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Sodium carbonate mediated regioselective synthesis of novel *N*-(hydroxyalkyl)cinnamamides

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Dedicated to Dr. Sunita Dhingra on her 65th birthday

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ABSTRACT

A synthetic protocol for the direct synthesis of *N*-(hydroxyalkyl)cinnamamides from cinnamates and aminoalcohols in the presence of sodium carbonate as the base is presented. A wide variety of *N*-(hydroxyalkyl)cinnamamides were isolated in up to 99% yields. The reaction is highly regioselective and yields only *N*-acylated products by 1,2-addition of aminoalcohols to cinnamates.

Amide functionality is present in a variety of natural products, biologically active compounds, pharmaceutical drugs, polymeric materials, insecticides, etc. It is also the key linkage in peptides and proteins. Generally, the synthesis of amide bond is carried out by amidation of an acid chloride or ester with an amine in the presence of a base, under harsh conditions for example use of strong base, high reaction temperature or pressure, etc.[1] In the past many new methods for the synthesis of amide bond have been reported. However, most of these methods use expensive reagents or catalysts for amidation.[2] Recent reports on the use of inexpensive catalysts like boric acid[3] and activated alumina balls[4] for amide bond formation from carboxylic acids and amines are promising synthetic strategies, but these procedures require high reaction temperatures.

As part of our ongoing research on the synthesis of biologically active compounds, we were interested in the synthesis of new *N*-(hydroxyalkyl)cinnamamides because this class of compounds have shown promising anti-convulsant,[5] muscle relaxant[6] and anti-depressant[5b,7] activities (Fig. 1). *N*-(hydroxyalkyl)cinnamamides are also important building blocks for the preparation of synthetically useful molecules such as oxazolines, oxazolinium salts, benzoxazoles,[8] and photoresponsive polymers.[9]

Generally, *N*-(hydroxyalkyl)cinnamamides are synthesized by conventional methods of amidation that require hazardous chemicals like thionyl chloride or methylchloroformate to generate activated carboxylic acids.[5,10] Thus we became interested in exploring the possibility of using less hazardous reagents for the synthesis of *N*-(hydroxyalkyl)cinnamamides. We came across reports on amidation of unactivated esters by aminoalcohols under mild conditions in the presence of catalytic amount of expensive organobases.[11] We reasoned that aminoalcohols, being reactive amines, should be able to react with cinnamates in the presence of readily available bases. Our reasoning was further supported by a recent report on amidation of a benzoate by ethanolamine using catalytic amount of sodium methoxide as a base, wherein a mixture of hydroxyl amide and amino ester was obtained.[12] Herein, we wish to report a new route to *N*-(hydroxyalkyl)cinnamamides via 1,2-addition of aminoalcohols to methyl cinnamates in the presence of inexpensive and readily available Na_2CO_3 as the base. It is noteworthy that no corresponding amino esters or 1,4-addition products were isolated.

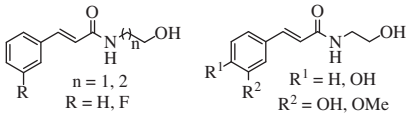

Figure 1. Examples of some biologically active *N*-(hydroxyalkyl)cinnamamides.

Various cinnamates were synthesized by Pd-catalyzed cross-coupling reactions of aryl bromides with acrylates.[13] We started our work by trying amidation of methyl 4-acetylcinnamate **1a** with ethanolamine **2a** in methanol in the presence of a variety of

