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Intramolecular Friedel–Crafts Acylation Reaction Promoted by 1,1,1,3,3,3-Hexafluoro-2-propanol

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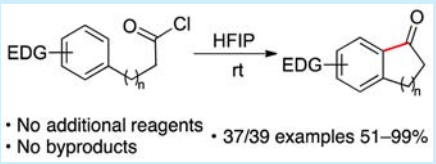
Supporting Information

ABSTRACT: Simple dissolution of an arylalkyl acid chloride in 1,1,1,3,3,3-hexafluoro-2-propanol promotes an intramolecular Friedel–Crafts acylation without additional catalysts or reagents. This reaction is operationally trivial in both execution and product isolation (only requiring concentration followed by purification) and accommodates a broad range of substrates. Preliminary studies that bear upon potential reaction mechanisms are reported.



The venerable Friedel–Crafts (FC) acylation reaction is one of the most powerful tools for the synthesis of aromatic ketones.[1] The reaction is traditionally promoted by excess amounts of Lewis or Brønsted acids such as $AlCl_3$ and H_2SO_4 and utilizes acyl halides, anhydrides, or sometimes carboxylic acids as acylating reagents (Scheme 1).[1e,2] The need for superstoichiometric amounts of an acid catalyst has been ascribed to product inhibition arising from complexation between the ketone product and the acid catalyst and often necessitates tedious product isolation involving aqueous workup to hydrolyze the formed complex, leads to the loss of the catalyst, and contributes to toxic and corrosive waste streams.[1c,d] The importance of the FC acylation reaction for the synthesis of aromatic ketones has spurred efforts to develop more efficient and ecofriendly versions that overcome the limitations of product inhibition and harsh reaction conditions, often including >100 °C temperatures.[1c,d,2c,3] Strategies to accomplish this include the use of zeolites,[4] solid superacid[5] or mixed acid systems,[6] specialized ionic liquids,[7] or highly electrophilic acylating reagents as substrates.[2c] Here, we show that the intramolecular version of this reaction may be simply accomplished by dissolving readily available acid chlorides in the strong hydrogen-bond-donating solvent 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) at room temperature without any additional reagents or catalysts, providing product *unaccompa-*

Scheme 1. Comparison between Classical FC Reactions and the HFIP-Promoted Version

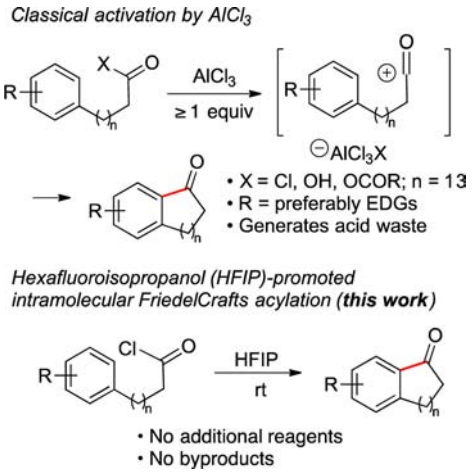
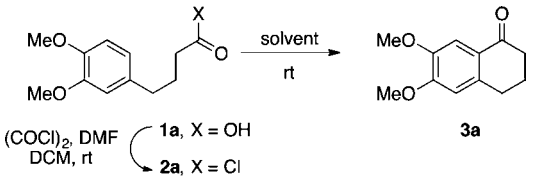


Table 1. Exploration of Reaction Conditions[a]



entry	solvent	HFIP (equiv)	time (h)	yield of **3a**[b] (%)
1	HFIP (0.20 M)		2	95
2	HFIP (0.40 M)		2	97
3	HFIP (1.2 M)		2	95
4	DCM/HFIP (4:1)	9.5	2	96
5	DCM/HFIP (8.4:1)	5.0	2	95
6	DCM/HFIP (22.8:1)	2.0	3	93
7	CH_3CN/HFIP (4:1)	9.5	6	93
8	CH_3NO_2/HFIP (4:1)	9.5	6	91
9	$C_6H_5CF_3$/HFIP (4:1)	9.5	4	94
10	THF/HFIP (4:1)	9.5	6	34
11	CF_3CH_2OH (TFE)		4	31
12	$(CF_3)_3COH$ (PFTB)		0.75	> 98
13	CF_3CH_2SH (TFET)		4	7

[a]The acid **1a** (1.0 equiv) was converted to **2a** using oxalyl chloride (2.0 equiv) and catalytic DMF in DCM under N_2 atmosphere for 30 min. The reaction mixture was concentrated under N_2 and vacuum; crude **2a** was dissolved in the solvent(s) noted and stirred at rt for a specified period. [b]Isolated yield of purified **3a** based on starting acid, except for entries 11–13 (NMR yields). Products were ≥96% pure by NMR except for entry 10, which was ca. 85% pure, and entry 13, which contained numerous byproducts.

