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Hydroperfluoroalkylation of electron-deficient olefins with perfluoroalkyl iodides promoted by zinc/viologen†

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The hydroperfluoroalkylation of electron-deficient olefins with perfluoroalkyl iodides promoted by a zinc/viologen system is described. Interestingly, no iodoperfluoroalkylation product was observed without the presence of radical H-donor.

As the incorporation of a fluoroalkyl group into a drug candidate may result in profound modification of its physicochemical properties including increased lipophilicity and superior metabolic stability,[1] significant efforts have been directed towards the exploration of efficient methods for fluoroalkylation.[2] Although the use of perfluoroalkyl moieties as pharmacophores has been less investigated compared with other fluorinated functionalities such as trifluoromethyl and difluoromethyl groups,[1] the development of perfluoroalkylation strategies may open up avenues for further study on the biological potential of perfluoroalkyl groups. Therefore, a number of general and mild perfluoroalkylation approaches have been developed.[3] As one of the most convenient and straightforward protocols, radical perfluoroalkylation has received a great deal of attention recently.[2d,3g,4] Since perfluoroalkyl radicals exhibit electrophilic reactivity, these species are reactive towards perfluoroalkylation of electron-rich substrates.[5] However, radical perfluoroalkylation of electron-deficient olefins remains a largely ignored research area.

The readily commercially available source for perfluoroalkyl radical is perfluoroalkyl halide. The conversion of electron-deficient olefins with perfluoroalkyl halides usually results in haloperfluoroalkylation.[6] In order to suppress the halogenation process, the addition of a radical hydrogen donor into the reaction system may be required.[7] Interestingly, perfluoroalkylation without halogenation could also occur well promoted by an appropriate initiator, such as bimetal system,[8] photocatalyst,[9] and triethylborane.[10] But these reactions suffer from narrow substrate scope, low yields, or the use of expensive initiator. On the basis that viologens[11] and arenes[12] have served as valuable electron-transfer reagents, we speculated that viologen should be able to be used in perfluoroalkylation of electron-deficient olefins *via* a single-electron-transfer process. In continuation of our research interest in the chemistry of fluoroalkylation,[13] we have now investigated the hydroperfluoroalkylation of α,β-unsaturated ketones and esters with perfluoroalkyl iodides promoted by zinc/viologen system.

Our initial attempt at the hydroperfluoroalkylation of α,β-unsaturated ketone **1a** with iodide **2a** promoted by zinc powder and butyl viologen in DMF at 110 °C was successful to afford the desired product **3a**, albeit in low yield (entry 1, Table 1). A brief survey of the reaction solvents (entries 1–6) revealed that chloroform was a suitable solvent (entry 5). Both zinc powder and viologen were necessary for this conversion, as evidenced by the results that no expected product was observed with the absence of either one (entries 7–8). Decreasing the loading of viologen led to the dramatic decrease in the yield (entries 9–10 *vs.* entry 5), but increasing its loading can't increase the yield (entry 11 *vs.* entry 5). Lower yields were obtained with lowering the reaction temperature (entries 12–14). 4 h of reaction time can guarantee the full conversion of substrate **1a**. Shortening the reaction time to 2 h, the yield was decreased (entry 15 *vs.* entry 5). The transformation was not particular sensitive to water, and 38% yield could be obtained with the presence of 4 equiv. of water (entry 16). Refluxing the reaction mixture in a Schlenk tube under N_2 atmosphere gave the desired product only in 47% yield (entry 17).

With the optimal reaction conditions in hand (entry 5, Table 1), we then investigated the substrate scope for the hydroperfluoroalkylation of electron-deficient olefins promoted by zinc/viologen system. As shown in Table 2, the reactions occurred smoothly to give the desired products in moderate to

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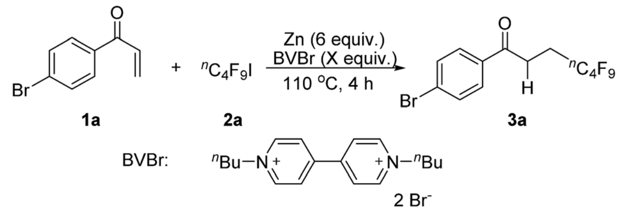
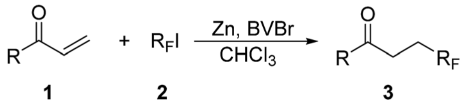
Table 1 Screening reaction conditions[a]



