Hydrogen Bond Donor Solvents Enabled Metal and Halogen-free Friedel–Crafts Acylations with Virtually No Waste Stream

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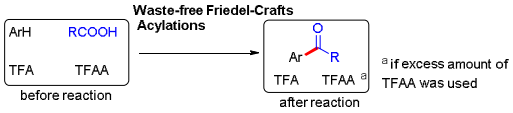

1. Trifluoroacetic acid (TFA, bp 72°C) and TFAA (bp 40 °C) can be recovered by distillation and reused - virtually no waste generation.
2. works for less reactive aromatics.
3. halogen-free

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*Guangchang Liu, Bo Xu**
College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China

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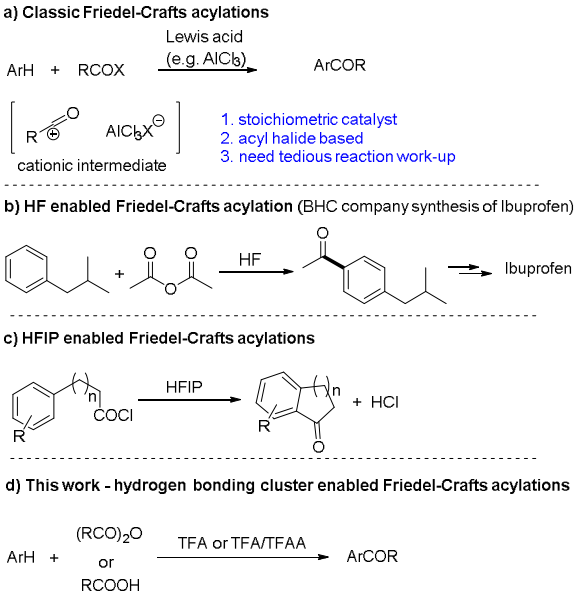
ABSTRACT

We have developed a metal and halogen-free Friedel–Crafts acylation protocol with virtually no waste stream generation. We propose a hydrogen bonding donor solvent will form a hydrogen bonding network and may provide significant rate enhancement for Friedel–Crafts reactions. Trifluoroacetic acid is one of the strongest H-bond donor solvents, which is also volatile and can be easily recovered by distillation without need for reaction workup. Our protocol is a 'green' Friedel–Crafts acylation process: 1) the catalyst can be recovered and reused; 2) using halogen free starting material (carboxylic acids anhydride or carboxylic acids); 3) no need for aqueous reaction work-up; 4) minimum or no waste steam generation.

The Friedel–Crafts acylation is one of the most commonly used transformations in drug and material synthesis. Its classical version normally requires stoichiometric quantities of Lewis acid catalysts and/or using of acyl halides as starting materials (Scheme 1a). Acyl halides are often needed to be prepared from carboxylic acids in an additional step. What is more, tedious aqueous reaction work-up is needed in most cases to remove stoichiometric quantities of Lewis acids such as $AlCl_3$, this work-up generates large amount of waste stream. In 2005, the ACS Green Chemistry Institute (GCI) roundtable program identified that Friedel–Crafts reaction on unactivated systems was one the most important reactions which need improvements from point view of green chemistry.[1]

There were many important progresses for 'greener' Friedel–Crafts acylation reactions like use of heterogenous acid catalysts or metal free Brønsted acid catalysts, but most of these systems only works for activated electron-rich arenes and/or the catalysts can't be easily recovered.[2] And in many cases, aqueous reaction work-up is still needed to remove catalyst or other byproducts. An ideal 'green' Friedel–Crafts acylation should meet the following criteria: 1) the catalyst can be recovered and reused; 2) using halogen free starting materials (carboxylic acid anhydrides or carboxylic acids); 3) no need for aqueous reaction work-up; 4) minimum or no waster steam generation.

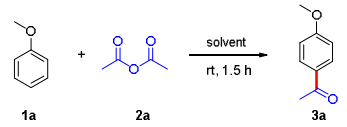


Scheme 1. Literature reports on Friedel–Crafts acylations.

Hydrogen bonding donor solvents like hydrogen fluoride (HF) and HFIP (hexafluoro-isopropanol) have been shown to provide significant rate enhancements for Friedel–Crafts type reactions[3] and several other reactions.[4] Along this line, one particular successful story of 'green' Friedel–Crafts

acylations is the BHC company (now part of BASF corporation) synthesis of Ibuprofen, which won the Presidential Green Chemistry Challenge in 1997 (Scheme 1b).[5] BHC company synthesis uses a strong H-bond donor - hydrogen fluoride as the catalyst and also the solvent that is recovered and reused repeatedly. Large volumes of aqueous wastes stream normally associated with such pharmaceutical manufacturing are virtually eliminated and no other solvent is needed. Recently, Aubé and coworkers reported intramolecular Friedel–Crafts acylation in hydrogen bonding donor solvent - HFIP (Scheme 1c), HFIP can also be recovered and reused.[6] However, these syntheses are not without problem. HFIP system only works for reactive substrates and needs use of acyl halides as starting material. And HF is a highly toxic gas at room temperature, which means HF system is only practical in large-scale synthesis like production of Ibuprofen.

