, 146.2
6a	2.01 (s, 3H), 3.14 (s, 3H), 7.70–7.90 (m, 4H), 10.37 (s, 1H, NH)	24.6, 43.5, 119.1, 119.2, 128.6, 144.2, 169.6
7a	2.20 (s, 3H), 2.60 (s, 3H), 7.40 (s, 1H, NH), 7.61 (d, 2H, $J = 8.5$ Hz), 7.94 (d, 2H, $J = 8.5$ Hz)	24.6, 26.8, 118.6, 129.9, 131.9, 144.1, 169.4, 196.9
8f	3.19 (s, 3H), 7.88 (d, 2H, $J = 8.7$ Hz), 8.03 (d, 2H, $J = 8.7$ Hz), 8.18 (d, 2H, $J = 8.7$ Hz), 8.38 (d, 2H, $J = 8.7$ Hz), 10.97 (s, 1H, NH)	44.2, 120.6, 124.1, 128.6, 129.9, 136.0, 140.4, 143.7, 149.8, 165.0
10a	7.52–8.25 (m, 16H), 10.78 (s, 1H, NH)	122.4, 124.5, 125.8, 126.9, 127.9, 128.3, 128.4, 128.9, 129.3, 129.4, 130.3, 131.6, 132.3, 133.9, 134.0, 134.8, 137.4, 138.3, 166.8, 197.3.

a) All compounds showed IR absorption at 3150–3420 for N-H and 1620–1680 cm^{-1} for C=O

Table 4
Mps and Combustion Data of **2a-e**, **3a-d**, **5**, **6a**, **7a**, **8f**, and **10a**

			Elemental Analysis (Found)		
Cmpd	mp (°C)	lit. (°C)	C	H	N
2a	124–125	124[13]	—	—	—
2b	152–153	154–155[14]	—	—	—
2c	112–113	112[19]	—	—	—
2d	190–191	189–191[15]	—	—	—
2e	117–119	—	79.58 (79.65)	6.21 (6.03)	6.63 (6.46)
3a	156–158	157–159[16]	—	—	—
3b	163–165	—	65.03 (64.95)	3.55 (3.45)	3.79 (3.73)
3d	176–178	—	80.21 (80.12)	5.92 (5.80)	4.25 (4.15)
3e	169–171	—	80.21 (80.02)	5.92 (5.70)	4.25 (4.10)
5	57–58	58–59[17]	—	—	—
6a	181–183	183–184[18]	—	—	—
7a	166–168	166–167[16]	—	—	—
8f	282–284	—	52.49 (52.55)	3.79 (3.70)	8.75 (8.60)
10a	167–169	—	82.02 (81.85)	4.89 (4.82)	3.99 (4.05)

General Procedure for the Fries Rearrangement of Anilides in the Presence of P_2O_5 in Methanesulfonic Acid

In a 50 mL round bottom flask, a mixture of P_2O_5 (1 g) in methanesulfonic acid (5 mL) was stirred for 10 min at 80°C. The anilide (3 mmol) was added to the mixture and the reaction mixture was heated at 100–115°C for 48 h (The reaction progress was followed by TLC). The reaction mixture was quenched by adding water, neutralized with NaOH solution (50 mL, 10%) and extracted with chloroform (2 × 50 mL). The *p*-aminoaryl ketone was easily removed from the reaction mixture by extraction with HCl (50 mL, 10%). The aqueous phase was neutralized with NaOH (50 mL, 10%) and the product extracted with diethyl ether (4 × 25 mL). The solvent was evaporated and the product recrystallized from acetone. After separation of the *p*-aminoaryl ketone from the reaction mixture, the mother liquor (chloroform) containing unreacted anilide and other rearrangement products that were separated by column chromatography with *n*-hexane/ethyl acetate as eluting solvents (the ratio of solvent depends on the amides).

4-Phenyl-3,4-dihydroquinolin-2(1*H*)-one (11) white crystals, mp. 187–189°C (*n*-hexane/EtOAc); ^{1}HNMR (250 MHz, $CDCl_3$): δ 2.95 (d, 2H, J = 7.0 Hz), 4.31 (t, 1H, J = 7.2 Hz), 6.90–7.05 (m, 3H), 7.15–7.48(m, 6H), 9.52 (s, 1H, NH); ^{13}C-NMR (62.9 MHz, $CDCl_3$): 38.4, 41.9, 115.8, 123.4, 126.6, 127.2, 127.8, 128.0, 128.3, 128.9, 137.0, 141.5, 171.2.

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.68; H, 5.87; N, 6.28. Found: C, 80.45; H, 5.80; N, 6.21.

4-(4-(Methylsulfonyl)phenyl)-3,4-dihydroquinolin-2(1*H*)-one (12) white crystals, mp. 233–235°C (*n*-hexane/EtOAc); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.73 (dd, 1H, J = 6.5 and 16.0 Hz), 2.88 (dd, 1H, J = 6.5 and 16.0 Hz), 3.18 (s, 3H), 4.47 (t, 1H, J = 6.5 Hz), 6.85–6.98 (m, 3H), 7.15–7.25(m, 1H), 7.43 (d, 2H, J = 8.2 Hz), 7.94 (d, 2H, J = 8.2 Hz),

10.31 (s, 1H, NH); ^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 37.9, 38.9, 43.9, 116.0, 122.9, 125.7, 127.9, 128.5, 128.6, 128.9, 138.5, 139.8, 149.0, 169.2.
Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.70; H, 4.89; N, 4.50

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