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XtalFluor-E® mediated proteo functionalization of *N*-vinyl amides: access to *N*-acetyl *N,O*-acetals

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Abstract

XtalFluor-E® has been extensively used in a broad range of reactions in the past few years. Here we report its use with protic nucleophiles in a catalytic manner for the *in situ* generation of protons that lead to the proteo functionalization of activated olefins. Utilizing the latter protocol, proteo etherification of enamides gives rise to *N,O*-acetals in nearly quantitative yields.

Graphical abstract

Within the family of organic reactions, functionalization of olefins is one of the most well studied and important transformations. Some of the milestone reactions in this realm are epoxidation,¹ dihydroxylation,² aminohydroxylation,³ dihalogenation,⁴ and halofunctionalization⁵ to name a few. Proteo-functionalization of olefins i.e., activation of a double bond with a proton and interception of the resulting carbocation with a nucleophile, is one of the early discovered reactions. These generally require the application of strong acids and relatively harsh reaction conditions,⁶ not compatible with molecules bearing sensitive functionalities. There are milder conditions, although not with Brønsted acid sources.⁷ In this vein, introduction of approaches that catalyze the reaction by *in situ* generation of proton under mild conditions are of interest.⁸ Here we report such a system and utilize this mild condition towards proteo functionalization of enamides to access *N,O*-acetals.

To date, several strategies have been devised that give rise to *N,O*-acetals (Scheme 1a). These include condensation of aldehydes with amides in the presence of titanium ethoxide,⁹ benzotriazole^{10, 11} or sodium benzenesulfinate,¹² as well as the reduction of nitriles with Schwartz reagent followed by the reaction of the resulting intermediate with acyl chloride

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Conflicts of interest

There are no conflicts to declare.

and alcohol.¹³ Szymura and coworkers used the Hofer-Moest reaction for the electrochemical decarboxylative methoxylation of *N*-acetyl- α -amino acids to generate *N*-(α -methoxyalkyl)-amides.¹⁴ Our approach takes advantage of the high reactivity of enamides. Reaction of XtalFluor-E[®] with alcohols leads to a mild method for generation of protons that promote the described transformation. Noteworthy, is Toste and coworkers' development of an enantioselective oxyfluorination of enamides using chiral phosphoric acid and selectfluor.¹⁵

XtalFluor-E[®] is best known as a reagent for deoxyfluorination of carbonyl compounds and alcohols (Scheme 1b).^{16–23} This reagent can activate oxygenated organic compounds towards substitution reactions.^{16, 21–23} In this manner, deoxyfluorination^{20, 24} and halogenation^{16, 19} as well as formation of 2-oxazolin from β -hydroxyamide^{25, 26} and activation of benzyl alcohols for Friedel-Crafts benzylation²³ are realized. The commonality of these transformations is the activation of the hydroxyl group with XtalFluor-E[®] into a good leaving group for the subsequent displacement reaction. Moreover, XtalFluor-E[®] has been extensively used to activate carboxylic acids for the synthesis of amides and nitriles,^{13, 27, 28} and the fluoride opening of aziridines.^{21, 29} Recently the synthesis of perfluorinated esters using XtalFluor-E[®] as the activating agent of carboxylic acid was reported, in which fluorinated alcohols are utilized as the nucleophile.²⁷ XtalFluor-E[®] consists of a sulfur nitrogen double bond with a highly electron deficient sulfur atom, bearing two electronegative fluorine atoms. Indeed, this polarized bond is the key feature for its reactivity. It is the activation of the carbonyl or hydroxyl groups with XtalFluor-E[®] that initiates the reaction. Based on these observations, we envisioned that *catalytic* XtalFluor-E[®] with a protic nucleophile (alcohol, thiol, acid, *etc.*) will function as a source for *in situ* generation of protons, which in turn can initiate activation of olefins toward proteo functionalization reactions.

We began our investigations with the addition of stoichiometric amount of XtalFluor-E[®] to enamide **1a** in presence of methanol as the solvent and nucleophile source (entry 1, Table 1). Reaction at room temperature resulted in the quantitative formation of the *N,O*-acetal after 36 h. Next we pursued the application of catalytic amount of XtalFluor-E[®]. Gratifyingly, we realized that 10 mol% of the catalyst can lead to the expected *N,O*-acetal product, although not as efficiently (entry 2, Table 1), requiring longer reaction time. We surmised this to be due to the attenuated activity of the *in situ* generated proton in methanol, thus we resorted to aprotic solvents.

The screening of a variety of solvents revealed higher efficiency of the reaction in less polar solvents and in the presence of excess methanol as the nucleophile. Ultimately, dichloromethane was chosen as the optimal solvent (entry 4, Table 1). The reaction is not limited to XtalFluor-E[®], as XtalFluor-M[®] (Scheme 1c) showed similar efficiency for *N,O*-acetal formation (entry 9, Table 1). The amount of methanol proved to have a profound effect on the rate of the reaction (with excess methanol increasing the rate of the reaction). A 1:1 (v:v) DCM:MeOH solvent ratio led to the optimal reaction condition (entry 10, Table 1). In case of alcohols with low molecular weight, the excess amount is not an issue since the remainder can be evaporated. However, for less volatile alcohols, stoichiometric amounts

(1.1 equiv) of the protic nucleophile can be used, yielding the desired product, albeit with longer reaction time (see entry 7, Table 2 for an example).