Table 1. Optimization of the reaction conditions [a]



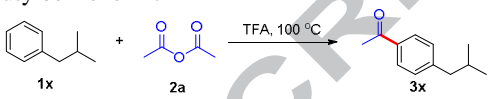
entry	equiv of **2a**	Solvent	Yield [b] / %
1	2	TFA (1 mL)	100
2	2	50:50 TFA/DCM	69
3	2	80:20 TFA/DCM	95
4	2	50:50 TFA/HFIP	14
5	2	80:20 TFA/HFIP	44
6	2	TFA (0.5 mL)	95
7	2	TFA (0.8 mL)	100 (95 [c])
8	1.2	TFA (0.8 mL)	84
9	1.5	TFA (0.8 mL)	96

[a] Reaction conditions: **1a** (0.75 mmol), **2a**, solvent, rt, 1.5 h. [b] Yields determined by GC. [c] Yield of isolated product.

It has been found that a hydrogen bonding aggregation or an H-bond network will form preferentially due to so-called σ-cooperativity or non-additivity,[7] H-bond network formed from HF or HFIP may play a crucial role in Friedel–Crafts acylations. Based on the success of strong H-bond donor solvents - HF and HFIP, we decide to search stronger yet volatile hydrogen bonding donors, which has good reactivity and can be recycled easily by distillation and reused. Abraham and coworkers had reported a scale of solute hydrogen-bond acidity based on log K_A values for complexation in tetrachloromethane.[8] In this scale, bigger log K_A indicates higher H-bond acidity. Abraham's database offered us a rational guidance for selection of H-bond networks for Friedel–Crafts acylations. In Abraham's database, trifluoroacetic acid (TFA) (log K_A = 3.31) is a much stronger H-bond donor than other common H-bond donors like HFIP (log K_A = 2.47) and acetic acid (log K_A = 1.58). We envision TFA is a superior H-bond donor solvent for Friedel–Crafts acylations (Scheme 1d). TFA has a low boiling point (72 °C), so it can be recovered easily by distillation and reused. We are glad to report a TFA and/or TFAA (trifluoroacetic acid anhydride) based metal- and halogen-free Friedel-Crafts acylation methodology with virtually no waste streams directly using readily available carboxylic acid anhydrides or even form carboxylic acid directly as starting material (Scheme 1d).

First, we used the Friedel–Crafts acylation of relatively electron rich substrate **1a** as our model reaction (Table 1). We were glad to observe 100% conversion when TFA was used as solvent (Table 1, entry 1) at room temperature. Solvent mixture of TFA and other solvents like DCM or HFIP led to slower reactions (Table 1, entries 2-5). We could reduce the amount of TFA usage (Table 1, entry 6) and reduce the equivalents of acid anhydride to 1.2 or 1.5 (Table 1, entries 8-9), which still gave satisfactory conversions. Then we moved our focus to less reactive substrate isobutylbenzene (**1p**), which is the starting material in BHC Ibuprofen synthesis (Table 2). Our condition also works well, albeit higher temperature and longer reaction time was needed.

Table 2. Optimization of the reaction conditions for acylation of isobutylbenzene **1x**. [a]