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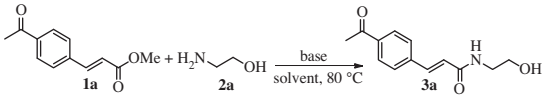
organic (Et_3N, DBU, NaOAc) as well as inorganic (KOH, K_2CO_3, Na_2CO_3) bases. With these bases, (*E*)-*N*-(2-hydroxyethyl)-4-acetylcinnamamide **3a** was obtained in moderate to excellent yields (Table 1, entries 1–6). Na_2CO_3 turned out to be the best base, the amidation of **1a** was accomplished at 80 °C within 1.25 h to give **3a** in 99% isolated yield (Table 1, entry 6). Next, we tried the amidation with catalytic amount of Na_2CO_3 (20 mol %), however, the yield of **3a** reduced to 82% (Table 1, entry 7). Also, the product yield reduced drastically to 44% on attempting the amidation with ethyl 4-acetylcinnamate **1j** (Table 1, entry 8). Interestingly, when ethanol was used as the solvent, the yield of **3a** reduced to 60% (Table 1, entry 9). Other solvents like DMF, NMP, or toluene also reduced the yield of **3a** (Table 1, entries 10–12). The concentration of ethanolamine **2a** (5.0 mmol) was also crucial for the success of this reaction as a decrease in the concentration of **2a** from 5.0 to 2.5 mmol, decreased the yield of **3a** to 54% (Table 1, entry 13). The amidation of ester **1a** can also be carried out at room temperature, however, only 77% yield of **3a** was isolated even after performing the reaction for 7 h (Table 1, entry 14). In addition, this transformation was also feasible in the absence of any base, but the reaction was sluggish giving only 46% of **3a** in 2 h (Table 1, entry 15). Furthermore, this transformation was not air and moisture sensitive, and therefore all the reactions were performed in air, without drying methanol prior to use.

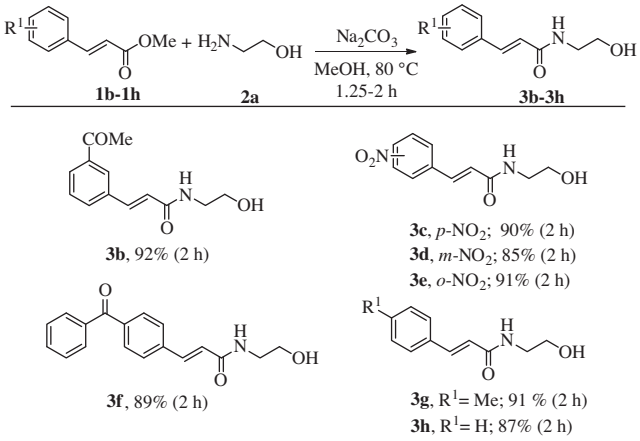
Next we examined the amidation of a variety of cinnamates (**1b**–**1h**) with **2a** in the presence of Na_2CO_3 (Scheme 1). All the esters bearing electron withdrawing or electron donating groups on the aromatic ring afforded the corresponding cinnamamides **3b**–**3h** in excellent yields (85–92%). It is noteworthy that these reactions showed high regioselectivity as the amidation proceeded exclusively via 1,2-addition of **2a** to the ester carbonyl group of the α,β-unsaturated esters **1a**–**1h** followed by the elimination of the methoxide anion to afford the corresponding cinnamamides **3a**–**3h**. No products arising out of 1,4-addition to α,β-unsaturated esters[14] were observed and only clean *N*-acylated products were isolated.

Table 1
Optimization of reaction conditions[a]

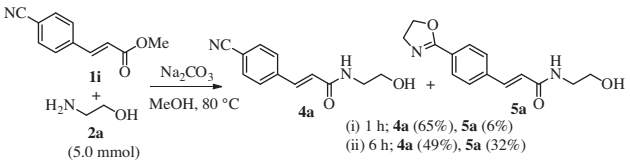


Entry	Base	Solvent	Time (h)	Yield[b] (%)
1	Et_3N	MeOH	2	56
2	DBU	MeOH	1	88
3	NaOAc	MeOH	2	66
4	KOH	MeOH	0.5	87
5	K_2CO_3	MeOH	1.25	93
6	Na_2CO_3	MeOH	1.25	99
7[c]	Na_2CO_3	MeOH	1.25	82
8[d]	Na_2CO_3	MeOH	1.25	44
9	Na_2CO_3	EtOH	2	60
10	Na_2CO_3	DMF	2	41
11	Na_2CO_3	NMP	2	63
12	Na_2CO_3	Toluene	2	40
13[e]	Na_2CO_3	MeOH	1.25	54
14[f]	Na_2CO_3	MeOH	7	77
15	—	MeOH	2	46

