ORGANIC LETTERS

2007
Vol. 9, No. 15
2783−2786

Samarium Triflate-Catalyzed Halogen-Promoted Friedel–Crafts Alkylation with Alkenes

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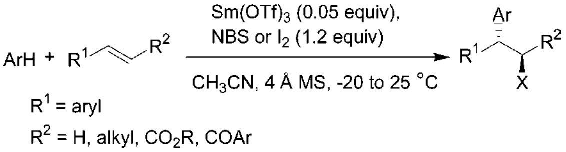
Received April 5, 2007

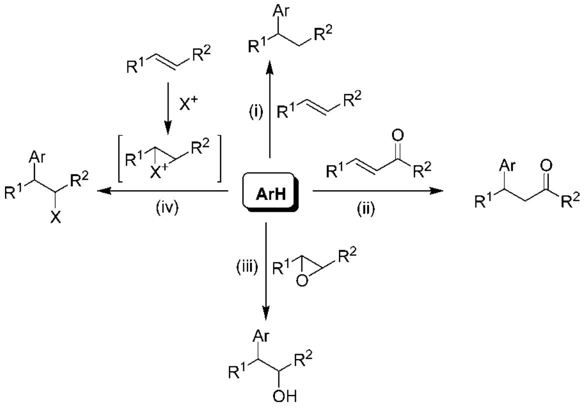
ABSTRACT



A versatile and efficient halogen-promoted highly regio- and stereoselective Friedel–Crafts (F-C) alkylation with alkenes has been developed with use of easily available and inexpensive NBS or I_2 as the efficient halogen sources. Lewis acids, in particular metal triflates, are found to be effective catalysts for this halogen-promoted F-C alkylation. Among these, $Sm(OTf)_3$ was the best catalyst. Electron-rich arenes smoothly underwent F-C alkylation with a variety of alkenes including α,β-unsaturated carbonyl compounds.

Friedel−Crafts (F-C) alkylation with alkenes is one of the most important C−C bond-forming reactions in organic chemistry.[1] These reactions are usually assisted by either protic acid or Lewis acid. On the basis of the mode of reaction, this F-C alkylation might be categorized as (i) reaction of arenes with normal alkenes via carbocation-like intermediates, (ii) reaction with electron-deficient alkenes via 1,4-conjugate addition, (iii) reaction of arenes with stable intermediate compounds derived from alkenes such as epoxides, and (iv) reaction with reactive intermediates generated in situ from alkenes such as three-membered halonium ions (Scheme 1). Among these, reactions with normal alkenes catalyzed by protic acid or Lewis acid have been extensively investigated. 1,4-Conjugate addition of arenes to electron-deficient alkenes are mostly limited to indoles as arenes.[2] Ring-opening of epoxides with arenes is also known in the literature.[3] However, to the best of our knowledge, intermolecular F-C alkylation with alkenes via halonium ions has not been reported. Interestingly, these alkylated arenes containing α-halo functionality could provide a further avenue for structural elaboration. Herein we report NBS/I_2-promoted intermolecular Friedel−Crafts alkylation with a variety of alkenes including α,β-unsaturated carbonyl compounds catalyzed by $Sm(OTf)_3$ that provide an alternate method for synthesis of 1,1-diaryl-2-halo alkanes and α,α-diaryl-β-halocarbonyl compounds, respectively.

Scheme 1. Different Modes of F-C Alkylation with Alkenes



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[1] For reviews of Friedel−Crafts alkylation reactions, see: (a) Olah, G. A. *Friedel−Crafts and Related Reactions*; Wiley-Interscience: New York, 1964; Vol. II, part 1. (b) Roberts, R. M.; Khalaf, A. A. *Friedel−Crafts Alkylation Chemistry*: *A Century of Discovery*; Dekker: New York, 1984. (c) Olah, G. A.; Krishnamurthi, R.; Prakash, G. K. S. *Friedel−Crafts Alkylations in Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991. (d) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550-556.

