Tetrahedron Letters 52 (2011) 4353–4356

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Brønsted acid-catalyzed C–C bond forming reaction for one step synthesis of oxazinanones

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ARTICLE INFO

Article history:
Received 10 December 2010
Revised 10 June 2011
Accepted 13 June 2011
Available online 2 July 2011

Keywords:
Brønsted acid catalysis
Boc-imines
Oxazinanones
Tandem elimination-cycloaddition

ABSTRACT

An efficient Brønsted acid-catalyzed synthesis of oxazinanones (**2**) from corresponding Boc-imines (**1**) in one-step has been developed. Oxazinanones are obtained via an unprecedented tandem elimination-cycloaddition reaction. The reaction is remarkably significant given its novelty, mild reaction conditions, simplicity and low cost of the catalyst system.

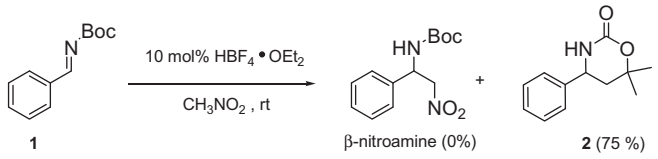
Nitro-Mannich (or aza-Henry) reactions involve catalytic formation of β-nitro amines from Boc-imines and nitroalkanes. Recently, there has been a surge of research in this area of organic chemistry due to the importance of β-nitro amines in organic syntheses.[1] For example, the organocatalytic nitro-Mannich reaction[2,3] has newly become an essential reaction in this area of research, while Brønsted acids[4,5] have been found to be especially effective catalysts. Johnston et al. have investigated several aspects of the chiral Brønsted acid-catalyzed nitro-Mannich reactions of Boc-imines and nitromethane.[4b,c] At about the same time, using various nitroalkanes to aromatic N-Boc imines, Jacobsen et al. reported thiourea-catalyzed nitro-Mannich reactions.[5d] These reactions ultimately form β-nitro amines in excellent yields and in high enantioselectivity.

Our group is actively working with strong Brønsted acid-catalyzed organic reactions in the synthesis of important building blocks of biologically active compounds.[6] In order to expand the scope of strong Brønsted acid-catalyzed reactions in organic chemistry; we investigated nitro-Mannich reactions using Boc-imine with nitromethane in the presence of fluoroboric acid ($HBF_4{\cdot}OEt_2$). Surprisingly, nitromethane did not participate in the reaction and no formation of β-nitro amine product was observed. Instead, we observed the formation of 1,3-oxazinan-2-one in high yield (Scheme 1).

Herein, we report on an unprecedented catalytic tandem elimination-cycloaddition reaction in which the formation of oxazinanones occurs when employing various Boc-imines in the presence of a strong Brønsted acid.

The major difference in our reaction conditions compared to the aforementioned nitro-Mannich reactions is the use of fluoroboric acid. In order to determine whether fluoroboric acid is exclusively unique, we screened several Brønsted acids (Table 1). Several attempts, including a control reaction and reactions employing weaker acids such as acetic acid or triflyl amide, did not yield any oxazinanone product. However, by employing stronger acids such as trifluoroacetic acid, oxazinanone product was efficiently produced in yields of 40% (Table 1, entries 4 and 5). Indeed, Brønsted acids with lower pK_as[7] provided even greater yields of oxazinanone product. Ultimately, the stronger triflic and fluoroboric acids were found to be the most effective catalysts for the reaction as shown in Table 1. A 10 mol % catalyst loading was also found to be most effective; however, an increase in the catalyst loading does not improve the yield (Table 1, entries 1–3 and 7–9).

In order to optimize the yield of the product, we investigated the reaction in different solvents. A preliminary screening revealed that polar aprotic solvents, with the exception of DMF, gave higher yields of the product (entries 1–3, Table 2). A plausible explanation



Scheme 1. $HBF_4{\cdot}OEt_2$ reaction of Boc-imine and nitromethane.

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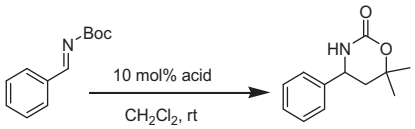
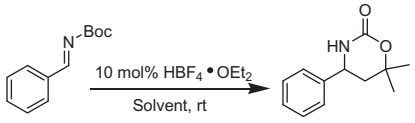
doi:10.1016/j.tetlet.2011.06.054

Table 1
Optimization of catalyst



Entry	Catalyst	$pK_a(H_2O)$	Catalyst loading (mol %)	Yield (%)
1	Triflic acid	−14	10	70
2	Triflic acid		20	70
3	Triflic acid		50	70
4	Trifluoroacetic acid	0.52	20	40
5	Trifluoroacetic acid		30	40
6	Triflyl amide	6.33	20	0
7	Fluoroboric acid	−0.4	10	75
8	Fluoroboric acid		20	75
9	Fluoroboric acid		30	72
10	No acid		—	0
11	Acetic acid	4.76	10	0

