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Hexafluoro-2-propanol-Promoted Intermolecular Friedel–Crafts Acylation Reaction

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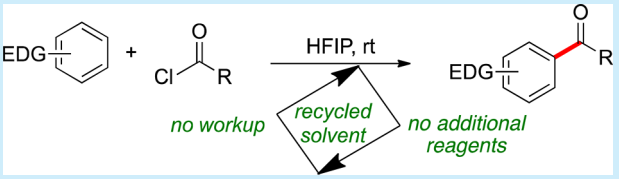
Supporting Information

ABSTRACT: The intermolecular Friedel–Crafts acylation was carried out in hexafluoro-2-propanol to yield aryl and heteroaryl ketones at room temperature without any additional reagents.



The Friedel–Crafts (FC) acylation is a fundamental way of generating aromatic ketones.[1] In its traditional form, the reaction is promoted by Lewis acids (most commonly $AlCl_3$) or protic acids, generally requiring a full equivalent of catalyst or more due to product inhibition. In recent years, numerous researchers have sought to improve the FC reaction through the development of effective catalysts.[2] In related approaches, researchers have also employed novel media such as ionic liquids[3] and heterogeneous supports and catalysts (e.g., zeolites, clays, metal oxides, acids, nafion, and graphene).[4] The FC acylation can utilize a number of activated carboxylic acid equivalents in place of the classical acyl chlorides,[5] a recent example being the use of twisted amides reported by Szostak and co-workers.[6]

Hexafluoro-2-propanol (HFIP) is a useful solvent, cosolvent, and additive in organic synthesis with a nearly unique set of properties that include high ionizing power, strong hydrogen bond donating ability, mild acidity, and low nucleophilicity.[7] All of these properties are favorable for electrophilic aromatic substitution reactions, and accordingly, a number of investigators have studied FC alkylation chemistry in HFIP (Scheme 1). In 1994, Cativiela et al. studied the Diels–Alder reactions of furan and acrolein in HFIP and observed an FC alkylation product 3-(2-furyl)-propanal as a byproduct.[8] Subsequent FC alkylations have been reported from allylic alcohols,[9] epoxides,[10] and benzyl halides[11] in HFIP. In addition, HFIP has been a critical additive in asymmetric FC alkylations catalyzed by chiral Lewis acids.[12] Recently, we reported an intramolecular FC *acylation* reaction in HFIP toward numerous heterocyclic ring systems.[13] Given the importance of the standard FC acylation for synthesizing aromatic ketones, we sought to extend the intramolecular reaction to the more demanding intermolecular case and report our initial results here.

The intermolecular FC acylation between 1,3-dimethoxybenzene (**1a**) and benzoyl chloride (**2a**) was used in our initial studies (Table 1). Thus, benzoyl chloride was added to 1,3-dimethoxybenzene in HFIP solvent and the reaction mixture was stirred for 5 h at rt. Solvent evaporation followed by chromatographic purification afforded **3a**/**3a′** in 66% yield (Table 1, entry 1). When added to DCM, it was necessary to utilize 80:20 HFIP/DCM (corresponding to 10 equiv of HFIP) to achieve results comparable to those obtained in HFIP alone (Table 1, entries 2–4; cf. 2 equiv needed in the intramolecular reactions[13]). As previously observed,[13] H-bond accepting solvents THF and acetonitrile had strongly inhibiting effects; in the former case, 4-chlorobutyl benzoate resulting from THF cleavage was also obtained (entries 5 and 6).[14]

A comparison of HFIP with the fluorinated alcohols trifluoroethanol (TFE) and perfluoro-*tert*-butyl alcohol (PFTB) was interesting insofar as neither afforded the FC product at all (Table 1, entries 7–8). In TFE, only solvolysis of benzoyl chloride occurred. In contrast, when PFTB was