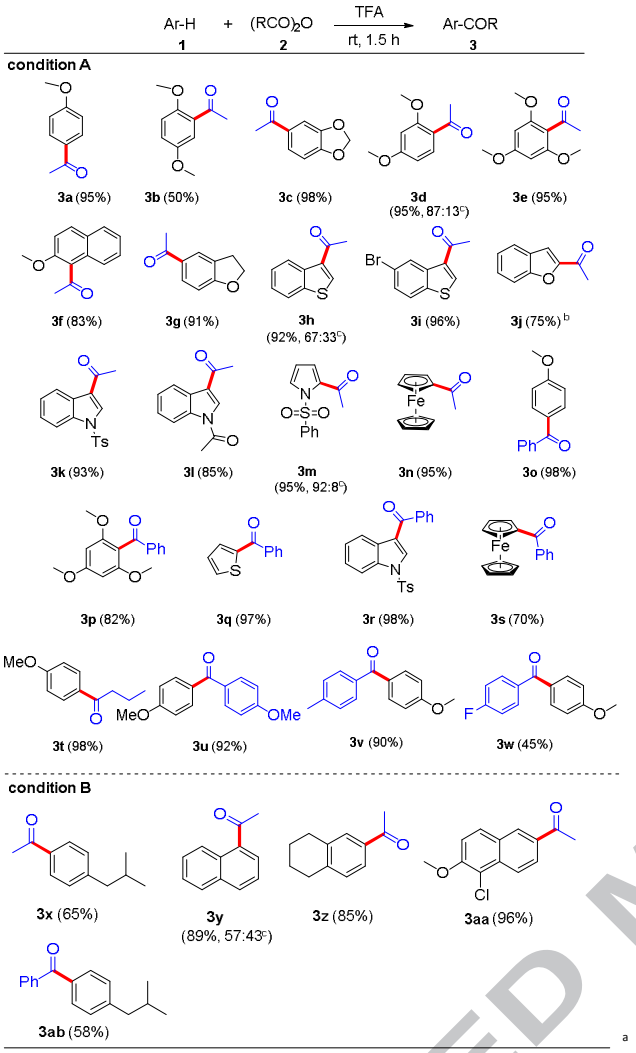


entry	equiv of **2a**	Solvent	Yield [b] / %
1	1	TFA (1 mL)	53
2	1.5	TFA (1 mL)	62
3	2	TFA (1 mL)	50
4	3	TFA (1 mL)	62
5	1.5	TFA (2 mL)	78 (65 [c])
6	1.5	TFA (3 mL)	71

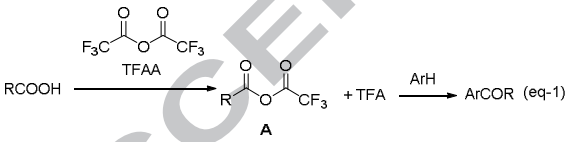
[a] Reaction conditions: **1p** (0.75 mmol), **2a**, TFA, 100 °C, 56 h. [b] Yield determined by GC-MS. [c] Yield of isolated product.

With the optimized conditions in hand, we explored the substrate scope of this new methodology (Table 3). First, we investigated the reaction of various arenes with acetic acid anhydride **2a** (Table 3, **3a** – **3n**). This protocol works for diverse types of aromatic and heteroaromatic substrates (benzylic compounds, naphthalene, thiophene, benzothiophene, indole, benzofuran), they all gave excellent results. We also evaluated the substrate scope of carbonyl acid anhydrides (Table 3, **3o** – **3w**). Both aromatic and aliphatic carbonyl acid anhydrides worked very well. We also tested reaction of less reactive aromatics (Table 3, **3x**–**3ab**) using condition shown in Table 2 (condition B). In general, our protocol works well for alkyl substituted phenyl rings, and for phenyl rings substituted with electron withdrawing groups like ketone, ester, nitrile, the reactions were very sluggish.

Table 3. Substrate scope of the reaction [a]

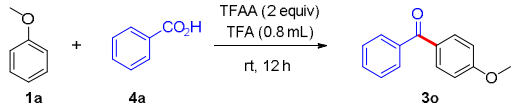


Reaction conditions **A**: **1** (0.75 mmol), **2** (1.5 mmol), TFA (0.8 mL), rt, 1.5 - 10 h; all yields are isolated yields. Reaction conditions **B**: **1** (0.75 mmol), **2** (1.125 mmol), TFA (2 mL), 100 °C, 56 h, Ar; all yields are isolated yields. [b] TFA (0.4 mL), DCM (0.6 mL), rt, 10 h. [c] Ratio of major regioisomer and minor isomer.



Because it is possible to use TFAA to convert a carboxylic acid into a mixed anhydride **A** (eq 1),[9] **A** could react with arenes to give Friedel–Crafts acylation products. This process only generates TFA, which is the system solvent, no extra compound is generated. So, we tried to use carboxylic acids as starting material directly in the presence of TFAA. We used the Friedel–Crafts reaction of **1a** with benzoic acid as our model reaction (Table 4). 2 Equivalents of TFAA is enough to complete the reaction (Table 4, entry 2), and excess TFAA can be recovered along with TFA and reused.