To demonstrate the generality of the reaction, a handful of enamide substrates were synthesized and subjected to the reaction condition (Table 2). Gratifyingly, the reaction resulted in the corresponding *N,O* or *N,S*-acetals with nearly quantitative yield for most of the substrates. The electronic and steric influence of the aryl group on the reactivity of the enamide was screened, with minimal effect on the yield and efficiency of the reaction. Nevertheless, the *p*-methoxy benzoyl group generally gave better results. The transformation was equally effective with aliphatic enamides, delivering high yield of the *N,O*-acetal products. The reaction is not limited to secondary enamides, as cyclic-tertiary enamides resulted in products with excellent yield. Furthermore, the cyclic nature of the enamide did not diminish the reaction outcome. With regard to the nature of the protic nucleophile, light alcohols can be used to successfully give the corresponding *N,O*-acetal products. Thiols also yield *N,S*-acetals with excellent yields (**2f**, **2g**). The thiol mediated reactions typically proceed faster as compared to alcohols as nucleophiles. The reaction can also be performed on a large scale without deterioration in efficiency (**2b**, entry 9, Table 2). The stereoisomerism of the starting enamide (*cis* or *trans*) had minimal effect on the reaction. Of note is the incompatibility of the methodology with bulky nucleophiles. As illustrated in Table 2, hydroalkoxylation of enamide with *n*-propyl alcohol results in high yield of **2d**, however the reaction is less efficient with *iso*-propyl alcohol (**2e**, Table 2). The reaction of **1b** with *tert*-butyl alcohol failed to give any product.

To propose a reasonable mechanism, we conducted a few control experiments. As reported by Paquin and coworkers, alcohols can react with XtalFluor-E[®] to give a non-reversible adduct.^{19, 22} In our optimized reaction condition, catalytic XtalFluor-E[®] is exposed to protic nucleophiles in large excess. As a result, the formation of the putative adduct and its implication on the reaction progress is obscured by the presence of excess nucleophile. To circumvent this issue, the reaction of **1j** was conducted in presence of only one equivalent of methanol and the loading of XtalFluor-E[®] was varied. As illustrated in Scheme 2a the yield of *N,O*-acetal product **2o** decreases as XtalFluor-E[®] loading increases. At a 1:1 ratio of methanol:XtalFluor-E[®], no product was detected based on ¹H NMR analysis. Of note is the complete disappearance of the enamide **1j** in the reaction with methanol and XtalFluor-E[®] (1 equiv each) illustrative of the fact that the protonation of the enamide most likely is taking place under this condition, however in the absence of free methanol the protonated enamide undergoes deleterious side reactions. This set of experiments does suggest the formation of an adduct such as **I**, depicted in Scheme 3 (dashed box).

Since the nucleophile acts as the proton source in this reaction, we designed experiments to investigate the contribution of nucleophilicity as well as the acidity of the protic nucleophiles on the course of the reaction. As illustrated in Scheme 2b, comparing reactions of the enamide **1a** revealed that the reaction with sulfur-based nucleophiles is faster than oxygen-based nucleophiles (compare entries 1 and 2, Scheme 2b). On the other hand, the acidity of the protic nucleophile proved to have minimal effect on the reaction progress i.e., benzoic acid, despite its higher acidity, was an incompetent reagent (Scheme 2b). This can be interpreted by the weaker nucleophilicity of benzoic acid that prevents adduct formation

with XtalFluor-E[®]. This hypothesis is in accordance with the reported data that adduct formation of carboxylic acids with XtalFluor-E[®] requires the presence of a base. The increased nucleophilicity of thiobenzoic acid in comparison resulted in the fast consumption of **1a** and formation of the corresponding product **2t** was observed.

Upon addition of methanol to a solution of XtalFluor-E[®] in *d*₃-acetonitrile, substantial changes in the ¹⁹F NMR of the mixture were observed. XtalFluor-E[®] has two peaks in the ¹⁹F NMR that correspond to the fluorine atoms on the sulfur (12.9 ppm) and the tetrafluoroborate anion (−151.6 ppm). Addition of one equivalent of methanol resulted in the disappearance of the peak at 12 ppm concomitant with the appearance of multiple peaks in the 50–60 ppm range. Addition of two equivalents of methanol simplified the spectrum into a single peak at 54 ppm (see Figure S1 for NMR traces). This newly emerged peak did not undergo any further changes upon increasing the equivalents of methanol (up to 10 equivalents). These results further suggest the formation of the putative adduct **I**.