10.1021/ol070813t CCC: $37.00

A current interest in our laboratory is the stereoselective 1,2-halo functionalization of alkenes.[4] We found that Lewis acids, in particular metal triflates, activate NXS to facilitate the formation of halonium ions from alkenes. Recently we have reported Lewis acid-catalyzed and *N*-halosuccinimide (NXS)-promoted intramolecular F-C alkylation with tethered alkenes for the synthesis of annulated arene heterocycles and carbocycles (Scheme 2).[4e] Accordingly, we anticipated that a suitable Lewis acid might, similarly, catalyze NXS-promoted intermolecular F-C alkylation of arenes with alkenes. For this purpose, we screened different Lewis acids, in particular metal triflates, as catalysts for halogen-promoted F-C alkylation of 1,2-dimethoxybenzene with 1,2-dihydronaphthalene (Table 1). $Mg(OTf)_2$, $La(OTf)_3$, $Yb(OTf)_3$, $Y(OTf)_3$, $Cu(OTf)_2$, $Zn(OTf)_2$, and $Sm(OTf)_3$ showed good catalytic activity (entries 7−13). Among these, $Sm(OTf)_3$ was found to be the best catalyst and acetonitrile a suitable solvent. It is noteworthy that in the absence of metal triflates, the reaction did not produce any F-C alkylated product (entry 1).

Scheme 2. Halogen-Promoted Intramolecular F-C Alkylation with Tethered Alkenes

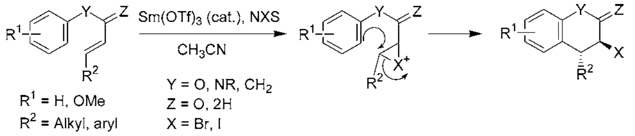
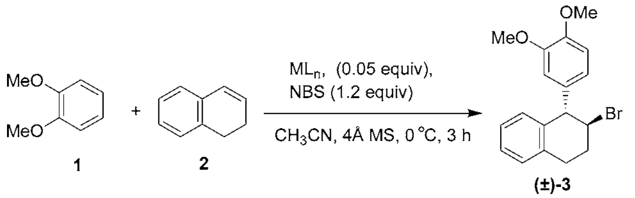


Table 1. Screening of Lewis Acids as Catalysts for the Halogen-Promoted F-C Alkylation with Alkenes

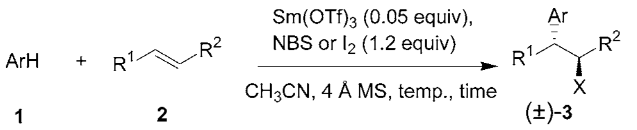


	ML_n	conv.^{a} (%)	yield^b of **3** (%)
1	none	20	<5 (12)^c
2	$CoCl_2$	40	<5 (20)^c
3	$MgCl_2$	65	8 (25)^c
4	$NiCl_2$	80	<5 (35)^c
5	$CuCl_2$	93	7 (35)^c
6	Cu_2Cl_2	90	12 (27)^c
7	$Mg(OTf)_2$	100	41 (18)^c
8	$La(OTf)_3$	100	43 (21)^c
9	$Y(OTf)_3$	100	61 (17)
10	$Yb(OTf)_3$	100	65 (18)
11	$Zn(OTf)_2$	100	72 (12)
12	$Cu(OTf)_2$	100	71 (10)
13	$Sm(OTf)_3$	100	78 (7)

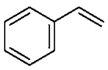
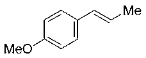
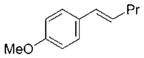
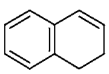
[a] Determined from the ^{1}H NMR spectra of the crude reaction mixture with anthracene as internal standard. [b] Yields in parentheses refer to the yields of 1,2-dibromotetralin. [c] Along with 10−25% of nonseparable unidentified byproducts.