Scheme 1. Examples of HFIP-Promoted FC Chemistry

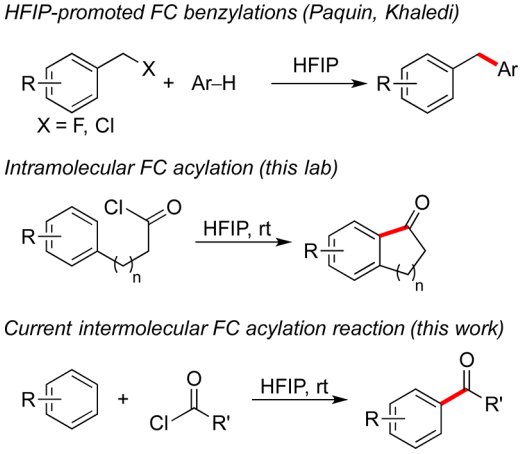


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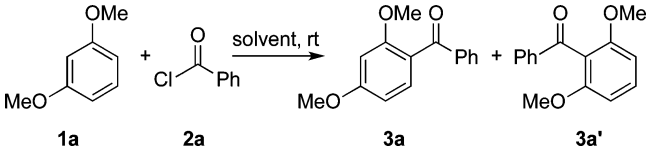
Table 1. Effect of Solvent on Yield[a]



1a 2a 3a 3a'

entry	solvent	yield,%[b]
1	HFIP	66
2	8:92 HFIP/DCM[c]	0
3	40:60 HFIP/DCM	39
4	80:20 HFIP/DCM	63
5	80:20 HFIP/THF	16[d]
6	80:20 HFIP/CH_3CN	23
7	CF_3CH_2OH (TFE)[e]	0
8	$(CF_3)_3COH$ (PFTB)[c]	0

[a]To 1,3-dimethoxybenzene (0.75 mmol, 1.0 equiv) in solvent (1 mL) was added benzoyl chloride (0.75 mmol, 1.0 equiv). The reaction mixture was stirred at rt for 5 h. [b]Isolated yields (**3a**/**3a**′ ratios ca. 92:8 in each case). [c]No FC reaction observed. [d]In addition to **3a** and **3a**′, 4-chlorobutyl benzoate was obtained in 28% yield. [e]TFE ester of benzoyl chloride was observed by GCMS.

employed, only starting materials were observed (this phenomenon has been observed in another context[15]). These results point to the privileged position of HFIP for the promotion of these reactions and specifically downplay the role of solvent acidity in promoting these reactions (pK_a values: TFE, 12.8; HFIP, 9.3; PFTB, 5.4[16]). Curiously, PFTB was found to be equally efficient in promoting the intramolecular version of this reaction as HFIP,[13] raising the possibility that in the intermolecular reaction PFTB could tightly hydrogen bond with the acyl chloride, thus activating it toward attack, but the relative bulk of the solvent could prevent attack by an external nucleophile (which would not be a problem in the intramolecular cases).

Best results were obtained when the nucleophilic arene was used in excess, with the optimal ratio being about 3:1 (Table S1, Supporting Information). In addition, no dependence of yield on bolus vs slow addition of benzoyl chloride was noted. Our currently optimized conditions employ 3:1 arene/acyl chloride stoichiometry and a 0.75 M concentration of the acyl chloride.

The scope of the reaction was then studied (Figure 1). As observed in the intramolecular examples, electron-rich arenes worked best, affording aryl ketones in moderate to good yields

