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A convenient synthesis of bisamides with BF_3 etherate as catalyst

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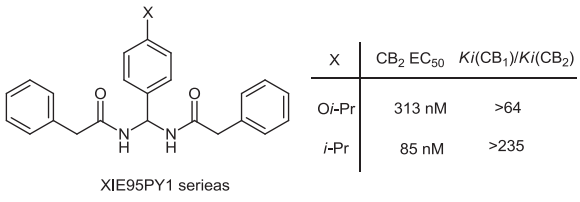
ABSTRACT

A convenient synthesis of bisamide from aldehyde and amide with BF_3 etherate as catalyst was reported. Both aryl and aliphatic bisamides could be prepared with this procedure in high yield at room temperature and the catalyst loading as low as 0.5 mol % was achieved. Fine-tuned solvent was utilized for both rapid conversion and simple isolation. Two CB_2 receptor inverse agonists were synthesized with this protocol in high yield.

1. Introduction

Aminal compounds have been applied in the treatment of high blood pressure and arise the interests from synthetic community.[1] Several enantioselective syntheses of acyclic and cyclic aminal compounds were reported using organocatalysts by Antilla,[2] List,[3] Rueping,[4] and Tian groups,[5] respectively. Recently, Kesavan showed Lewis acid was highly stereoselective catalyst to construct the cyclic aminal chiral center as well.[6] Another type of aminal compound, the methylidene bisamides bearing two *gem*-amide units showed their application as a new class of CB_2 receptor inverse agonist with high efficacy along with the significant CB_1/CB_2 selectivity ($K_i(CB_1)/K_i(CB_2)$) as high as 235 folds. Similar compound could inhibit the osteoclast formation with the IC_{72} of 0.1 μM. The computational studies show the scaffold is important in terms of activity and selectivity (Fig. 1).[7] Besides this significant biological potency, the bisamides were also applied as the ligands in the Ullmann coupling reactions by Pan and co-workers.[8]



X	CB_2 EC_{50}	$Ki(CB_1)/Ki(CB_2)$
O*i*-Pr	313 nM	>64
i-Pr	85 nM	>235

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Fig. 1. The CB receptor inverse agonist with bisamide backbone.

The first synthesis of *gem*-bisamide was achieved via condensation reaction between aldehyde and amide in 1933 by Noyes.[9] There were some good catalytic syntheses of bisamides employing Brønsted acids or Lewis acids as catalysts as well.[10]

Though with these progresses, there were still some challenges: in some conversions utilizing different catalysts, for example, H_2SO_4,[10a] supported sulfonic acid,[10h] *p*-TsOH, $FeCl_3 \cdot 3H_2O$, $ZnCl_2$,[10f] and silica-supported $BaCl_2$,[10g] elevated temperature was required. So far, only TMSOTf[7,10d] was reported as catalyst to effect the conversion at room temperature with 10 mol % loading, which limited the scale-up regarding the catalyst cost. On the other hand, in the solvent free version, the reactions still require the wet workup and purification with organic solvent,[10f,g] which increased the overall E factor.[13] The substrate scope with good yield is still a major concern in the catalysis system. The searching for an inexpensive catalyst for room temperature reaction will also facilitate the syntheses of the bisamides.

We reasoned that the typical pKa values for the protonated aldehyde and amide are −10[11] and −0.5,[12] respectively, which suggests the Brønsted acid is captured by amide instead of the aldehyde. Thus the activation of aldehyde with minor part of Brønsted acid incurs the elevated temperature frequently. So our effort was focused on the Lewis acid catalyzed condensation of aldehyde and amide (Scheme 1). Herein, we would like to report our BF_3 etherate catalysis for more efficient synthesis under mild condition with simple workup for broad substrate range.

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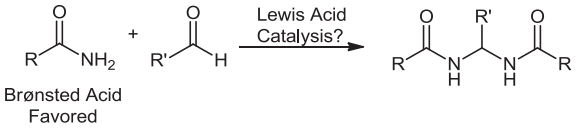
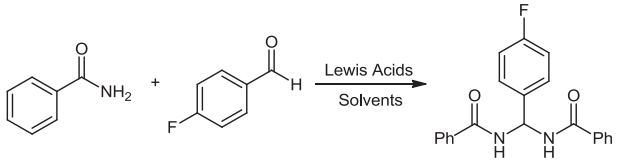


Scheme 1. Catalyzing the reaction with Lewis acid.

