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A facile one-pot domino reaction for the stereoselective synthesis of acryl derivatives promoted by $Ca(OTf)_2$

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ABSTRACT

A facile one-pot domino reaction for the stereoselective synthesis of acryl derivatives has been reported using alkaline earth catalyst [$Ca(OTf)_2$]. Initially aryl amine reacts with ethyl propiolate to form β-enamino ester which further reacts with aryl aldehyde and indole in the presence of $Ca(OTf)_2$ to give indolyl acrylates. It is interesting to note that in the absence of indole the reaction leads to the formation of benzylidene bisacrylates. Similarly β-enamino ester reacts with another electrophilic partner isatin in the presence of $Ca(OTf)_2$ to give oxindolyl acrylates. The products were isolated in good yields by simple filtration.

Multicomponent reactions and domino reactions provide a sustainable and diversity oriented synthesis of novel heterocyclic molecules in one-pot.[1] In addition they offer atom economy and step economy synthesis, domino reactions are also treated as eco-friendly reactions because they minimize the usage of large amounts of organic solvents which are used to purify the intermediates in each step through column chromatography.[1] On the other hand, the active intermediate β-enamino ester which results from the addition of primary amines to electron deficient alkynes is known as a key building block for the synthesis of various heterocycles and pharmaceutical compounds.[2,3] Several domino reactions were developed to trap the β-enamino ester with a wide variety of electrophiles and nucleophiles in a sequence to generate the novel nitrogen containing heterocyclic scaffolds.[4–10] When we looked into the literature there are very few reports available for the synthesis of indolyl acrylates (**5**), oxindolyl acrylates (**8**), and benzylidene (**6**) bisacrylates from the active β-enamino ester.[11,12] Yan et al. reported an efficient $FeCl_3$ catalyzed domino synthesis of indolyl acrylates at rt with moderate yields and the reaction took 30 h for completion.[11] Later the same group reported the synthesis of arylidene bisacrylates and oxindolyl acrylates using $FeCl_3$ as the catalyst.[12] Albeit the elegant methods available for the synthesis of indolyl acrylates, oxindolyl acrylates, and arylidene bisacrylates, it is highly desirable to develop an alternative catalytic system (non-transition metal catalyst) to reduce the reaction time and enhance the product yields. In continuation of our research aimed toward the novel synthesis of heterocyclic molecules using alkaline earth catalysts (as an alternative to transition metal catalysts)[13] herein we report a $Ca(OTf)_2$ catalyzed domino reaction for the synthesis of indolyl acrylates, oxindolyl acrylates, and arylidene bisacrylates.

Initially we planned to study the synthesis of indolyl acrylates which involves the four component domino reaction of aniline, ethyl propiolate, aryl aldehyde, and indole. Literature studies illustrate that there are two stages in the reaction. First stage aniline and ethyl propiolate react at rt in ethanol to give active β-enamino ester, but the second stage requires activation (in the form of a catalyst) to trap the β-enamino ester with suitable electrophilic reagents.

We commenced our synthesis by reacting stoichiometric amounts of aniline and ethyl propiolate in ethanol at rt and observed the formation of β-enamino ester after 12 h; the stoichiometric amounts of benzaldehyde and indole were added to the above reaction mixture along with 5 mol % of $Ca(OTf)_2$ and 5 mol % Bu_4NPF_6 (additive) and continuously stirred at rt for 12 more

