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"Greener" Friedel–Crafts Acylations: A Metal- and Halogen-Free Methodology

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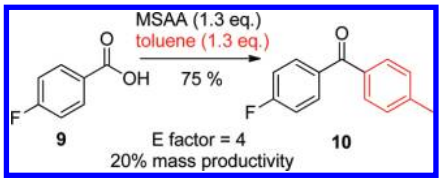
ABSTRACT



The utility of methanesulfonic anhydride for promoting the Friedel–Crafts acylation reaction of aryl and alkyl carboxylic acids is disclosed. This reagent allows the preparation of aryl ketones in good yield with minimal waste containing no metallic or halogenated components, clearly differentiating it from other available methodologies.

Recently the desire for "greener" or "sustainable" methodology for bond forming steps fundamental to the fine chemical and pharmaceutical industries has significantly increased.

One example of such a fundamental transformation is the Friedel–Crafts acylation reaction. There has and continues to be a tremendous amount of research in this field. The union of a carboxylic acid with an aromatic component promoted by a single substoichiometric catalyst would be the ideal solution. While progress has been made,[1] and not to overlook exciting developments in heterogeneous catalysis (perhaps best suited for bulk fine chemicals),[2,3] there is still a requirement for improved methods suitable for the batch manufacture of pharmaceuticals. This is reflected in the ACS Green Chemistry Institute Pharmaceutical Roundtable highlighting a desire for improved methodologies in the area, especially for unactivated systems.[4] A disappointingly high proportion of the prior work focuses on electron-rich aromatic systems (e.g., anisole) on which Friedel–Crafts acylations are relatively easy to promote and may also rely on a large excess of the aromatic nucleophile. For the synthesis of the complex aromatic motifs typical in the pharmaceutical industry, mass efficient reactions on more electron deficient systems are essential.

We now wish to report our development of a metal- and halogen-free Friedel–Crafts acylation methodology with minimal waste streams, albeit still currently relying on a stoichiometric reagent. Reactions are possible with chlorobenzene, the archetypical electron-poor Friedel–Crafts substrate, and generally require just 2 equiv of the aromatic nucleophile with no further solvent.

Defining what truly constitutes a "green" methodology is difficult, but the guiding principles for this work have

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been waste minimization (atom economy) and generation of benign waste streams.

We have previously examined the utility of trifluoroacetic anhydride (TFAA) mediated Friedel–Crafts acylation methodology for the preparation of pharmaceutical intermediates.[5] While this methodology was useful, it suffered from three drawbacks: (1) The fluorinated waste streams were difficult to process for disposal. (2) The reaction appeared limited to activated aromatics (at least as electron rich as toluene). (3) The mass of waste associated with stoichiometric reagents.

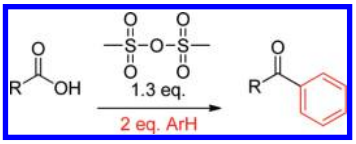
We began to consider how to improve this methodology. We reasoned a stronger acid than TFA may extend the reaction to less activated aromatics. Thus we sought a strong acid, with a low molecular weight, and preferably not halogenated to aid waste treatment. This logic led us to methanesulfonic acid (MSA) and the corresponding methanesulfonic anhydride (MSAA). MSA is attractive from a sustainability point of view as it can be derived from biomass and as such is not reliant on petrochemical sources. It can also be biodegraded and suitable industrial processes have already been disclosed,[6] which would be a significant benefit for waste steam processing. We believe the use of MSAA for Friedel–Crafts reactions to be novel, although intermolecular acylations with Eaton's reagent (P_2O_5/MSA) have been reported previously.[7] Similar reactions promoted by graphite,[8] or alumina,[9] using MSA as solvent have also been detailed.