Entry	Solvent	X (equiv.)	Yield[b] (%)
1	DMF	2	22
2	CH_3CN	2	26
3	C_2H_5OH	2	19
4	THF	2	30
5	$CHCl_3$	2	62
6	Cyclohexane	2	7
7[c]	$CHCl_3$	2	0
8	$CHCl_3$	0	0
9	$CHCl_3$	1	36
10	$CHCl_3$	0.5	28
11	$CHCl_3$	3	59
12[d]	$CHCl_3$	2	44
13[e]	$CHCl_3$	2	55
14[f]	$CHCl_3$	2	59
15[g]	$CHCl_3$	2	52
16[h]	$CHCl_3$	2	38
17[i]	$CHCl_3$	2	47

[a] Reaction conditions: the mixture of substrate **1a** (0.1 mmol), perfluoroalkyl iodide **2a** (0.3 mmol), zinc powder (0.6 mmol), dibutyl-4,4′-bipyridinium dibromide and solvent (1 mL) was stirred in a sealed tube at 110 °C for 4 h. [b] Isolated yields. [c] No zinc powder was used. [d] Reaction temperature was 50 °C. [e] Reaction temperature was 70 °C. [f] Reaction temperature was 90 °C. [g] Reaction time was 2 h. [h] H_2O (4 equiv.) was used as an additive. [i] The reaction mixture was refluxed in a Schlenk tube under N_2 atmosphere.

Table 2 Substrate scope for hydroperfluoroalkylation



Entry	R	R_F	Yield[a] (%)
1	*p*-BrC_6H_4 (**1a**)	$^nC_4F_9$	**3a**, 62
2	*o*-BrC_6H_4 (**1b**)	$^nC_4F_9$	**3b**, 50
3	*m*-BrC_6H_4 (**1c**)	$^nC_4F_9$	**3c**, 54
4	*p*-ClC_6H_4 (**1d**)	$^nC_4F_9$	**3d**, 78
5	*p*-$NO_2C_6H_4$ (**1e**)	$^nC_4F_9$	**3e**, 38
6	C_6H_4 (**1f**)	$^nC_4F_9$	**3f**, 71
7	*p*-PhC_6H_4 (**1g**)	$^nC_4F_9$	**3g**, 71
8	*p*-MeC_6H_4 (**1h**)	$^nC_4F_9$	**3h**, 74
9	*p*-$MeOC_6H_4$ (**1i**)	$^nC_4F_9$	**3i**, 64
10	β-Naphthyl (**1j**)	$^nC_4F_9$	**3j**, 64
11	*p*-BrC_6H_4 (**1a**)	$^iC_3F_7$	**3k**, 42
12	*p*-BrC_6H_4 (**1a**)	$^nC_6F_{13}$	**3l**, 54
13	Cyclohexyl (**1m**)	$^nC_4F_9$	**3m**, 76
14	*p*-$PhCH_2O$ (**1n**)	$^nC_4F_9$	**3n**, 80

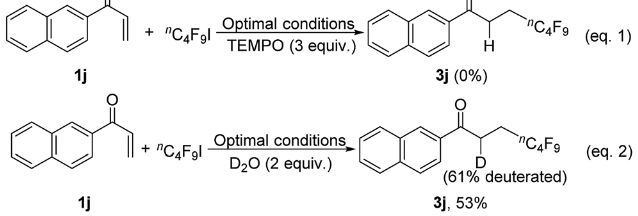
[a] Isolated yields.

good yields. It is noteworthy that no iodoperfluoroalkylation product was detected. The examination of electronic effects (entries 1–10) revealed that both weakly electron-withdrawing groups (entries 1–4) and electron-donating groups (entries 6–10) showed no side effect on the conversion of unsaturated aryl ketones. But a strong electron-withdrawing group led to a low yield (entry 5), which is because the substrate is reactive towards zinc powder. Besides perfluorobutyl iodide, other perfluoroalkyl iodides were also efficient radical source for this transformation (entries 11–12). The hydroperfluoroalkylation is not only applicable to α,β-unsaturated aryl ketones, but also to α,β-unsaturated aliphatic ketone (entry 13) and α,β-unsaturated ester (entry 14).