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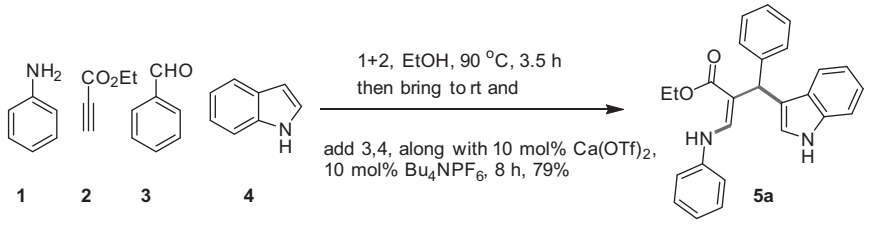
hours and isolated ethyl (*Z*)-2-((1*H*-indol-3-yl)(phenyl)methyl)-3-(phenylamino)acrylate (**5a**) in 65% yield. The product was confirmed by ^{1}H & ^{13}C NMR and mass data.[15,16] The stereoselectivity of the product was established previously using single crystal X-ray diffraction and proved that due to the hydrogen bonding interactions between ester oxygen and amines proton the compound exists only in the *Z*-form.[11] In order to decrease the reaction time the catalyst was added in the first stage and found that there was no change in the reaction time. Nevertheless when aniline and ethyl propiolate were refluxed in ethanol at 90 °C the formation of β-enamino ester took place in 3.5 h only. Addition of catalyst had no role in the first step as the reaction was thermodynamically accelerated (reaction time decreased from 12 h to 3.5 h). Having improved the first stage of synthesis we were interested to optimize the second stage addition (Table 1). Among the several catalyst loadings tried, we found that the second stage was better with 10 mol % of $Ca(OTf)_2$ and 10 mol % Bu_4NPF_6 at rt which gave 79% yield after 8 h (Scheme 1). When the reflux was continued in the second stage we observed the formation of bis(indolyl methane) as the major product (Table 1, entry 4) and hence reaction was brought to rt and continued there. The reaction could not yield better when refluxed in water (20%, 20 h) acetonitrile (35%, 20 h) and under solvent free conditions (50%, 24 h). Entry 12 (Table 1) describes that when KPF_6 was used as the additive instead of Bu_4NPF_6 only 30% of the product was isolated. Similarly we replaced $Ca(OTf)_2$ with another calcium salt $CaCl_2$ which yielded 48% of the product after 18 h (entry 13). After discovering the suitable reaction conditions we were interested to study the substrate scope of our methodology. Initially we chose to test the participation of various aromatic aldehydes bearing electron withdrawing substitutions, electron donating groups and halogen atoms and found that all these aldehydes equally participated in the reaction to give the desired products in moderate to good yields (**5a**–**5k**, Table 2). Encouraged by the broad scope of aldehydes we further looked into the scope of 5-bromo indole and 5-methoxy indole to furnish respective indolyl acrylates **5l**–**5p** and **5q**–**5u** in good yields (Table 2). 4-Chloro aniline was also used along with indole and different aryl aldehydes to prepare the acrylates **5v**–**5y** in good yields. 4-methyl aniline (electron donating group) when treated with ethyl and methyl propiolates yielded **5z** and **5aa** in 73% and 70%, respectively (Table 2). When *ortho*-substituted anilines (2-bromoaniline and 2-hydroxy aniline) were used in the reaction with methyl propiolate we could notice only traces of β-enamino ester and hence the second stage addition was not performed. Probably the reaction is prohibited by the steric factor.

Driven by this observation we went on for making the arylidene bisacrylates (**6**, Table 3) taking the advantage that the above reaction should be performed in the absence of external nucleophile (indole). As proposed we treated aniline and ethyl propiolate in ethanol at 90 °C for 3.5 then added 0.5 equiv of benzaldehyde along with 10 mol % of catalyst and additive. The reaction was continued at reflux for 6.5 h more to isolate diethyl (2*Z*,4*Z*)-3-phenyl-2,4-bis((phenylamino)methylene)pentanedioate (**6a**) in 81% yield after simple filtration (Table 3). Though the first step has a temperature effect, the second one was not influenced by the raise in temperature (second stage took 7 h at rt) and hence we continued the second step at rt. Benzylidene bisacrylates **6b** and **6c** were made using same conditions in 82% and 80% yields. Methyl propiolate was treated with aniline and 4-nitrobenzaldehyde to make compound

Table 1
Screening of reaction conditions for the second step of the reaction[a]