Table 2
Optimization of the solvent system



Entry	Solvent	Yield (%)
1	Dichloromethane	70
2	THF	60
3	Acetonitrile	70
4	DMF	0
5	Toluene	0
6	75% Toluene in dichloromethane	35
7	Methanol	20
8	Nitromethane	70

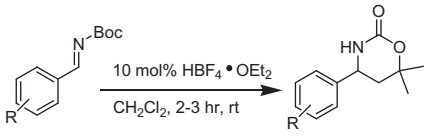
for the apparent absence of yield in DMF is explained by the formation of an iminium ion, produced in consequence of the protonation of DMF by fluoroboric acid. The presence of this ion effectively reduces the acidic strength of the fluoroboric acid catalyst itself (entry 4, Table 2). Reactions in a polar protic solvent such as methanol displayed low yield; conversely, non-polar aprotic toluene exhibited no reaction at all. However, a 3:1 toluene: dichloromethane mixture provided a 35% yield of the product (Table 2, entry 6). Overall, the polar aprotic solvents THF, dichloromethane, acetonitrile, and nitromethane were found to be the best solvents.

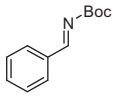
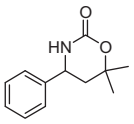
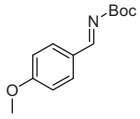
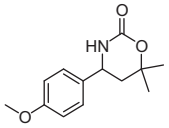
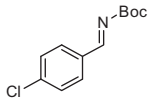
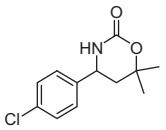
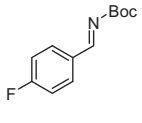
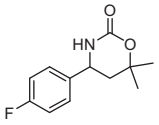
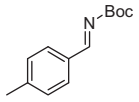
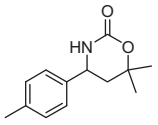
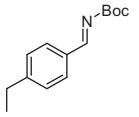
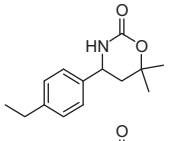
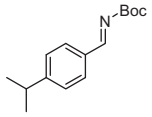
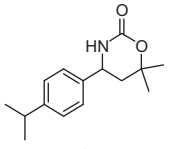
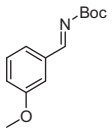
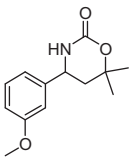
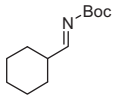
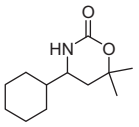
In order to determine the scope of this unprecedented reaction, a number of various Boc-imines were subjected to the newly optimized reaction conditions. Both aromatic and aliphatic Boc-imine provided the corresponding oxazinanones in good yields. However, aromatic imines (Table 3, entries 1–8) were found to be more reactive in these cyclization reactions, resulting in high yields of oxazinanones (65–75%). Electron donating or electron withdrawing groups did not appreciably affect the yields of the products. An aliphatic N-Boc-imine (Table 3, entry 9) could also be used in these reactions with a moderate yield of 50%.

To understand the mechanism of the reaction, we investigated the reaction by NMR spectroscopy.[1]H NMR revealed the presence of 2-methylpropene (Fig. 1) in the reaction mixture which is likely formed from the decomposition of the protonated N-Boc imine **3** (Scheme 2). The resulting 2-methylpropene reacts with Boc-imine in the presence of acid, followed by cyclization to form the oxazinanone product **2**. Evidence of this process is also supported directly by observation using NMR. Indeed, the formation of the phenylmethaniminium ion (**5**, Fig. 1) in the reaction mixture is believed to result from the rapid decarboxylation of **4** in Scheme 2. Several other intermittent species are observed by low temperature NMR, the exact nature of which is still under investigation.

In order to substantiate the formation of 2-methypropene as an intermediate, the reaction was carried out by adding excess 2-methylpropene. The yield of oxazinanone product **2** was

Table 3
Optimized $HBF_4 \cdot OEt_2$-catalyzed reactions of Boc-imine



Entry	Imine	Product	Yield[a] (%)
1			75
2			70
3			75
4			75
5			72
6			72
7			70
8			74
9			50

[a] Isolated yields, the average of at least two runs. In a typical reaction, the *N*-Boc-imines (1.5 mmol) were dissolved in 5 ml CH_2Cl_2 under a N_2 atmosphere and stirred 2–3 h at room temperature with 10 mol % of the Brønsted acid such as fluorobric acid or triflic acid. Acid was removed from the reaction mixture by passing the solution through a plug of neutral alumina. The solvent was removed under reduced pressure and the pure oxazinanone was recrystallized from 5% to 10% CH_2Cl_2 in pentane.