To study the scope of this halogen-promoted F-C alkylation, reactions of arenes with various types of alkenes were carried out (Table 2). In all cases, the reactions successfully proceeded to afford the corresponding alkylated products containing an α-halofunctionality in moderate to good yields. Toluene and *o*-xylene were used as cosolvents along with CH_3CN to afford clean products (entries 1 and 2). Electron-rich arenes such as anisole and 1,2-dimethoxybenzene underwent smooth reaction with styrene, when I_2 was used as a halogen source along with $NaHCO_3$ as an additive (entries 3 and 4). Halogen-promoted F-C alkylations with

Table 2. $Sm(OTf)_3$-Catalyzed Halogen-Promoted F-C Alkylation with Alkenes^a



1a: toluene
1b: *o*-xylene
1c: anisole
1d: 1,2-dimethoxy benzene
1e: 1,2,3-trimethoxy benzene

	alkene **2**	ArH **1**	temp (° C)	halogen source	time (h)	yield of **3**^{b} (%)
1^c		**1a**	25	NBS	12	40
2^c		**1b**	25	NBS	12	43
3^d		**1c**	25	I_2	4	58
4^d		**1d**	25	I_2	3	52
5^d		**1d**	-20	NBS	0.5	51
6^d		**1c**	-20	NBS	0.5	62
7		**1c**	0	NBS	4	52
8		**1d**	0	NBS	3	75
9		**1e**	0	NBS	2	72^e

[a] $Sm(OTf)_3$ (0.05 equiv)-catalyzed F-C alkylation was performed with 1.0 equiv of alkene, 1.2 equiv of arene, 1.2 equiv of NBS (or 1.2 equiv of I_2 and 1.2 equiv of $NaHCO_3$) in CH_3CN. [b] Isolated yields of **3** after column chromatography; also 5−20% of halogen addition products were obtained. [c] Arene **1** was used as a cosolvent along with CH_3CN (CH_3CN:ArH 4:1). [d] Alkene **2** was used in excess (2−3 equiv). [e] Along with 20% of trimethoxy bromobenzene as a nonseparable mixture.

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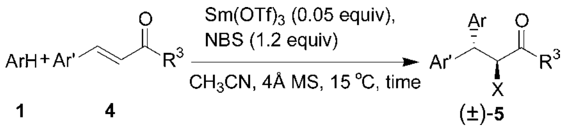
Table 3. $Sm(OTf)_3$-Catalyzed Halogen-Promoted F-C Alkylation with α,β-Unsaturated Carbonyl Compounds[a]



entry	ArH **1**	Ar′	R^3	time (h)	yield[b] (%)
1	**1c**	$4\text{-}MeOC_6H_4$	OMe	12	77
2	**1d**	$4\text{-}MeOC_6H_4$	OMe	12	91
3	**1e**	$4\text{-}MeOC_6H_4$	OMe	12	80[c]
4	**1d**	$3,4\text{-}MeOC_6H_3$	OMe	12	85
5	**1e**	$3,4\text{-}MeOC_6H_3$	OMe	12	76[c]
6	**1d**	2-furyl	OMe	1	51
7	**1d**	$3,4\text{-}MeOC_6H_3$	C_6H_5	3.5	79
8	**1e**	$3,4\text{-}MeOC_6H_3$	C_6H_5	3.5	71[c]
9	**1d**	$4\text{-}MeOC_6H_4$	$2\text{-}MeOC_6H_4$	4	90
10	**1e**	$4\text{-}MeOC_6H_4$	$2\text{-}MeOC_6H_4$	4	90[c]