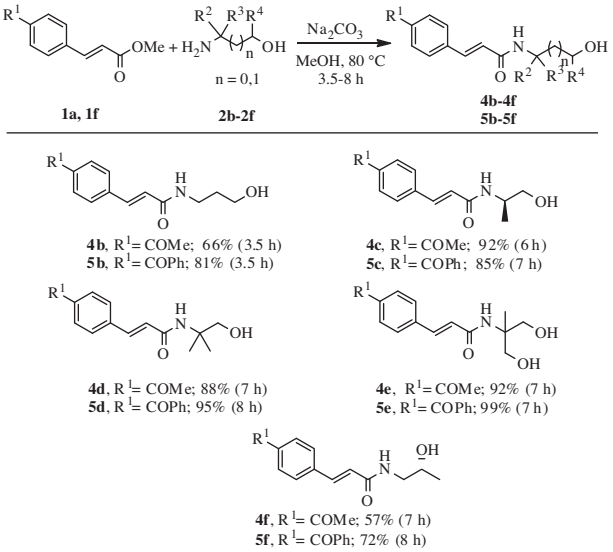
[a] Unless otherwise noted, reaction was carried out with ester **1a** (1.0 mmol), ethanolamine **2a** (5.0 mmol), base (1.0 mmol), solvent (1.0 mL) at 80 °C.
[b] Isolated yields.
[c] Using 20 mol % of Na_2CO_3.
[d] Using ester **1j**.
[e] Using 2.5 mmol of **2a**.
[f] At room temperature.



Scheme 1. Scope of amidation for esters.



Scheme 2. Amidation of ester **1i** with ethanolamine **2a**.



Scheme 3. Scope of amidation for aminoalcohols.

Interestingly, on performing amidation of methyl 4-cyanocinnamate **1i** with **2a** in the presence of Na_2CO_3 for 1 h, 65% of desired cinnamamide **4a** was isolated along with 6% of oxazoline **5a**, and some unidentified product (Scheme 2). When we tried to increase the yield of **4a** by carrying out the same reaction for a longer duration (6 h), the yield of **4a** dropped to 49% with an increase in the isolated yield of oxazoline **5a** to 32%. Thus, we concluded that oxazoline **5a** was being formed due to the reaction of nitrile group with an excess of ethanolamine. To the best of our knowledge, this is the first example of direct oxazoline formation from nitrile and ethanolamine under mild reaction conditions without the use of any metal catalysts and/or high temperatures.[15]

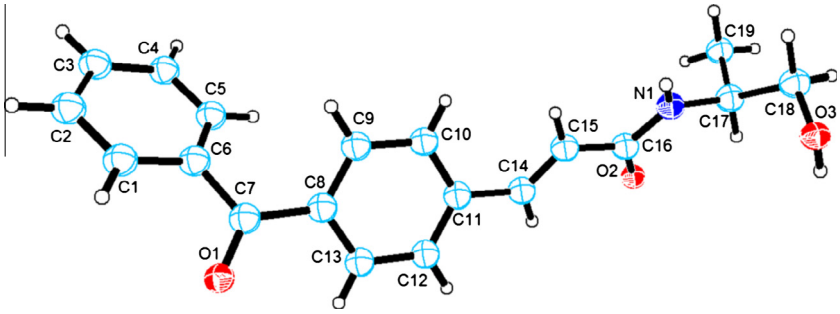


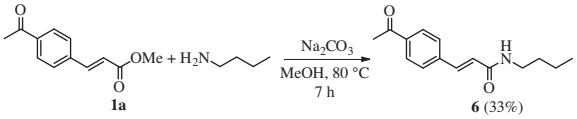
Figure 2. ORTEP view of (*E*)-*N*-((2*R*)-1-hydroxypropan-2-yl)-4-benzoylcinnamamide **5c**. Thermal ellipsoids are drawn at 50% probability level for non-hydrogen atoms.