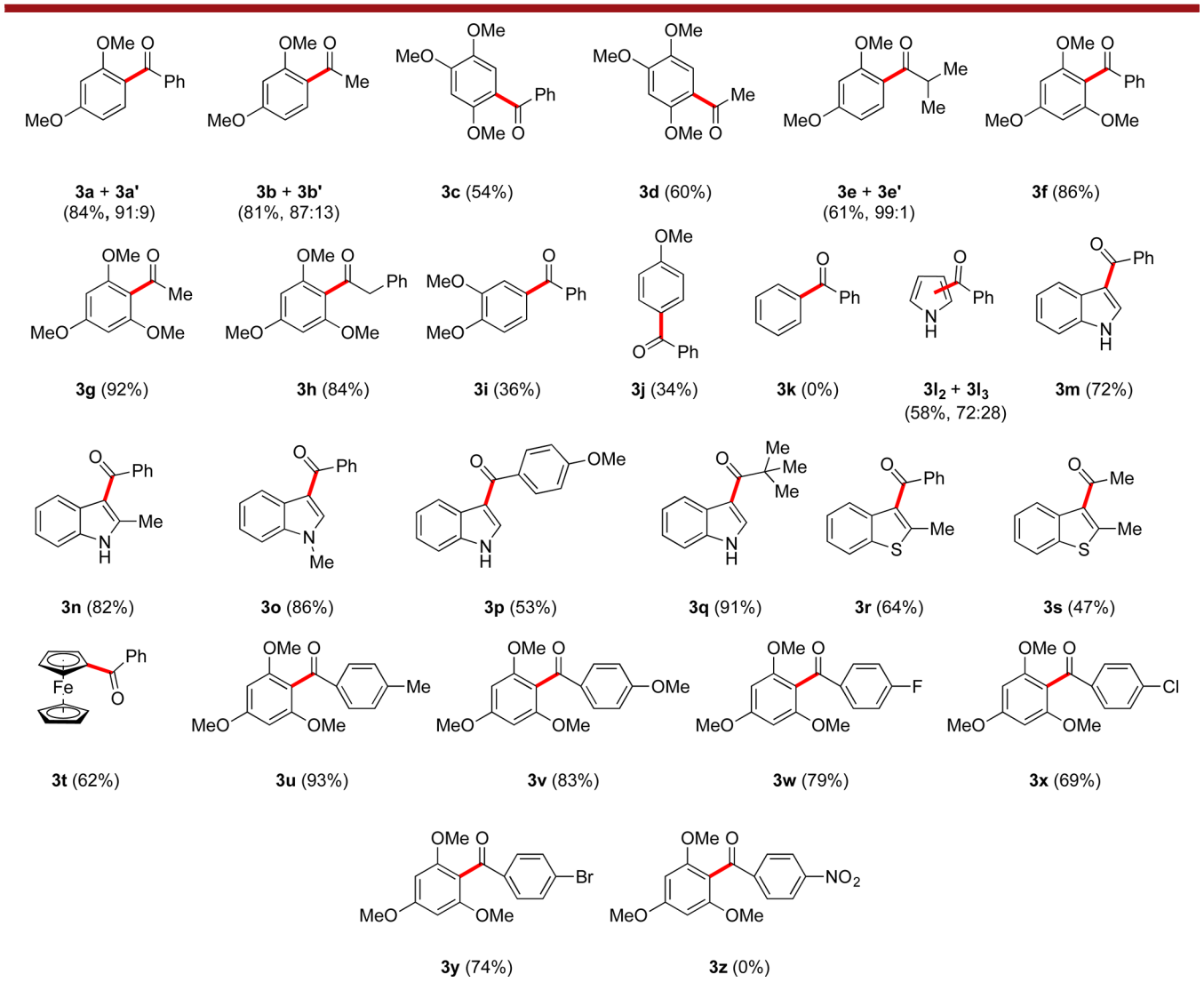


Figure 1. Reaction scope.

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(**3a**–**3i**). The singly activated anisole reacted with benzoyl chloride to give **3j** in 34% yield, but benzene did not give FC product **3k** under these conditions. Electron-rich heteroarenes, including pyrrole, indoles, and benzothiophenes, reacted with acyl chlorides to give corresponding heteroaryl ketones (**3l**–**3s**). Ferrocene reacted with benzoyl chloride to give benzoylferrocene **3t** in 62% yield.

Various substituents at the *para*-position of benzoyl chloride were explored. Both electron-donating and electron-withdrawing substituents worked well under FC acylation conditions with 1,3,5-trimethoxybenzene (**3u**–**3y**). Interestingly, the strongly deactivated *p*-NO_2-benzoyl chloride did not react with 1,3,5-trimethoxybenzene to give an FC product (**3z**); in this case, only starting materials were observed. Since this compound also does not undergo esterification in HFIP (data not shown), we presume that the lack of reactivity here is due to poor activation of the acid chloride by HFIP.

A common complaint is that HFIP is too expensive to use in fine organic synthesis. Although not cheap, HFIP can be had at relatively low prices from specialty vendors ($0.16/g for 1 kg, Oakwood Products, Inc.), and the lack of need for any other reagents along with the trivial workup goes a long way toward making up for this perceived deficiency. Moreover, the reaction can be readily scaled up and the solvent recycled with ease. Thus, 1,3,5-trimethoxybenzene **4** (22.71 g, 135 mmol) was reacted with benzoyl chloride **2a** (6.33 g, 45 mmol) in HFIP (12 equiv, 57 mL) at rt to give 10.51 g of **3f** (86%) (Figure 2).