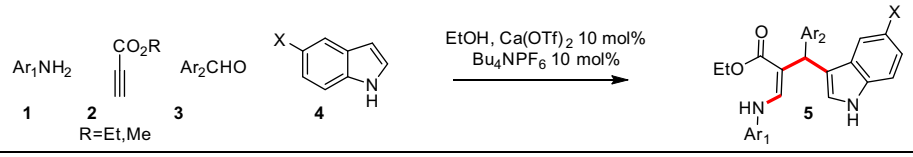
Entry	Catalyst (mol %)	Additive (mol %)	Solvent	Temperature (°C) & time[b]	Yield[c] (%)
1	$Ca(OTf)_2$, 5	Bu_4NPF_6, 5	EtOH	Rt, 12 h	50
2	$Ca(OTf)_2$, 10	Bu_4NPF_6, 5	EtOH	Rt, 12 h	62
3[d]	$Ca(OTf)_2$, 10	Bu_4NPF_6,10	EtOH	Rt, 8 h	79
4[e]	$Ca(OTf)_2$, 10	Bu_4NPF_6,10	EtOH	90, 12 h	15[e]
5	$Ca(OTf)_2$, 10	Bu_4NPF_6,10	Neat	Rt, 24 h[e]	50
6	$Ca(OTf)_2$, 10	Bu_4NPF_6,10	CH_2Cl_2	Rt, 24 h	30
7	$Ca(OTf)_2$, 10	Bu_4NPF_6,10	H_2O	Rt, 20 h	20
8	$Ca(OTf)_2$, 10	Bu_4NPF_6,10	MeCN	Rt, 20 h	35
9	$Ca(OTf)_2$,10	—	EtOH	Rt, 12 h	30
10	—	Bu_4NPF_6,10	EtOH	Rt, 12 h	35
11	—	—	EtOH	Rt, 18 h	5
12	$Ca(OTf)_2$, 10	KPF_6, 10	EtOH	Rt, 12 h	30
13	$CaCl_2$, 10	Bu_4NPF_6,10	EtOH	Rt, 18 h	48

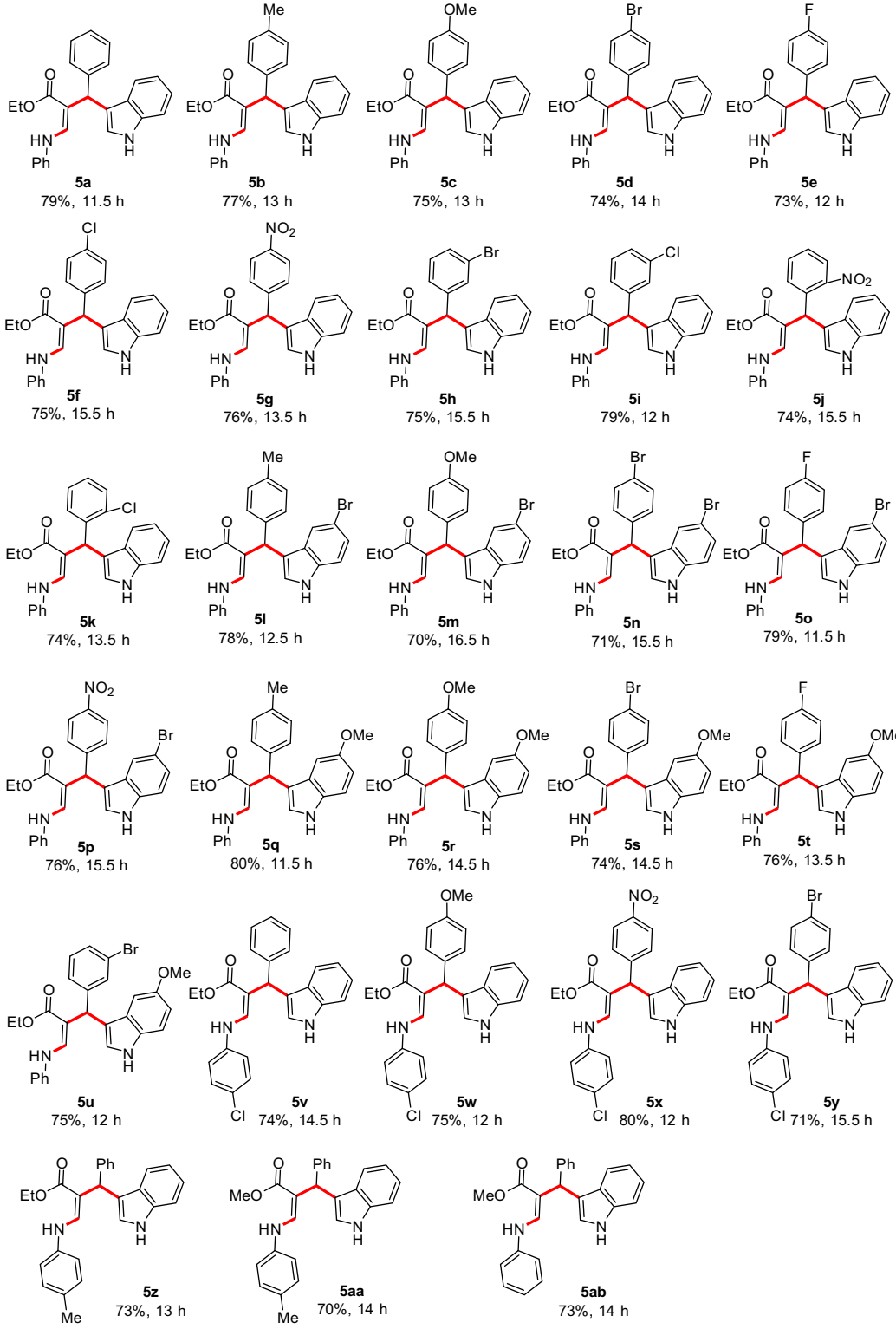
[a] First step of the reaction proved to be efficient at reflux condition (3.5 h).
[b] No progress was observed after the time mentioned.
[c] Isolated yields.
[d] Optimum conditions.
[e] Bisindolyl methane was observed as the major product.