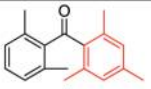
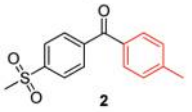
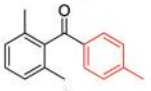
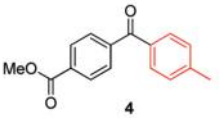
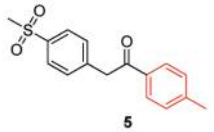
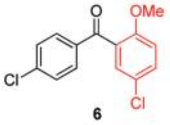
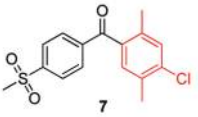
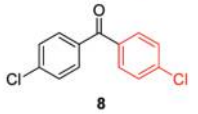
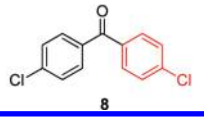
We began by screening conditions similar to those we had used previously with TFAA. We were delighted to observe excellent reactivity. Even more gratifyingly, this reactivity was preserved in the absence of an additional catalyst. Presumably the methanesulfonic acid generated by the reaction of the MSAA with the substrate acid is a sufficiently strong acid to catalyse the subsequent reaction of the mixed anhydride. A similar observation has been made in trichloroacetic anhydride promoted intramolecular Friedel–Crafts acylations.[10] The ability of this methodology to deliver aryl ketones is illustrated in Table 1.

Steric hindrance presented little difficulty, with the preparation of a tetra-ortho substituted benzophenone (entry 1). Pleasingly, a methyl ester was successfully carried through the reaction sequence (entry 4). Diaryl ethanones could also be prepared (entry 5). Reactivity was preserved with chlorinated aromatics (entrys 6–9), although the yields were reduced with these more challenging substrates. Also, additional MSAA was charged later in the reaction (entries 7–9) as competing formation of a methyl aryl sulfone derived from the aromatic nucleophile was observed. The reaction time for chlorobenzene was rather long (32 h, entry 8) but could be significantly reduced with the use of 2 mol % of indium triflate.[1f] The use of a metal catalyst rather undermines the aim of this work but may be beneficial if reaction time is an issue. Reactions with nitrated aromatics were not successful.

The reactions depicted in Table 1 required only 2 equiv of aromatic nucleophile. However, it was also demonstrated

Table 1. Friedel–Crafts Acylations Promoted by Methanesulfonic Anhydride (MSAA)



entry	reaction temp / time	product	isomer ratio	yield
1	80 °C / 30 min	 1	n/a	87%
2	112 °C / 5 h	 2	83:17 [a]	70%
3	100 °C / 1 h	 3	89:11 [a]	69%
4	101 °C / 2 h	 4	86:14 [a]	63%
5	80 – 90 °C / 2 h	 5	91:9 [a]	69%
6	100 °C / 2 h 30	 6	89:11 [b]	74%
7	138 °C / 6 h [c]	 7	90:10 [b]	63%
8	139 °C / 32 h [d]	 8	86:14 [b]	53%
9	141 °C / 9 h [e]	 8	86:14 [b]	58%

[a] Determined by NMR. [b] Determined by HPLC. [c] At 3 h 30, a further 30 mol % of MSAA was charged. [d] 1.8 equiv of MSAA used, and at 23 h, a further 40 mol % of MSAA was charged. [e] 2 mol % of $In(OTf)_3$ and 1.5 equiv of MSAA were used. At 5 h, a further 35 mol % of MSAA was charged.

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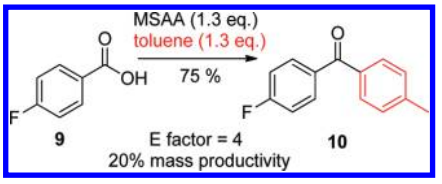
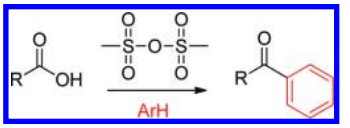
that even less aromatic component may be used. 4-Fluorobenzoic acid (1.0 equiv) was reacted with toluene (1.3 equiv) and methanesulfonic anhydride (1.3 equiv), and then the product crystallized directly from the reaction mixture with *n*-PrOH/H_2O. This minimization of the reagents correspondingly minimized waste, with only 50 g of waste for every 10 g of product produced (Scheme 1). Various metrics have been developed to compare the efficiency of chemical process, with this result corresponding to an *E* (environmental) factor of 4[11] or a mass intensity of 5 (mass productivity of 20%).[12,13] This is a pleasing result for a (albeit single stage) chemical process.