2. Results and discussion

The initial study was to screen different kinds of Lewis acids and solvents to identify the most reactive catalyst and medium for the condensation and the results were summarized in Table 1 where *p*-fluorobenzaldehyde and benzamide were employed as standard substrate. To achieve the mild condition, the reaction was locked at room temperature with 10 mol % catalyst. Lewis acids, such as $Ti(O^iPr)_4$, $Mg(ClO_4)_2$, $Sc(OTf)_3$, $Cu(OTf)_2$, CuBr, and $TiCl_4$ did not achieve any positive result (entries 1–6). Widely applied $AlCl_3$ (entry 7) gave only 25% yield. To our delight, BF_3 etherate, a well-known[14] and cheap[15] Lewis acid, increased the yield significantly to 47% in diethyl ether (entry 8). The following solvent optimization revealed that the solubility of both substrate and product play an important role in this process. It was found when the substrate was well soluble and the product could precipitate at low concentration, the reactivity, the ease of workup by filtration, and the high purity of product could meet together. Thus the toluene, DCM, THF, and ethyl acetate (entries 9–12) failed to obtain homogenous solution at the first stage, and in turn diminished the yield and purity of final product. Meanwhile highly polar solvents, such as DMF and EtOH (entries 14 & 15) also failed to enhance the reaction due to their perfect solubility for both substrate and product. To our surprise, acetone, a conventional aldol donor and a relatively green and healthy solvent for room temperature reaction,[16] boosted the yield to 82% (entry 13).

Table 1
The screening for optimum catalyst and solvent[a]



1a

Entry	Catalyst	Solvent	Yield[b]
1	$Mg(ClO_4)_2$	Et_2O	N. D.
2	$Ti(O^iPr)_4$	Et_2O	5%
3	$Sc(OTf)_3$	Et_2O	N. D.
4	$Cu(OTf)_2$	Et_2O	5%
5	CuBr	Et_2O	10%
6	$TiCl_4$	Et_2O	N. D.
7	$AlCl_3$	Et_2O	25%
8	$BF_3{}^*OEt_2$	Et_2O	47%
9	$BF_3{}^*OEt_2$	Toluene	62%
10	$BF_3{}^*OEt_2$	DCM	53%
11	$BF_3{}^*OEt_2$	THF	57%
12	$BF_3{}^*OEt_2$	EA	48%
13	**$BF_3{}^*OEt_2$**	**Acetone**	**82%**
14	$BF_3{}^*OEt_2$	DMF	25%
15	$BF_3{}^*OEt_2$	EtOH	31%

[a] 4-Fluorbenzaldehyde (1.0 mmol), benzamide (2.0 mmol), 0.2 M for aldehyde in solvent. Typical catalyst loading is 10 mol %. The reaction was carried out at room temperature for 120 min.

[b] Isolated yield by filtration for entries 7–15 and NMR yield for entries 2 and 4 and in turn diminished the yield and purity of final product. Meanwhile highly polar solvents, such as DMF and EtOH (entries 14 & 15) also failed to enhance the reaction due to their perfect solubility for both substrate and product. To our surprise, acetone, a conventional aldol donor and a relatively green and healthy solvent for room temperature reaction,[16] boosted the yield to 82% (entry 13).

For a straightforward reaction, it is ideal to get the pure product from reaction mixture directly even without recrystallzation.[17] Herein, the convenience of this protocol was demonstrated in Fig. 2, where the reaction (entry 13) started as a reddish clear solution of aldehyde, amide, and BF_3 etherate in acetone and ended as a white gel. The pure solid product **1a** could be collected by simple filtration.

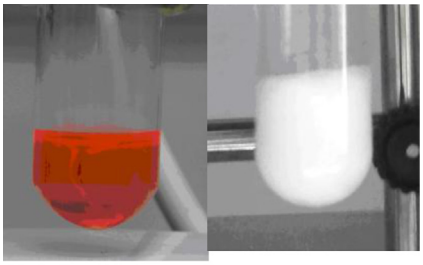


Fig. 2. The product **1a** was achieved as white gel.

Encouraged by these results, we explored a variety of aldehydes and amides with BF_3 etherate as the catalyst (Table 2). The aromatic aldehyde bearing electron-withdrawing group gave faster conversion than 3-methoxysalicylaldehyde (**1a** vs **1h**). The aromatic aldehydes containing bromide were favored due to the enhanced precipitation (**1d**–**f**). To our delight, several functional groups, such as phenol and thiophenyl were well compatible without significant impact on the yield (**1h**–**j**). The electronic effect on aromatic amide was also investigated and it was found that both electron withdrawing (**2a**–**c**) and electron donating groups (**3a**–**c**, **4a**,**b**) benefit the reactivity. The amides, such as cinnamide, acrylamide, phenylacetamide, and thienylacetamide gave corresponding bisamide (**5a**,**b**, **6**, **7a**–**e**, **8a**–**e**) as precipitate with high yield. Meanwhile, the fully aliphatic amides reacted with a variety of aldehydes, offering bisamides (**9a**–**e**, **10a**,**b**) in the same manner.