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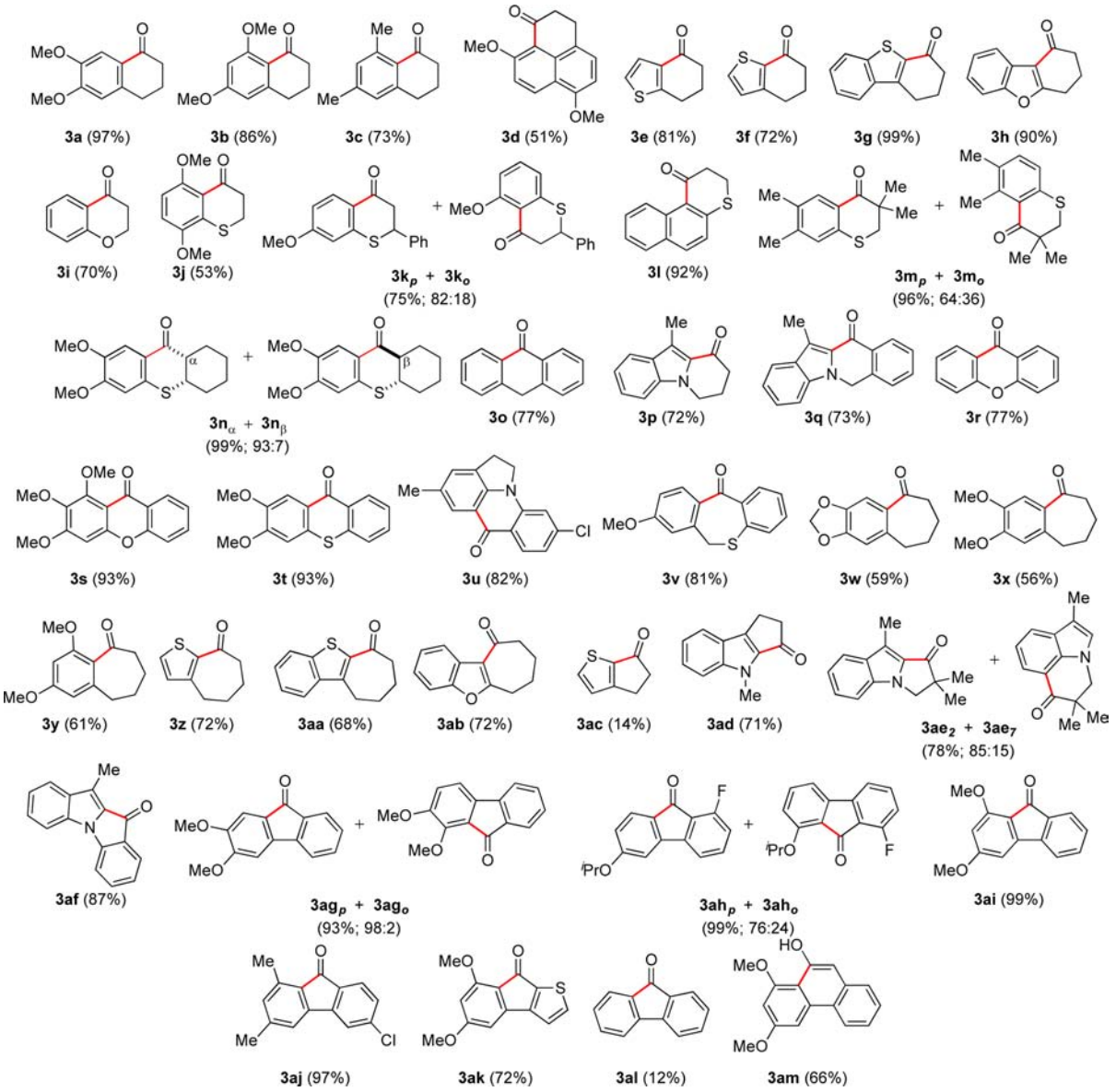

Figure 1. Yields and ratios of ketones prepared using standard conditions (see Table 1, entry 2). Compound **3ac** was reacted for 16 h. See the Supporting Information for details.

nied by byproducts through straightforward evaporation of the solvent (bp 58 °C) and standard purification protocols.