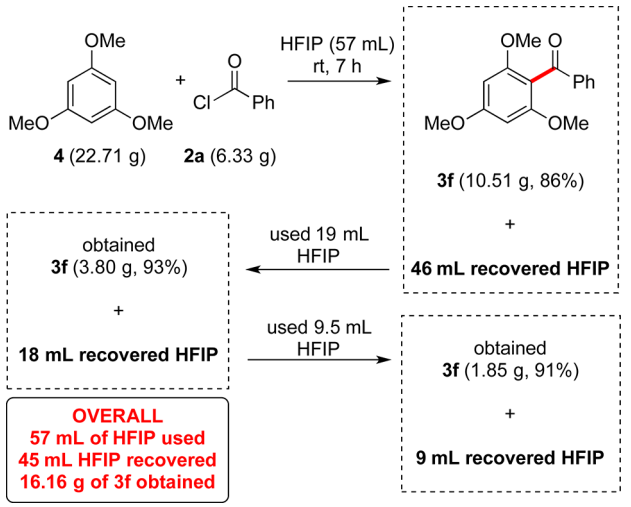
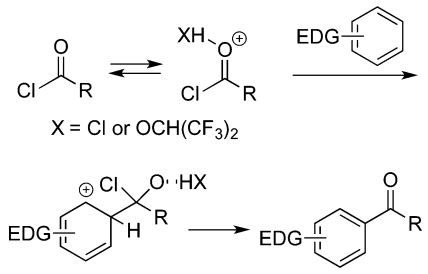


Figure 2. Gram scale reaction.

Distillation of HFIP directly from the reaction pot afforded 46 mL of solvent, 19 mL of which were reused in a subsequent reaction between **4** and **2a** to give 3.80 g of **3f** (93% yield) and permitting the recovery of 18 mL of HFIP. Repeating this procedure in a third cycle using this HFIP (9.5 mL) added 1.85 g of **3f** (91% yield). Overall, a total of 16.16 g of **3f** was obtained from the original batch of 57 mL of HFIP, which cost ca. $14.80 in total, leaving 45 mL of recovered solvent to use on other occasions (in other words, we lost about $3.17 of solvent). Most importantly, the recovered solvent was equally as good at promoting the FC reaction as the store-bought material (maybe even better, considering the possibility that these recovered samples could contain traces of HCl).

Porco and co-workers previously showed that a preformed HFIP ester led to FC cyclization in the presence of K_3PO_4 at 60 °C.[17] However, as previously reported[13] a preformed HFIP ester of an intramolecular acyl chloride substrate does not undergo FC reaction when HCl is added. This observation was also found to be true in the intermolecular version reported here, and together these experiments strongly suggest that HFIP acylation is not on the reaction pathway leading to ketone. We also previously suggested that the in situ formation of an acyl cation might be a possible reaction pathway in accord with the mechanism usually ascribed to a classic FC reaction (e.g., promoted by $AlCl_3$).[1e] However, preliminary in situ IR examination of the current reaction reveals direct transformation into product without any sign of an acyl cation (reported to appear at about 2308 cm^{-1} for the metal complexed version[18]).[19] Due to the absence of evidence to the contrary, we contemplate a mechanism whereby H-bond activation of the acyl chloride activates it for nucleophilic attack by the arene, followed by the usual final steps of a traditional FC reaction (Scheme 2).

Scheme 2. Plausible Reaction Mechanism



In conclusion, we have shown that our previously reported HFIP-assisted FC acylation reaction can be carried out intermolecularly. Both electron-rich arenes and heteroarenes worked efficiently with a variety of acyl halides to give FC acylation products. The workup of reaction avoids water-waste generation which is a common drawback of traditional Lewis acid catalyzed FC acylation reactions. In addition, we have successfully demonstrated that HFIP can be recovered and reused without loss of efficiency on the decagram scale.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01460.

Experimental procedures, characterization data, and NMR spectra of new and previously reported compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(19) In addition, no signal ascribable to an acyl cation was observed when the *p*-methoxybenzoyl chloride was dissolved in HFIP in the absence of a nucleophile partner.

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