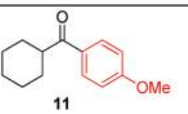
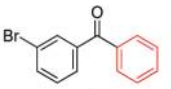
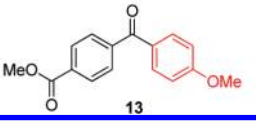
Scheme 1. Friedel–Crafts Acylation with Minimal Waste



Despite one of the guiding principles of this work being waste reduction by eliminating unnecessary solvent, some reactions did benefit from the introduction of small amounts of a cosolvent (Table 2). Alkyl acids gave the desired products successfully but appeared to undergo further reaction and decomposition. This was mitigated by reduction of excess aromatic component and introduction of cosolvent (entry 1). Benzene was a successful aromatic nucleophile in this methodology, but the reactions were slow because of its low boiling point. The introduction of a higher boiling cosolvent enabled higher reaction temperatures, with corresponding quicker reactions and higher isolated yields. Because of the high reactivity of anisole in Friedel–Crafts acylations, aryl ketones such as **13** produced by acylation of this solvent were observed to undergo further reaction and side product formation. This undesired over-reaction was much reduced by the introduction of a diluting cosolvent (entry 3).

Table 2. MSAA-Promoted Friedel–Crafts Reactions Benefiting from Co-solvent

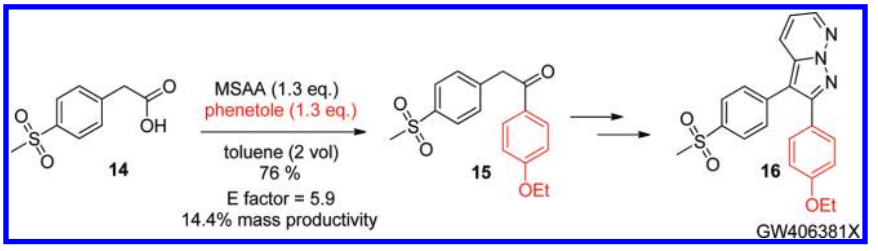


entry	reaction conditions	product	yield
1	1.2 eq anisole, 1.3 eq MSAA, 4 vol toluene [a] 85 °C / 90 min	 **11**	64%
2	2.4 eq benzene, 1.9 eq MSAA, 0.6 vol DCB [b] 117 °C / 26 h	 **12**	64%
3	1.2 eq anisole, 1.3 eq MSAA, 2 vol toluene 110 °C / 1 h	 **13**	80%

[a] 1 volume = 1 mL per 1 g of limiting reagent. [b] DCB = 1,2-dichlorobenzene.

The utility of this methodology for the synthesis of pharmaceutical intermediates has been demonstrated. The diaryl ethanone **15** was an intermediate in the synthesis of COX-2 inhibitor GW406381X, which has potential therapeutic applications to chronic inflammatory pain.[14] Using the MSAA methodology it was prepared as shown in good yield with minmal waste (Scheme 2).

Scheme 2. Synthesis of Phenyl Benzyl Ketone Intermediate to GW406381X



In conclusion, we report a novel methodology for Friedel–Crafts acylation reactions, which allows the preparation of various aryl ketones with minimal waste containing no halogenated or metallic components, clearly differentiating it from other methodologies. The reactions proceed on the parent carboxylic acids via 1.3 equiv of a activating agent (methanesulfonic anhydride) and as little as 1.3 equiv of an aromaric nucleophile, with in general no additional solvent. All products (with the exeption of low melting **12**) were isolated by crystallization from the reaction mixture giving an efficient one-pot process suitable for further scale up.

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(13) Mass productivity = 100 ÷ (mass intensity).
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Supporting Information Available. Experimental details and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.