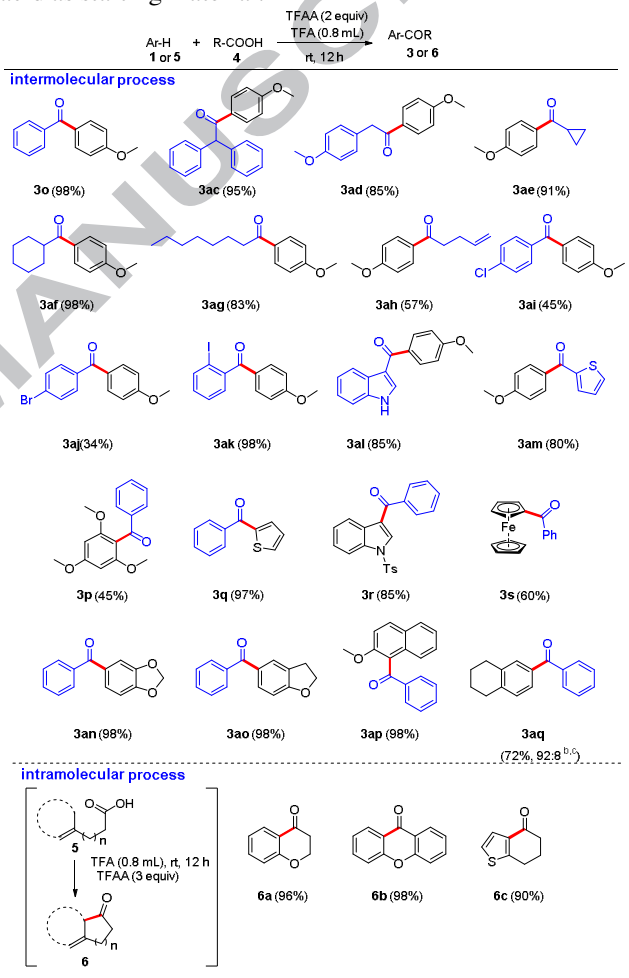
Table 4. Optimization for using carboxylic acid as starting material.



Entry	equiv of **1a**	Yield [b] / %
1	1	48 [c]
2	1.2	95
3	1.5	98
4	2	98

[a] Reaction conditions: **1a**, **4a** (0.75 mmol), TFAA (1.5 mmol), TFA (0.8 mL), rt, 12 h. [b] Yields of isolated products. [b] Yield determined by GC-MS. [c] Yield of isolated product.

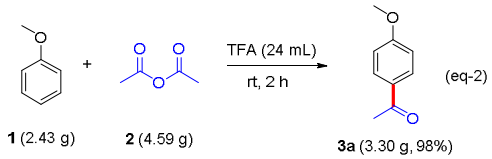
Table 5. Substrate scope acylation for using carboxylic acid as starting material.[a]



[a] Reaction conditions: **1** (1.125 mmol), **4** (0.75 mmol), TFAA (1.5 mmol), TFA (0.8 mL), rt, 12 h, Ar; all yields are isolated yields. [b] Microwave 100 °C, 1 h. [c] Ratio of major regioisomer and minor isomer.

With the optimized conditions in hand, we explored the substrate scope of this new protocol (Table 3). This protocol also works for many types of aromatic and heteroaromatic substrates (benzylic compounds, naphthalene, thiophene, benzothiophene, indole, benzofuran), they all gave excellent results (Table 5, **3a** – **3n**). We also evaluated the substrate scope of carboxylic acids (Table 5, **3o** – **3w**). Many types of aromatic and aliphatic carbonyl acids all worked very well.

We also tested the intramolecular Friedel–Crafts acylations (Table 5, **6a**– **6c**). Unlike a literature report,[6a] our protocol worked well without extra step to preparing acid anhydrides or acid halides.



Our protocol worked well in multi-gram scale synthesis without need for reaction workup (eq-2). Our protocols have significant advantages over many industrial Friedel–Crafts acylation operations. As shown in Table 2, our protocol worked very well in synthesis of **3x** for Ibuprofen synthesis, without the need for use of toxic hydrogen fluoride (Scheme 1b, BHC Ibuprofen synthesis). Compound **3aa** (Table 3) is the key intermediate for production of one of the most important nonsteroidal anti-inflammatory drug (NSAID) - S-Naproxen and triple reuptake inhibitor, and the one industrial synthesis of **3aa** is still based on environmentally unfriendly $AlCl_3$/acid chloride system.[10] And pyrrole **3m** is an important industrial intermediate, which synthesis is based on $AlCl_3$/acid chloride system also.[11]

In summary, we have developed a metal and halogen-free Friedel–Crafts acylation protocol with virtually no waste stream generation enabled by strong hydrogen bond solvent - TFA. Our methods worked well for carboxylic acid anhydrides/ carboxylic acids and less reactive aromatics like alkyl substituted benzenes.

Acknowledgments

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