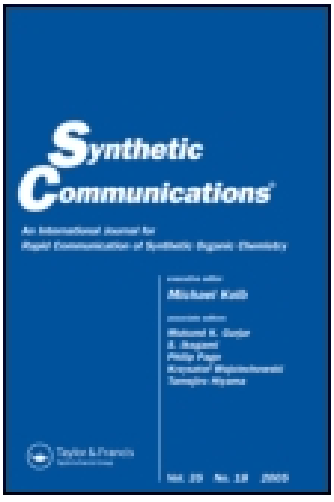

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Facile Synthesis of 1-Aryl-2-propanones from Aromatic Amine

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Facile Synthesis of 1-Aryl-2-propanones from Aromatic Amine

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Abstract: A facile synthesis of aryl propanones using aromatic amines as precursors, via an improved Meerwein arylation reaction under mild conditions, is reported.

Keywords: Aryl propanones, aromatic amines, improved Meerwein arylation reaction

Aryl propanones are essential intermediates for the synthesis of fine chemicals, particularly for pharmaceutical synthesis.[1] For example, 1-[3-(trifluoromethyl)phenyl]-2-propanone is an intermediate for the synthesis of benfluorex and its analogues, an ideal emaciated agent,[2] 1-(1,3-benzodioxol-5-yl)-2-propanone is an intermediate for the synthesis of *L*-α-methyldopa or the like, which has an antihypertensive function.[3] 1-Phenyl-2-propanone is a precursor for the synthesis of prenylamine lactic acid, used as antianginals, as well as for the synthesis of phenylisopropylamine, a precursor of a pseudo adrenal gland agent.[4]

Several methods have been developed for the synthesis of 1-aryl-2-propanones. These methods include (1) oxidative rearrangements of arylalkenes

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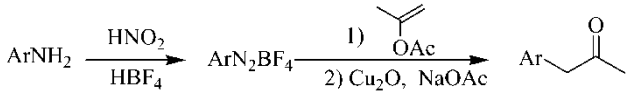
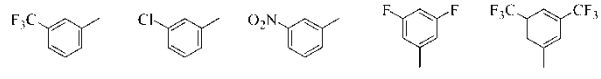
with [hydroxy(tosyloxy)iodo]benzene,[5] (2) a benzyl Grignard reagent reacts with acetonitrile and subsequent hydrolysis,[6] (3) an aryl Grignard reagent reacts with 1,2-epoxypropane and subsequent oxidation,[7] (4) a methyl Grignard reagent reacts with benzimidazole and subsequent hydrolysis,[8] and (5) epoxidation of allylbenzenes and subsequent isomerization.[9] Despite the usefulness and neatness of these approaches, some of them suffer from a few drawbacks, such as the high cost of the reagents employed, the system from which water has been strictly removed, and less than satisfactory overall reaction yields.

We herein report a facile two-step synthesis of aryl propanones using commercially available aromatic amines as precursors via an improved Meerwein arylation reaction. Although the arylation of unsaturated compounds by diazonium salts has been investigated extensively,[10] and the procedure was also developed by Raucher,[11] the yields of Meerwein adducts were always lowered because of significant amounts of undesired by-products. To circumvent this difficulty, not only were the corresponding diazonium tetrafluoroborates prepared but also the reactions were carried out in organic phase rather than in a water solution. Improved Meerwein arylation of these salts with isopropenyl acetate gave the desired adducts in higher yields and greater purity than those obtained from the corresponding diazonium chlorides. The aromatic amines may have electron-withdrawing groups, electron-releasing groups, and steric effect groups respectively, as outlined in Scheme 1.