Next we explored the scope and limitations of various aminoalcohols in the amidation reaction (Scheme 3). All the aminoalcohols reacted regioselectively to give the corresponding cinnamamides (**4b–4f**; **5b–5f**) in good to excellent yields (57–99%). Increasing the chain length from ethyl to propyl in aminoalcohol moiety, reduced the yields of cinnamamides **4b** (66%) and **5b** (81%). The influence of steric factors was quite apparent, the reactions involving sterically hindered aminoalcohols **2c–2f** required a longer reaction time (6–8 h) to produce the corresponding cinnamamides in high yields. However, in all the cases, exclusively *N*-acylated products were obtained by 1,2-addition to α,β-unsaturated esters.

The reaction with chiral aminoalcohols **2c** and **2f** proceeded with complete retention of configuration. The single crystal X-ray analysis confirmed the absolute configuration of **5c** and **5f** to be *R* which is the same as the starting chiral aminoalcohols **2c** and **2f** (Fig. 2; see Fig. S2–S6 and Table S1 in SI). Also, the crystal structures showed the *trans*-configuration of the amide bond as well as the olefinic bond.[16]

Amidation of ester **1a** with *n*-butylamine afforded only 33% of (*E*)-*N*-butyl-4-acetylcinnamamide **6** in 7 h (Scheme 4). Thus these reaction conditions are more suitable for reactive amines such as aminoalcohols.

To gain an insight into this Na_2CO_3 mediated transformation of cinnamates into cinnamamides with respect to time, the progress of the reaction of ester **1a** with aminoalcohol **2a** was monitored by ^1H NMR. The reaction profile shown in Figure 3 provides information regarding the change in % of ester conversion as a function of time. Within the first 20 min, 83% of the ester **1a** was converted into cinnamamide **3a**. Interestingly, the rate of ester conversion slowed down afterward and reached >99% at 75 min. The decreased rate of ester conversion could be due to increased aggregation of the active centers as the reaction mixture became very viscous after 20 min.



Scheme 4. Amidation of ester **1a** with *n*-butylamine.

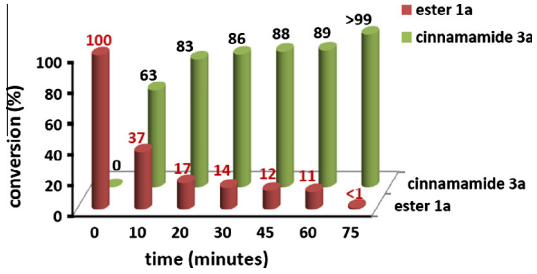


Figure 3. Reaction profile for amidation of ester **1a** with ethanolamine **2a** in the presence of Na_2CO_3.

The literature reports suggest that the conversion of unactivated esters into amidoalcohols proceed via transesterification followed by subsequent *N*,*O*-acyl rearrangement[11c,17] to give the corresponding amidoalcohols. However, despite our numerous efforts we could not isolate any amino ester. So, at this stage it is difficult to comment on the involvement of *N*,*O*-acyl rearrangement under our reaction conditions.

In conclusion, we have reported a direct and efficient synthetic protocol for the synthesis of *N*-(hydroxyalkyl)cinnamamides from cinnamates and aminoalcohols in the presence of inexpensive, non-toxic, and readily available Na_2CO_3 as the base. This reaction is highly regioselective as the addition of aminoalcohols to cinnamates follows 1,2-addition pathway exclusively to give *N*-(hydroxyalkyl)cinnamamides. Further studies on the biological activities of the newly synthesized *N*-(hydroxyalkyl)cinnamamides and the mechanistic aspects of the transformation are currently underway in our laboratory.

Acknowledgment

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Supplementary data

Supplementary (^1H, $^{13}C\{^1H\}$ NMR spectroscopic and HRMS) data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.10.086. These data include MOL files and InChiKeys of the most important compounds described in this article.

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16. Crystallographic data for compound 5c and 5f have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 957164 and 957165. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax:+44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or via http://www.ccdc.cam.ac.uk/data_request/cif).
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