Our experimental and NMR data, along with observations and mechanistic suggestions that have appeared in the literature, lead us to the mechanistic proposal depicted in Scheme 3. We surmised addition of an alcohol to XtalFluor-E[®] provides a *catalytic* proton source as the initial step of the reaction. The protonated enamide can be intercepted by the excess nucleophile to yield the protonated *N,O*-acetal product. This protonated *N,O*-acetal product can act as proton source to activate another enamide. Putative complexes (shown in the dashed box, Scheme 3) can potentially collapse to generate tetrafluoroboric acid (HBF₄) and subsequently this acid can protonate the enamide. This suggest that HBF₄ itself should be able to catalyze this reaction. Indeed, we find the latter statement is true (Table S1).

Conclusions

We report a mild method for the generation of protons from the reaction of XtalFluor-E[®] with a protic solvent. Reaction of enamides under the prescribed conditions lead to the proteo functionalization of olefins, yielding *N,O*-acetals when alcohols are used as the nucleophilic proton source. The *N,O*-acetal products can be accessed in nearly quantitative yield in most cases, often without the need for further purification. XtalFluor-E[®] is commercially available and the water-soluble side product can be easily removed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Previous Work**a. approaches to access *N,O*-acetals** **b. XtalFluor-E® and its application in organic synthesis***deoxofluorination* *halogenation* *esterification* **This Work****c. XtalFluor-E® for proteo functionalization of olefin: *N,O*-acetal synthesis** **Scheme 1.**

Synthesis of *N,O*-acetals, previous and current strategies in employing XtalFluor-E®

Control experiments

a. Probing the reversibility of XtalFluor-E® - alcohol association

Entry	XtalFluor-E® (equiv)	Yield ^a (%)
1	0.1	90
2	0.2	69
3	0.5	40
4	1.0	0
5 ^b	1.0	0

^aYield was estimated by ¹H NMR analysis of the crude reaction mixture. ^bAfter 2 h another 5 equivalents of methanol was added.

b. Assessment of the acidity versus nucleophilicity of protic nucleophiles

Entry	Product	NuH	Time (h)	Yield ^a (%)
1	2a	MeOH	12	>95
2	2s	EtSH	1	>95
3	2t	PhCOSH	0.3	>95
4 ^b	2u	PhCO ₂ H	48	0

^aYield was estimated by ¹H NMR analysis of the crude reaction mixture. ^b~65% starting material was recovered.

Scheme 2.

Control experiments and mechanistic insights.

Scheme 3.

Proposed mechanism of XtalFluor-E[®] mediated proteo functionalization of enamides.

Table 1Optimization results for the XtalFluor-E[®] mediated *N,O*-acetal formation of enamide

Entry	Solvent	Time (h)	Conversion (yield) ^a
1 ^b	MeOH	36	99% (>98%)
2	MeOH	48	88% (57%)
3	Toluene	22	74% (66%)
4	CH ₂ Cl ₂	10	95% (89%)
5	CHCl ₃	10	93% (83%)
6	Nitromethane	10	95% (85%)
7	ClCH ₂ CH ₂ Cl	10	95% (85%)
8	Acetonitrile	22	85% (68%)
9 ^c	CH ₂ Cl ₂	36	97% (86%)
10 ^d	CH ₂ Cl ₂	8	100% (>98%)

^aYields were estimated by ¹H NMR analysis of the crude reaction mixture.^bOne equivalent of XtalFluor-E[®] was used^cXtalFluor-M[®] (10 mol%) was used instead of XtalFluor-E[®].^dMeOH:DCM (1:1 v:v, 0.1 M) was used.

Table 2

Scope of XtalFluor-E[®] catalyzed synthesis of N,O-acetals.^a

Entry	Enamide	N,O-acetal		Yield (%)
1			<i>cis</i> enamide	95
2			<i>trans</i> enamide	98
3			2b, R = OMe	98
4			2c, R = OEt	95
5			2d, R = O ⁱ Pr	80
6			2e, R = O ⁱ Pr	40
7			2f, R = S ⁱ Pr	98 ^b
8			2g, R = S ⁿ Bu	85
9				85 ^c
10				98
11			<i>cis</i> enamide	91
12			<i>trans</i> enamide	72
13				60
14				98
15				71
				98 ^d
16				83

Reaction scheme showing the conversion of enamide **1a-1l** to **N,O-acetal 2a-2r** using XtalFluor-E® (20 mol%) and RXH in DCM (1:1 v/v), where X = O, S.

Entry	Enamide	<i>N,O</i> -acetal	Yield (%)
17			86
18			98
19			98 ^e
21			94
21			98 ^d

^a Reactions were performed at room temperature (0.1 mmol), reported yields are isolated unless otherwise indicated;
^b 1.1 equivalents of nucleophile was used, requiring 48 h for reaction completion, resulting in the same yield;
^c Reaction was performed at 1.0 mmol scale;
^d Yield was determined by ¹H-NMR with methyl *t*-butyl ether as internal standard;
^e HFIP:methanol (9:1 v:v) was used as solvent.