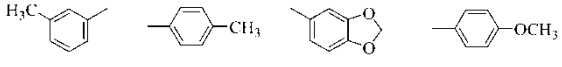
For example, 1-[3-(trifluoromethyl) phenyl]-2-propanone **2** is an important intermediate for the synthesis of medicines and chemicals. The synthesis of aryl propanone **2** was reported via two synthetic routes as



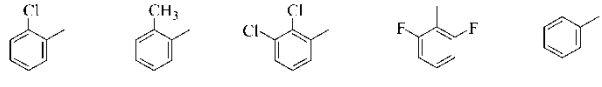
Ar: (1) with electron-withdrawing groups



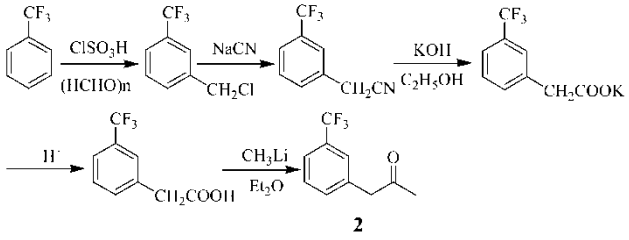
(2) with electron-releasing groups



(3) with steric effect groups or other



Scheme 1.



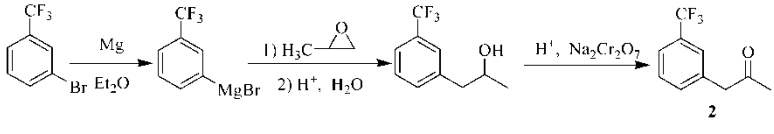
Scheme 2. Synthesis of 1-[3-(trifloromethyl)phenyl]-2-propanone.

follows: (1) As shown in Scheme 2,[12] aryl propanone **2** was synthesized by chloromethylazidation of trifluoromethyl benzene, followed by cyanidation, hydrolysis, acidation, and finally methylation. (2) As shown in Scheme 3,[13] the compound **2** was synthesized via Grignard reaction of *m*-bromo-α,α,α-trifluoromethyltoluene, followed by reaction with 1,2-epoxypropane to give 1-(m-trifluoromethylphenyl)-2-propanol, and finally oxidation to give aryl propanone **2**.

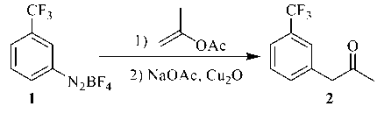
Our synthetic strategy is summarized in Scheme 4. For instance, *m*-trifluoromethylaniline, a commercially available cheap compound, is utilized as a precursor, through a known diazo-reaction, and *m*-trifluoromethylphenyl diazonium tetrafluoroborate **1** is easily synthesized in a high yield. The addition reaction of **1** with isopropenyl acetate in the presence of a catalyst gives the targeted 1-[3-(trifluoromethyl)phenyl]-2-propanone **2** in a good yield. In comparison to what described in the literature,[12,13] this two-step synthesis is obviously superior in synthetic steps and reaction conditions.

The reaction conditions were optimized as in Tables 1–3. For example, the reaction was carried out in the presence of a catalytic amount of cuprous oxide and anhydrous sodium acetate at 20–25°C for 6 h, and 95% yield of **2** was achieved.

Moreover, this two-step synthesis can be applied for the synthesis of new compounds, which are difficult to synthesize according to the methods as reported in the literature.[5–13] For instance, for the synthesis of product **3**. Spectra and some physical data for product **3**: White crystal. Mp: 52–53°C. IR (KBr): 1717, 1624, 1381, 1292, 1116, 1022, 991, 924, 900, 851, 823, 735, 705, 685, 673, 533 cm^{-1}. ^{1}HNMR ($CDCl_3$, 400 MHz, TMS): δ 7.8 (s, 1H), 7.6 (s, 2H), 3.9 (s, 2H), 2.3 (s, 3H). ^{13}CNMR ($CDCl_3$, 400 MHz, TMS):δ 203.5, 136.3, 132.1, 131.7, 129.8, 121.9, 121.2, 121.1, 49.6, 29.9.



Scheme 3. Synthesis of 1-[3-(trifloromethyl)phenyl]-2-propanone.



Isolated yield = 95%

Scheme 4. Novel synthesis of 1-[3-(trifloromethyl)phenyl]-2-propanone. Isolated yield = 95%.