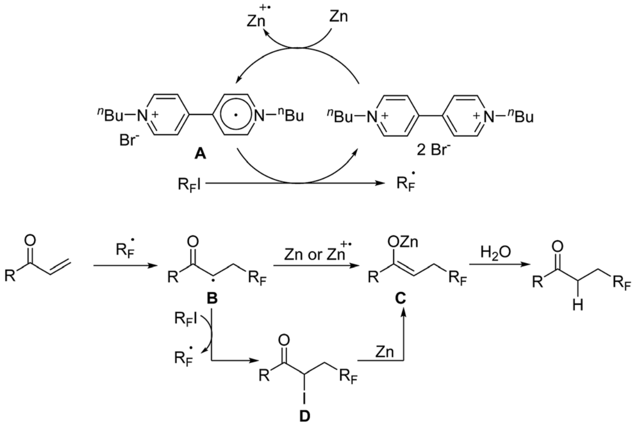
Since viologens are efficient electron-transfer reagents, it is reasonable to conceive that the hydroperfluoroalkylation proceeds *via* a single-electron-transfer process to generate perfluoroalkyl radical. The presence of the radical scavenger TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxyl] completely suppressed the desired transformation, further suggesting that the a radical process was involved (eqn (1), Scheme 1). In order to determine what the hydrogen source is for this hydroperfluoroalkylation reaction, more experimental evidences were collected. No deuterated product was detected by using $CDCl_3$ instead of $CHCl_3$ as the solvent for the conversion of naphthyl substrate **1j**, implying that the hydrogen is not from the solvent. The use of D_2O (2 equiv.) as an additive under the optimal reaction conditions gave the desired product in 53% yield, with 61% deuterated at the α-position of the carbonyl group (eqn (2), Scheme 1), which means that H_2O is the source for the hydrogenation.

Based on the above results, we propose the reaction mechanism as shown in Scheme 2. The redox reaction of viologen with zinc powder generates Zn(I) and radical cation species **A**. The transfer of one electron from intermediate **A** to perfluoroalkyl iodide produces perfluoroalkyl radical and regenerates viologen. The attack of the perfluoroalkyl radical at the double bond in substrate gives intermediate **B**, which would be readily reduced by Zn(0) or Zn(I) to afford stable enolate **C**. It can't be ruled out that species **B** may also undergo iodine abstraction from perfluoroalkyl iodide to generate iodoperfluoroalkylation product **D**. In the presence of excessive zinc powder, the reduction of product **D** would occur easily to give enolate **C**. Protonation of enolate **C** by H_2O furnishes the final product.

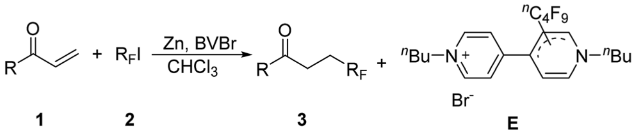
The viologen can't be used in a catalytic amount because species **A** undergoes not only electron transfer to regenerate



Scheme 1 Evidence for the elucidation of the reaction mechanism.



Scheme 2 Plausible reaction mechanism.



Scheme 3 Side reaction of viologen.

viologen, but also other conversions to afford side-products. For instance, the side product **E** formed by the combination of radical cation **A** with perfluorobutyl radical was detected by ESI† (Scheme 3).

Conclusions

In conclusion, we have described the hydroperfluoroalkylation of α,β-unsaturated ketones and esters with perfluoroalkyl iodides promoted by zinc/viologen system. It is noteworthy that no iodoperfluoroalkylation product was detected in this conversion. This zinc/viologen system-promoted hydroperfluoroalkylation strategy may find utilities in other research area.

Acknowledgements

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