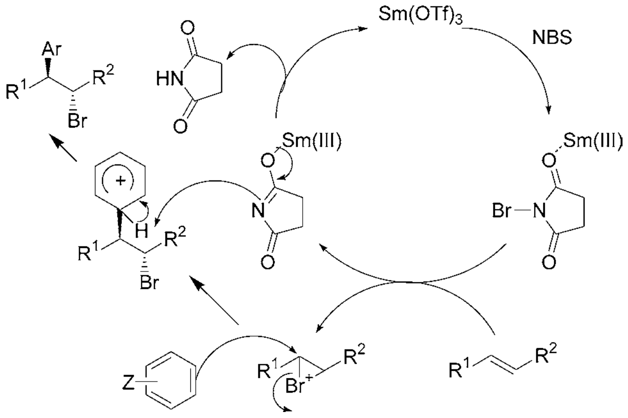
[a] $Sm(OTf)_3$ (0.05 equiv)-catalyzed F-C alkylation was performed with 1.0 equiv of alkene, 1.2 equiv of arene, 1.2 equiv of NBS in CH_3CN at 15 °C. [b] Isolated yields of **5** after column chromatography. [c] 10−15% of trimethoxy bromobenzene was obtained.

electron-rich alkenes, e.g., *p*-methoxy-β-methylstyrene and *p*-methoxy-β-propylstyrene, were carried out at −20 °C to afford clean F-C alkylated products. Improved yields were obtained when styrenes were used in excess (entries 5 and 6). Reactions of toluene and anisole with alkenes exclusively produced para-substituted adduct. No ortho-regioisomer was detected from the ^1H NMR of the crude reaction mixture. Reactions of anisole, 1,2-dimethoxybenzene, and 1,2,3-trimethoxybenzene with 1,2-dihydronaphthalene produced 1-aryl-2-halotetralins in good yields (entries 7−9). The other regioisomer 2-bromo-1-(3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydronaphthalene from 1,2,3-trimethoxybenzene was not detected. It is to be noted that 1-aryl-2-halotetralins could be key intermediates for the synthesis of many biologically important compounds[5] by replacing the halogen atom with suitable nucleophiles.

α,β-Unsaturated carbonyl compounds represent a synthetically useful class of substrates for various alkene addition reactions. In particular, halogen-promoted F-C alkylation of α,β-unsaturated carbonyl compounds, especially of cinnamate and chalcon would provide α-halo-β,β-diarylcarbonyl compounds, which could be transformed into various useful organic compounds by replacing the halogen with a series of nucleophiles. More interestingly, β,β-diarylcarbonyl compounds are important structural motifs found in many natural products and a number of pharmaceuticals.[6] Different electron-rich arenes smoothly underwent NBS-promoted F-C alkylation with a number of cinnamates and chalcones at 15 °C and produced α-bromo-β,β-diarylcarbonyl compounds in high yields (Table 3).

$Sm(OTf)_3$ was found to be an efficient catalyst for the halogen-promoted F-C alkylation with alkenes including α,β-unsaturated carbonyl compounds and provided *anti*-1,2-haloarylated products in moderate to good yields. It seems that $Sm(OTf)_3$ activates NBS by chelation to facilitate the formation of halonium ions from alkenes and the subsequent reactions with arenes led to the formation of F-C alkylated products along with regenaration of Sm(III) catalyst. Thus a plausible mechanism has been proposed for $Sm(OTf)_3$-catalyzed halogen-promoted F-C alkylation reactions (Scheme 3). However, further investigations are warranted to support this proposal.

Scheme 3. Proposed Mechanism for $Sm(OTf)_3$-Catalyzed Halogen-Promoted F-C Alkylation



We have developed a highly regio-, stereo-, and chemoselective halogen-promoted Friedel−Crafts alkylation of aromatic compounds with alkenes using inexpensive and easily available NBS or I_2 as a halogen source. These reactions are catalyzed by Lewis acids, in particular metal triflates. Among these, $Sm(OTf)_3$ was found be the best catalyst. Electron-rich arenes smoothly underwent chemoselective halogen-promoted F-C alkylation with a variety of alkenes. This method was also found to be very effective with α,β-unsaturated carbonyl compounds such as

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cinnamates and chalcones and produced α-halo-β,β-diarylcarbonyl compounds in high yields.

Acknowledgment. We thank DST (SR/S1/OC-13/2004), New Delhi for providing financial support. B.M. and S.B. thank UGC and CSIR, New Delhi for their fellowships, respectively.

Supporting Information Available: Detailed experimental procedures, and spectral data for all the compounds **3** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070813T