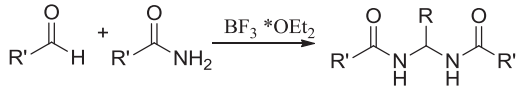
The catalytic efficiency of BF_3 etherate was measured with the reaction toward **7b** employing catalyst loading from 10 mol % to 0.5 mol % at room temperature. It was clear that with extended reaction time, 0.5 mol % catalyst worked well almost without any compromise of productivity (Table 3).

To explore the scalability of this conversion, the preparation of **1m** was scaled up to 1 mol with 1 mol % BF_3 etherate as catalyst. The reaction finished in 12 h in the yield of 82% and the product was pure as well as that from the routine scale.

A plausible mechanism for this conversion was illustrated in Scheme 2. The cycle commences from the coordination of aldehyde to the BF_3 and the activated carbonyl is attacked by the amide to form the hemi aminal intermediate **A** in which the hydroxyl is removed with the help of Lewis acid and *gem*-amide group. In turn, the enamide ion pair intermediate **B** may react with the second amide directly to give the bisamide intermediate **C** and yield the final bisamide after dehydration. On the other hand the enamide ion pair intermediate B may dehydrate prior to the nucleophilic addition of the second amide and gave the overall same product through intermediate **D**. In the presence of hydrogen bonding acceptor and lone electron pair donor, such as acetone and diethyl ether, the reaction between water and BF_3 to form fluoroboric acid can be inhibited, which ensures the BF_3 enter the next catalytic cycle.

As a demonstration, CB_2 receptor inverse agonists **11** and **12** were synthesized with BF_3 etherate as catalyst in ether, a solvent fine-tuned for the product (Scheme 3). The reaction gave rise to the target as precipitate in good to excellent yield.

Table 2
The substrate scope with BF_3 etherate as catalyst[a]



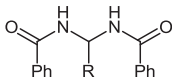
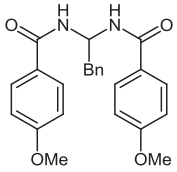
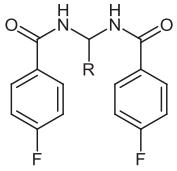
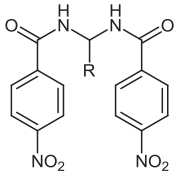
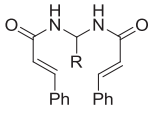
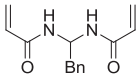
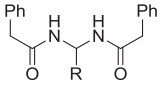
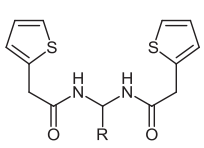
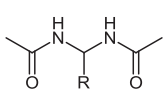
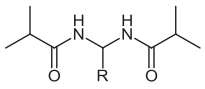
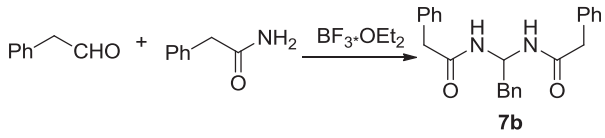
Backbone	Compound number	Reaction time (min)	Yield[b]
	**1a** R=4-F–Ph	120	82%
	1b R=2-F–Ph	90	88%
	1c R=2-Cl–Ph	200	72%
	1d R=4-Br–Ph	60	90%
	1e R=3-Br–Ph	180	82%
	1f R=2-Br–Ph	160	71%
	1g R=Ph	120	68%
	1h R=2-OH–3-OMe-Ph	400	80%[c]
	1i R=thiophene-3-yl	50	94%[c]
	1j R=5-Br–thiophene-2-yl	40	90%[c]
	1k R=Styrenyl	120	72%[c]
	1l R=Bn	60	91%
	1m R=*n*-Bu	15	86%
	**2a** R=4-F–Ph	300	71%
	2b R=4-Br–Ph	120	92%
	2c R=Bn	25	93%
	**3a** R=4-Br–Ph	30	90%
	3b R=Bn	40	90%
	3c R=*n*-Bu	30	93%
	**4a** R=Bn	5	98%
	4b R=*n*-Bu	20	98%
	**5a** R=Bn	25	90%
	5b R=*n*-Bu	25	90%
	**6**	200	81%
	**7a** R=2-Br–Ph	200	86%
	7b R=4-Br–Ph	160	78%
	7c R=2-F–Ph	300	70%
	7d R=Bn	25	94%
	7e R=2-Ph–ethyl	25	92%
	**8a** R=4-Br–Ph	45	92%
	8b R=Bn	30	90%
	8c R=5-Br–thiophene-2-yl	45	92%[c]
	8d R=Thiophene-3-yl	50	88%[c]
	8e R=*n*-Bu	36	91%
	**9a** R=4-Br–Ph	180	71%
	9b R=2-OH–3-OMe-Ph	400	70%[c]
	9c R=Bn	240	88%
	9d R=5-Br–thiophene-2-yl	30	89%[c]
	9e R=*n*-Bu	30	75%