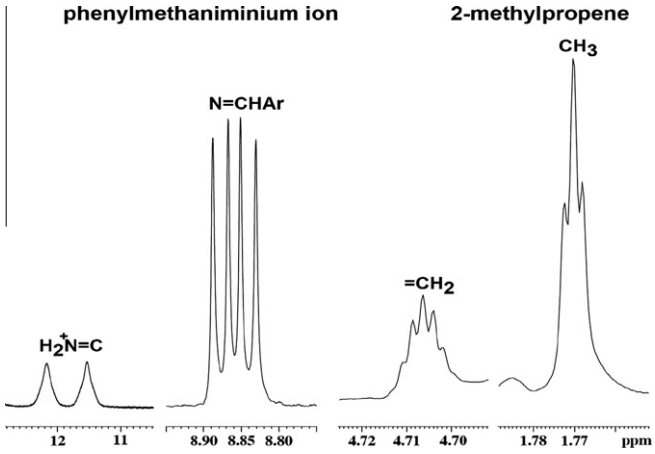
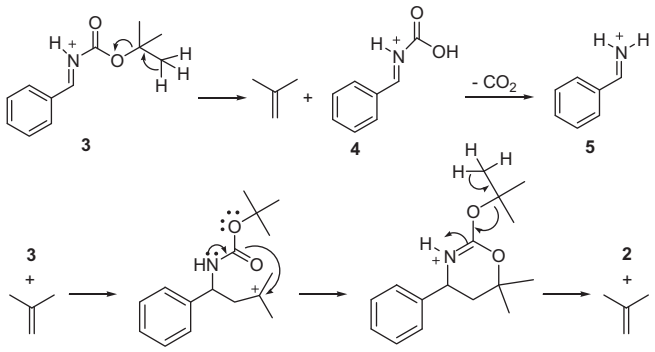


Figure 1. ^{1}H NMR (δ = 1.77 and 4.71 ppm) of 2-methylpropene and phenylmethaniminium ion (δ = 8.55 and 11.9 ppm) in reaction mixture.

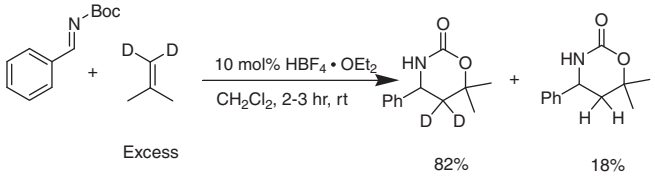


Scheme 2. Proposed mechanism

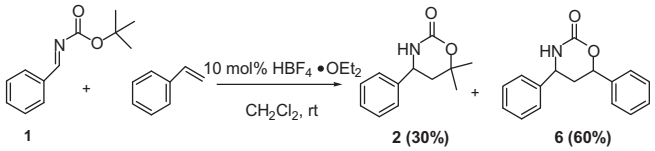
improved upto 95%, corroborating our proposed mechanism. In addition, to verify the incorporation of added 2-methylpropene in the product, a reaction was conducted with fresh Boc-imine and 2-methylpropene-1,1-d_2 in the presence of fluoroboric acid. The results were just as expected, 82% of the product was incorporated with deuterium (Scheme 3) confirming our assumptions of 2-methylpropene in the reaction.

To further understand the mechanism of the reaction, a competitive experiment was carried out in the presence of 1.2 equiv of styrene. In this situation, both alkenes, 2-methylpropene from **1** and styrene, competed with fresh Boc-imine to form the corresponding oxazinanone product. The reaction provided 4,6-diphenyl-(1,3)-oxazinan-2-one **6** along with 4-phenyl-6,6-dimethyl-(1,3)-oxazinan-2-one, **2** (Scheme 4), which strongly supports the proposed mechanism. Recently, a similar mechanism was proposed for the formation of selective oxazinanone ring systems using triflic acid-catalyzed reactions of vinylidene cyclopropanes with Boc-imines.[8]

This intermolecular reaction facilitated the generation of oxazinanones simply by Boc-imines reacting with different styrene derivatives. More exactly, several styrene derivatives were reacted



Scheme 3. $HBF_4{\cdot}OEt_2$ reaction of Boc-imine and 2-methylpropene-1,1-d_2.