Scheme 1. Calcium catalyzed one-pot, 4-component domino approach for the synthesis of indolyl-3-acrylates.

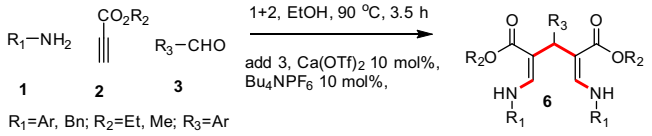
Table 2
$Ca(OTf)_2$ promoted one-pot, 4-component domino approach for the synthesis of indolyl-3-acrylates[a]

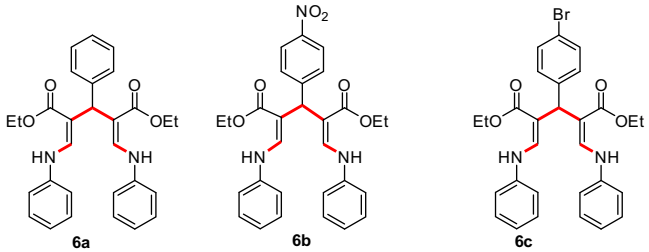




[a] Reaction conditions: 1.1 equiv of aniline and 1.1 equiv of ethyl propiolate were refluxed in ethanol at 90 °C for 3.5 h then reaction was brought to rt and 10 mol % $Ca(OTf)_2$, 10 mol % Bu_4NPF_6 were added along with 1 equiv of aldehyde and 1 equiv of indole. Yields are reported after filtration.

Table 3
Ca(II) catalyzed one pot three component domino reaction for the synthesis of arylidene bisacrylates[a]





[a] Reaction conditions: aniline (1.1. equiv) and ethyl propiolate (1.1 equiv) were refluxed in ethanol at 90 °C for 3.5 h then aldehyde (0.5 equiv) was added along with catalyst and additive. Yields are reported after isolation by filtration.

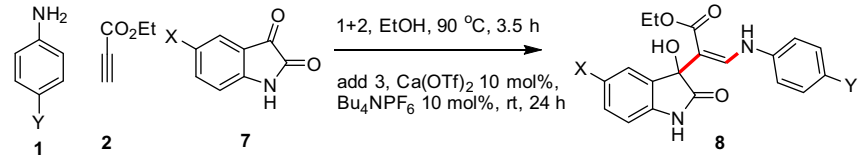
6d in 78% yield. Similarly benzylamine was also used to make the arylidene bisacrylates **6e** and **6f** in 76% and 75%, respective yields (Table 3).

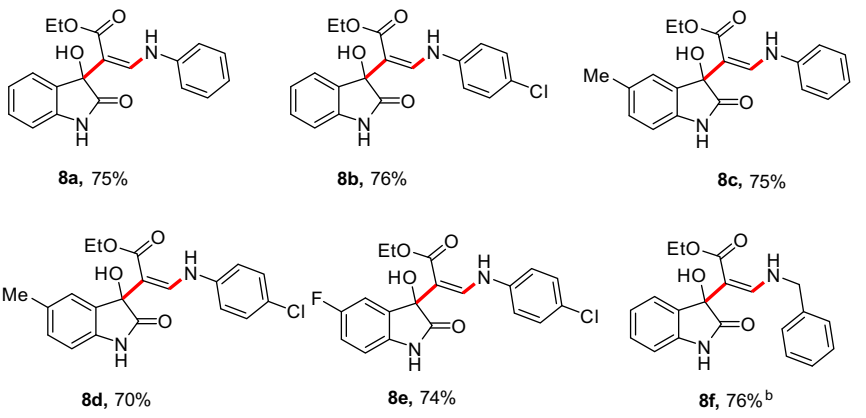
Due to the potential applications of oxindole derivatives in organic and medicinal chemistry[14] we aimed to use isatin as the electrophile in the second stage instead of aldehyde to make valuable oxindolyl derivatives. Aryl amine and ethyl propiolate were refluxed in ethanol at 90 °C for 3.5 h then reaction was brought to rt (as we did not notice any advantage in terms of time or yields to continue the reaction further at reflux) and isatin was added along with catalyst and additive (Table 4) to make the oxindolyl acrylates **8a** to **8f** in good yields.