Our approach was inspired by our recent observation that HFIP is able to suppress product inhibition in an intramolecular Schmidt reaction of alkyl azides and ketones[8] and a growing body of evidence that this solvent is highly effective in promoting reactions that involve ionic intermediates. Relevant here are FC alkylations in refluxing HFIP reported to occur on cations generated from ionization of allylic alcohols[9] or epoxides.[10] HFIP has also proven to be an effective medium for FC reactions promoted by Cu[11] or Li[12] Lewis acids, as well as H-bond activated Pictet–Spengler reactions.[13] Contemporary with our work, Paquin has described an FC benzylation reaction in HFIP occasioned by H-bonding to a benzyl fluoride substrate.[14] while Porco and co-workers have cyclized a preformed HFIP ester in the presence of K_3PO_4 at 60 °C.[15] We felt that an HFIP-enabled FC *acylation* reaction of commonly used acyl chlorides would have particular value for preparing a range of useful heterocyclic systems.

We began by studying the intramolecular FC reaction of 4-(3,4-dimethoxyphenyl)butanoic acid (**1a**) (Table 1). The acid was converted into acid chloride using oxalyl chloride in dichloromethane (DCM). Following concentration and drying under vacuum, HFIP was added to the crude acid chloride **2a** and the reaction allowed to stir at room temperature for 2 h. Concentration followed by chromatography afforded 6,7-dimethoxy-1-tetralone (**3a**) in 95% yield (Table 1, entry 1). Changing the molar concentration of the substrate had virtually no effect on the yield (entries 1–3). Good results were also obtained when HFIP was used as an additive to other solvents (entries 4–9), particularly DCM, where the addition of 2.0, 5.0, or 9.5 equiv of HFIP gave excellent results (entries 4–6), although a qualitative decrease in rate was noted. In contrast, THF had a deleterious effect, likely because it is a strong H-bond acceptor (entry 10).[16] Trifluoroethanol (TFE) was not an effective medium for the reaction, but perfluoro-2-methylpropan-2-ol (PFTB) gave excellent results (entries 11 and 12).[17]

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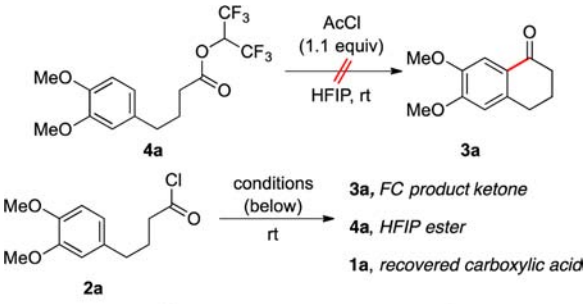
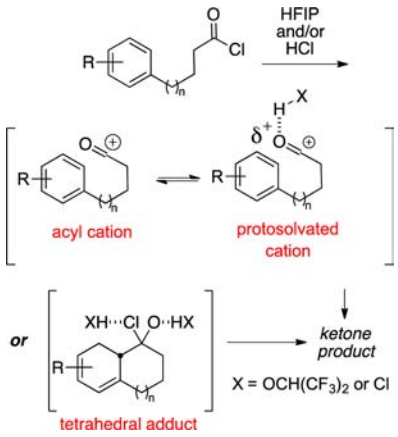
Scheme 2. Experiments Pertaining to Mechanism



conditions	products		
	3a	4a	1a
HFIP (1.0 equiv), DCM	71%	–	–
4.0 M HCl in dioxane (1.0 equiv), DCM	40%	–	44%
DTBMP (0.50 equiv), DCM/HFIP (4:1)	71%	22%	–
DTBMP (1.0 equiv), DCM/HFIP (4:1)	30%	66%	–
pyridine (2.0 equiv), DCM/HFIP (1:1)	–	95%	–
Ph_3PO (3.0 equiv), HFIP (9.5 equiv), DCM	96%	–	–
Ph_3PO (6.0 equiv), HFIP (5.0 equiv), DCM	6%	–	73%

Scheme 3. Potential Reaction Intermediates



Trifluoroethanethiol (TFET) gave lower conversion compared to TFE (cf. entries 11 and 13).