Table 1. Effect of reaction time on yield (20–25°C)

Yield (%)	Time (h)
85	2
91	4
95	6
84	8

Table 2. Effect of reaction temperature on yield (6 h)

Yield (%)	Temperature (°C)
95	20–25
90	40–45
85	50–60
87	60–70

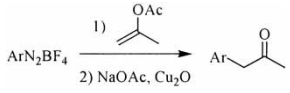
Table 3. Effect of catalyst on yield (at 20–25°C for 6 h)

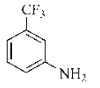
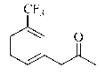
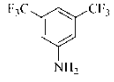
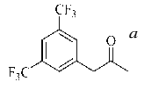
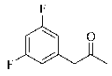
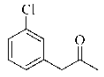
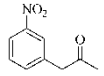
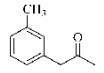
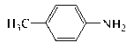
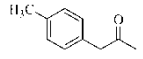
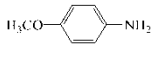
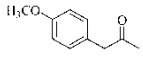
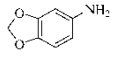
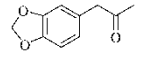
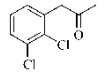
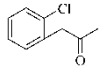
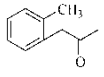
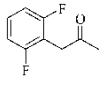
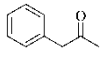
Yield (%)	Catalyst
87	CuCl
92	Cu_2O

ESI-MS: 269.2 $[M\text{-}H]^+$. elemental analysis calculated for $C_{11}H_8F_6O$: C, 48.90; H, 2.98; F, 42.19; found: C, 49.01; H, 3.01; F, 42.06.

A variety of aryl propanones were synthesized (see Table 4) using this strategy. Aromatic amines with electron-withdrawing groups, electron-releasing groups, and steric effect groups were easily converted to their corresponding aryl propanones.

Table 4. Synthesis of 1-aryl-2-propanones



Entry	Substrate	Product		Yield[b]	Yield[c]
1			**2**	95	90
2			**3**	93	88
3			**4**	92	82
4			**5**	93	85
5			**6**	91	86
6			**7**	80	66
7			**8**	73	60
8			**9**	76	58
9			**10**	61	45
10			**11**	60	50
11			**12**	75	53
12			**13**	70	52
13			**14**	50	38
14			**15**	90	75

[a]New compound.
[b]Yields based on diazonium tetrafluoroborates.
[c]Yields based on aromatic amines.

In summary, a facile synthesis of a series of 1-aryl-2-propanones was reported in this letter. This method offer several advantages, such as relatively cheap reagents, effortless experimental operation, and high overall process yield. Intensive studies for the synthesis of 1-heteroaryl-2-propanones are in progress but beyond the scope of this communication.

EXPERIMENTAL

Melting points were measured on a Kofler apparatus and are uncorrected. MS measurements were performed on ESI-MS spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM-400 instrument. Chemical shifts refer to TMS on the δ scale.

A procedure for the synthesis of product **2** is as follows: *m*-trifluoromethylaniline hydrochloride, prepared by heating a mixture of 24.26 g (0.15 mol) of *m*-trifluoromethylaniline, 38 mL of concentrated hydrochloric acid, and 55 mL of water for several minutes, was cooled to -5°C in an ice-salt bath, and a cold solution of 10.6 g (0.15 mol) sodium nitrite in 15 mL of water was added over 45 min with stirring. The temperature of the reaction mixture was held between -5 and 2°C. The mixture was stirred for an additional 15 min, and a cold solution of 12.04 g (0.19 mol) of boric acid in 39 mL 40% of hydrofluoric acid was slowly added with stirring. The mixture was stirred for an additional 30 min and then stored at about 0°C for 2 h. The mixture was filtered, and the solid was washed with the dilute solution of fluoroboric acid (30 mL), 50% ethanol (30 mL), 95% ethanol (30 mL), and anhydrous ether (2×30 mL) to yield 36.7 g (95%) of the colorless salt **1**.

To a stirred mixture of 20.5 g (0.25 mol) of anhydrous sodium acetate, 1.89 g (0.013 mol) of cuprous oxide, and 52.6 mL (0.468 mol) of isopropenyl acetate, 26.3 g (0.1 mol) of solid *m*-trifluoromethylphenyl diazonium tetrafluoroborate **1** were added over 30 min, while the temperature of the reaction mixture was held between 20 and 25°C. The reaction mixture was stirred an additional 6 h at 20–25°C. The mixture was filtered and washed with ether. The solution was collected and distilled under vacuum to give 19.4 g (95%) of the product **2** as a clear yellow liquid.

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