Plausible mechanism for the Ca(II) catalyzed domino reaction for the synthesis of acryl derivatives has been described in the Scheme 2. Initially conjugate addition of aniline to ethyl propiolate will take to provide the β-enaminoester. Since the formed intermediate is nucleophilic in nature it reacts with isatin in the presence of $Ca(OTf)_2$ to yield oxindolyl acrylate **8** via nucleophilic substitution mechanism (S_N^1). Similarly β-enamino ester reacts with aryl aldehyde **4** to yield alcohol **5A** which will further react with another mole of β-enamino ester in the presence of calcium triflate to provide dimeric compound **6** via same mechanism. Intermediate **5A** could also react with external nucleophile indole to give indolylacrylate **5** via S_N^1 mechanism.

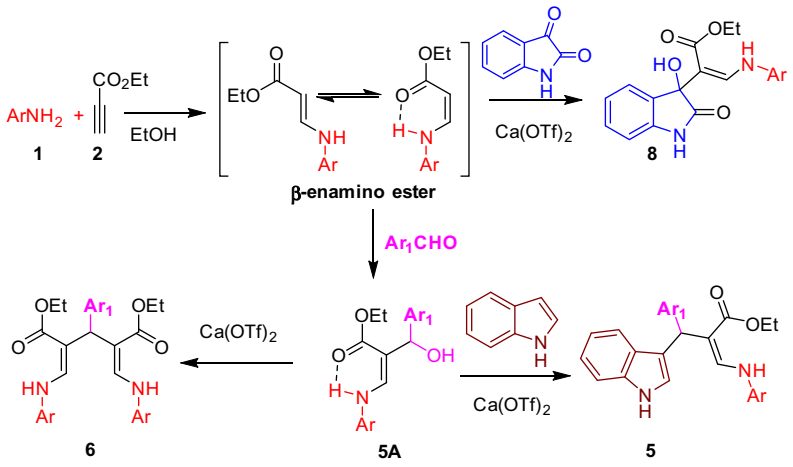
In summary, we described a novel one pot domino reaction for the stereoselective synthesis of acryl derivatives; indol-3-yl acrylate, bisarylidene acrylates, and oxindolyl substituted acrylates catalyzed by environmentally benign calcium catalyst. Substrate scope has been thoroughly investigated. The products were isolated in excellent yield by simple filtration. We believe that this will be one of the best and economic ways for making the said compounds which may be medicinally important due to the presence of indole and oxindole scaffolds.

Table 4
Ca(II) catalyzed one pot three component domino reaction for the synthesis of oxindolyl acrylates[a]





[b]Benzyl amine was used instead of aniline.
[a] Reaction conditions: aniline (1.1. equiv) and ethyl propiolate (1.1 equiv) were refluxed in ethanol at 90 °C for 3.5 h then reaction was brought to rt and isatin (1 equiv) was added along with catalyst and additive. Yields are reported after isolation by filtration.



Scheme 2. Plausible mechanism for the Ca(II) catalyzed domino reaction to synthesize acryl derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.03.098.

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15. *General experimental experimental procedure for the synthesis of indolyl acrylates (**5**):* A mixture of aniline (1.1 equiv) and ethyl propiolate (1.1 equiv) was refluxed in ethanol at 90 °C for 3.5 h then aromatic aldehyde (1.0 mmol), indole (1.0 equiv) and $Ca(OTf)_2$ (10 mol %) & Bu_4NPF_6 (10 mol %) were added to the above reaction and solution was stirred at room temperature for 8–10 h. After completion of the reaction (monitored by TLC) resulting precipitate was collected by vacuum filtration and was washed with cold ethanol to give the pure product.
16. See the Supporting information for the spectral data and copies of ^{1}H and ^{13}C NMR spectra.