The scope of this HFIP-promoted FC acylation reaction was probed applying the conditions in Table 1, entry 2, to a range of structurally diverse carboxylic acids (Figure 1). In an intramolecular FC acylation, the formation of six-membered rings is generally favored over seven- and five-membered rings.[2c] Thus, high yields of carbo- and heterocyclic compounds bearing six-membered ketones were obtained (**3a**–**u**). Consistent with known FC behavior, electron-rich aromatics and heteroaromatics were preferred substrates. We also examined seven- and five-membered ring-forming reactions (**3v**–**al**); the latter, in particular, can be challenging to make via standard FC chemistry.[2c] Here, cyclization to seven-membered rings proceeded in good yields (**3v**–**ab**), and although the formation of thiophene fused cyclopentanone (**3ac**) proved difficult, the indole-fused cyclopentanones (**3ad**–**af**) were readily obtained. Electron-rich biarylcarboxylic acids were favorable substrates affording corresponding fluorenones and related cyclic ketones in excellent yields (**3ag**–**am**). Finally, one example was scaled up to gram scale without incident. Thus, 1.14 g (5.0 mmol) of **1a** was converted to **3a** in 83% yield in 3 h using 3.0 equiv of HFIP without additional solvents.

Scheme 2 summarizes experiments carried out to probe the mechanism of this FC reaction. Treatment of HFIP ester **4a** in HFIP with 1.1 equiv of AcCl (HCl is generated in situ from the action of HFIP on AcCl)[8] showed that **4a** is not an intermediate en route to ketone **3a**. Comparing the FC promotion ability of 1 equiv of HCl with that of a similar amount of HFIP in DCM, HFIP appears to be a considerably better promoter. (It is conceivable that the miniscule amount of dioxane present (75 μL in a 1.5 mL reaction) has a dampening effect, but in our opinion this is unlikely.) The FC reaction was diminished but not completely inhibited in the presence of bases 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) or pyridine (which is both a hydrogen bond acceptor (pK_{HB} = 1.86) and a proton scavenger[18]). In these cases, HFIP ester **4a** was partly or exclusively obtained. Finally, the reaction was exquisitely sensitive to the stoichiometry between HFIP and the strong H-bond acceptor Ph_3PO, with even slight excesses of the latter leading to very poor conversions.

These experiments support a mechanism in which the H-bonding capabilities of HFIP are key as opposed to general acid catalysis (the pK_a of HFIP is 9.3 and HCl, likely a poorer promoter, is −8.0). Being able to rule out a role for an in situ formed HFIP ester by the inability of **4a** to provide product, one is left to consider some variation of the mechanism generally accepted for conventional FC reactions or an alternative suggested by Porco's work.[15] In the former case, HFIP could promote the in situ ionization of acid chloride (Scheme 3).[1e,2a] In this scenario, the strong hydrogen bond donor strength of HFIP, complemented by its high ionizing power and its ability to solvate chloride anions, could allow it to function as solvent, hydrogen bond donor catalyst, and a Lewis acid substitute.[19] At the present time, the role, if any, of HCl generated during the course of the reaction is unclear. Also, we note that protonated acylium ions have also been proposed as kinetically superior intermediates[20] and might be in play here due to the very strong H-bonding associated with HFIP. In the latter case, the intermediate arising from attack of the aromatic ring directly onto an acyl chloride hydrogen bonded at oxygen would form the tetrahedral adduct shown near the bottom of Scheme 3. Experiments to differentiate between these possibilities are underway.

In conclusion, we have demonstrated an efficient, metal-free variant of the intramolecular FC acylation reaction that simply requires dissolution of a trivially available acyl chloride in HFIP. These results are of both theoretical and practical importance given the stature of the FC acylation reaction in laboratory and industrial scale chemistry. In comparing the results of the present method with those previously published (see the Supporting Information, Table S1), these conditions are mild and avoid excesses of harsh acids. The lack of need for an aqueous workup provides a significant practical advantage over classic methods. Although further work to elucidate the mechanism of this reaction is necessary (and underway), the utility of the method for heterocyclic synthesis has been demonstrated and should lead to numerous applications in organic and applied organic chemistry.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02851.

Experimental procedures, characterization data, and NMR spectra of new compounds; comparison of results with previously reported examples (PDF)

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Notes

The authors declare no competing financial interest.

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