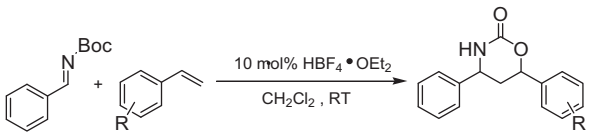


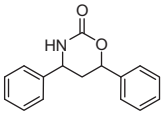
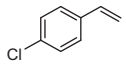
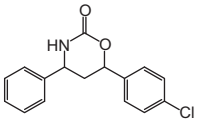
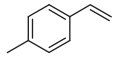
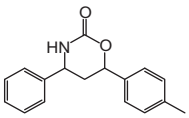
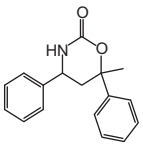
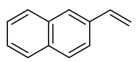
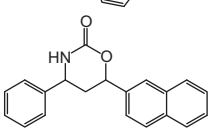
Scheme 4. $HBF_4{\cdot}OEt_2$reaction of Boc-imine and styrene.

with Boc-imines to form the corresponding oxazinanones in good yield (Table 4). Interestingly, α-methylstyrene (Table 4, entry 4) produced an oxazinanone possessed of a fairly congested tertiary carbon center with the highest yield of all. As shown in the earlier proposed mechanism (Scheme 2), the high yield of this product is accounted for by the increased relative stability of the tertiary benzylic carbocation. This latter result, concerning tolerance of steric congestion and the lack of discrimination concerning styrenes containing either EWG or EDG groups (Table 4, entries 2 and 3), further exemplifies the robustness and versatility of this reaction. In 1990, Overman reported a closely related reaction which involved intramolecular Boc-iminium ion-alkyne cycloaddition to form tricyclic systems containing the oxazinanone ring system.[9]

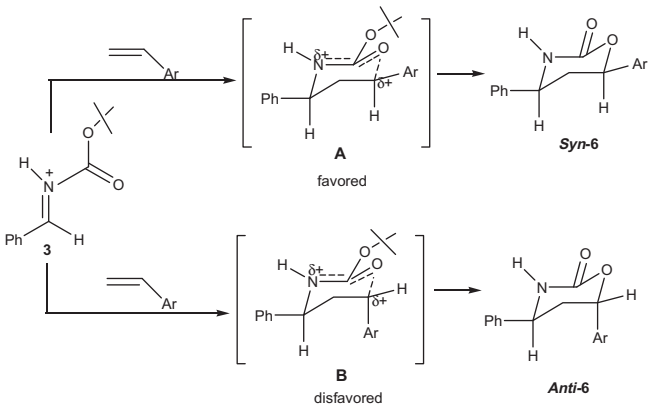
In all these intermolecular reactions, we observed formation of only the *syn*-diastereomer. The configuration of the product was determined by comparing the spin–spin coupling constants with known reported *syn*-compounds.[10] The six-membered transition state **A**, where both bulky aryl groups are equatorial positions (*syn*) will be favorable over transition state **B** with one aryl group

Table 4
$HBF_4{\cdot}OEt_2$-catalyzed reactions of Boc-imine and styrene derivatives



Entry	Styrene	Product	Yield[a] (%)
1			72
2			70
3			70
4			75
5			68

[a] Isolated yields, the average of at least two runs. In a typical reaction, the *N*-Boc-imines (1.3 mmol) and styrene derivative (1.6 mmol) were dissolved in 5 ml CH_2Cl_2 under a N_2 atmosphere and stirred 2–3 h at room temperature with 10 mol % tetrafluorobric acid. Acid was removed from the reaction mixture by passing the solution through a plug of neutral alumina. The solvent was removed under reduced pressure and the pure oxazinanone was recrystallized from 10% CH_2Cl_2 in pentane.



Scheme 5. Proposed rationale for the stereoselective formation of 4,6-diphenyloxazinanone.

at an axial position (Scheme 5). As a result, *syn*-4,6-diaryloxazinanone **6** is expected to be the only or a major product.

To our knowledge, the reaction depicted in Scheme 1 is the first recorded tandem elimination-cycloaddition reaction for the synthesis of an oxazinanone ring system. To date, all of the reported syntheses for making the oxazinanones **2** require three or more steps.[11] The chiral oxazinanones are employed as auxiliaries for asymmetric enolate alkylation and aldol reactions,[11b] and also in the synthesis of oxazolidinone derivatives.[12] Oxazinanone derivatives are of interest because they exhibit antibacterial activity against gram-positive bacteria and are useful as PR modulators.[13] Chiral Brønsted acid-catalyzed syntheses of optically active analogs of oxazinanones are currently under investigation.

In summary, a new C–C bond formation reaction has been developed using Brønsted acid catalysis. Cyclic oxazinanones are produced from Boc-imines in one step, resulting in medium to high yields. The atom-economic process presented here in Scheme 1 is unprecedented in the area of organic chemistry and should extend the scope of C–C bond forming reactions.

Acknowledgments

We thank Professors James M. Cook, Alan W. Schwabacher, and Dr. Matthew E. Dudley of the University of Wisconsin-Milwaukee for their suggestions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.054.

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