Table 2 (*continued*)

Backbone	Compound number	Reaction time (min)	Yield[b]
	**10a** R=Ph	10	75%
	10b R=*n*-Bu	180	81%

[a] Aldehyde (1.0 mmol), amide (2.0 mmol), and BF_3 etherate (10 mol %) was stirred in acetone at room temperature for the given time.
[b] Isolated yield by filtration.
[c] Et_2O was used instead of acetone to favor precipitation.

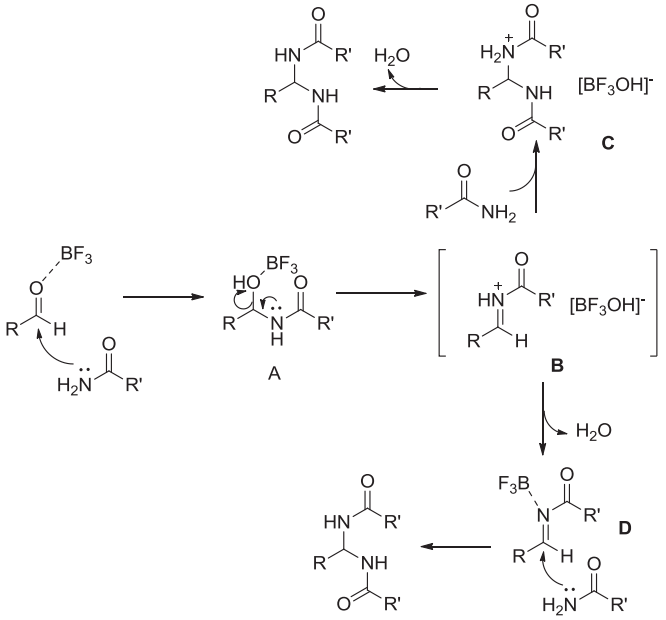
Table 3
The catalyst loading experiment[a]



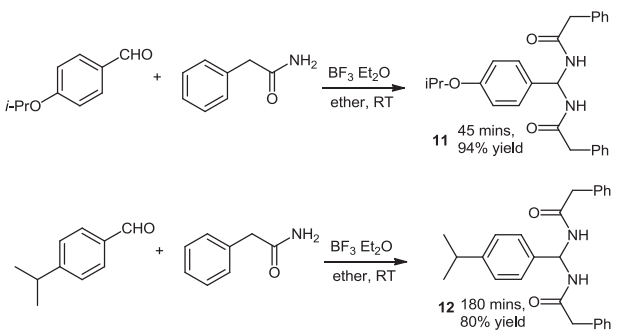
7b

Entry	BF_3*OEt_2 loading	Reaction time (h)	Yield[b]
1	10%	0.5	94%
2	5 mol %	6	91%
3	2 mol %	15	91%
4	0.5 mol %	23	89%

[a] Phenylacetaldehyde (1.0 equiv), phenylacetamide (2.0 equiv), 0.2 M for aldehyde in acetone at room temperature.
[b] Isolated yield by filtration.



Scheme 2. Plausible mechanism for the formation of bisamide.



Scheme 3. The synthesis of CB_2 receptor inverse agonists.

3. Conclusion

In conclusion, we developed a mild, efficient, and convenient procedure for bisamides using low-cost catalyst with substrate scope from aromatic to aliphatic compounds at room temperature. The catalyst loading could be lowered to 0.5 mol % with retained yield and the reaction could be scaled up to 1 mol. The procedure was applied in the synthesis of two CB_2 receptor inverse agonists.

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Supplementary data

The general procedure, analysis data of new compounds, and NMR spectra. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2013.11.017.

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