Efficient Syntheses of β-Amino-*N*-acylbenzotriazoles and Cinnamides through Regioselective 1,4- or 1,2-Addition of Amines to *N*-Cinnamoylbenzotriazoles

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Abstract: Amines react with *N*-cinnamoylbenzotriazoles to afford either β-amino-*N*-acylbenzotriazoles or cinnamides depending on the structure of the amines. Aromatic amines react with *N*-cinnamoylbenzotriazoles via 1,4-addition to give β-amino-*N*-acylbenzotriazoles in good yields. For *o*-phenylenediamine, the 1,4-addition products were further acylated to provide a facile route to substituted 1,3,4,5-tetrahydro-1,5-benzodiazepine-2-ones. Aliphatic amines, however, react exclusively through the 1,2-addition pathway to produce cinnamides in good yields.

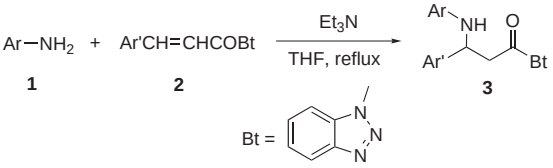
Key words: 1,4-addition, 1,2-addition, amines, cinnamides, 1,5-benzodiazepine-2-ones

Much attention has been paid to the amine-mediated aza-Michael addition to electron-deficient alkenes in recent years due mainly to the importance of the resulting β-amino derivatives thus formed.[1] Aliphatic amines undergo Michael addition more readily than aromatic ones in the presence of Lewis acid catalysts such as $CeCl_3 \cdot 7H_2O$/NaI,[2a] Clay,[2b] $Bi(OTf)_3$,[2c] $bmimPF_6$ (ionic liquid),[2d] $Pd(OAc)_2$–BINAP[2e] and solid $LiClO_4$,[2f] while these catalysts proved ineffective for aromatic amines under the same conditions.

Among a variety of Michael acceptors studied, α,β-ethylenic compounds (electron-poor alkenes) such as acrolein, methyl vinyl ketone, acrylonitrile, acrylate, acrylamide and vinylsulfonamide, in which there are no substituents at the β-position, were found particularly successful in the aza-Michael addition reactions.[3] Michael acceptors with β-substituents, especially aryl ones, were less effective acceptors because the amine-mediated Michael addition was found to be sensitive to steric hindrance.[4] For example, it was found that Michael addition of bulky amines to crotonate gave addition products in very poor yields, or in moderate yields under high pressure conditions.[5] Furthermore, most of the works conducted on β-substituted α,β-unsaturated compounds were looking at the enantioselectivity of the reactions.[3f–3j]

In this paper, we wish to report the regioselective reactions between *N*-cinnamoylbenzotriazoles and aromatic or aliphatic amines. Benzotriazole derivatives are a class of useful intermediates in organic synthesis because of the easy introduction and elimination of the auxiliary benzotriazole unit. The syntheses and applications of benzotriazole derivatives have been much developed, especially due to the contributions by the Katritzky group.[6] Previous studies found that the *N*-cinnamoyl-benzotriazoles were good acylating agents for anhydrous hydrazine.[7a] Our investigation also found that *N*-acylbenzotriazoles could acylate arylhydrazines smoothly.[7b] At this point, *N*-cinnamoylbenzotriazoles seemed to possess similar reactivity as *N*-acylbenzotriazoles, which have been found to be highly efficient N-acylating agents and were used for the acylation of both aliphatic and aromatic amines affording amides in good to excellent yields.[8]

However, our recent investigation revealed that *N*-cinnamoylbenzotriazoles showed quite different reactivity profile when reacting with amines. Hence, aromatic amines **1** undergo 1,4-addition to *N*-cinnamoylbenzotriazoles **2** producing Michael products **3** in good yields (Scheme 1). On the other hand, aliphatic amines following exclusive 1,2-addition pathway, afforded the corresponding cinnamides in excellent yields. The selectivity is in sharp contrast with most amine-mediated Michael addition as mentioned above.



Scheme 1

Our study began with aniline, which was chosen as a model substrate to react with *N*-cinnamoylbenzotriazole (**2a**) in THF at room temperature. Initially no additive was used in view of the mild reaction conditions reported in previous researches.[7] With no reaction observed, triethylamine was added as a base catalyst. However, no product could be detected after 12 hours. When the reaction was further carried out at elevated temperature (50 °C), new spots could be detected by TLC after 12 hours, albeit the amount of the new product increased very slowly. Finally, optimized reaction conditions were found by refluxing the mixture in THF with triethylamine as a promoter. The product was characterized as an 1,4-addition adduct

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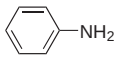
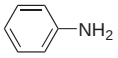
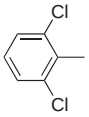
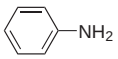
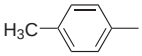
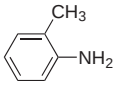
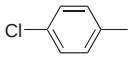
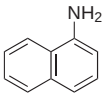
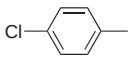
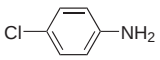
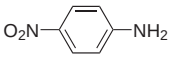
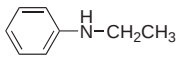
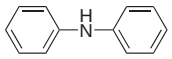
Table 1 Aza-Michael Addition of Aromatic Amines to *N*-Cinnamoylbenzotriazoles

Entry	Aromatic amines **1**	Ar′ of **2**	Products	Reaction time (h)	Yield (%)[a]
1		 **2a**	**3a**	18	73
2		 **2b**	**3b**	18	68
3		 **2c**	**3c**	18	52
4		 **2d**	**3d**	18	81
5		 **2e**	**3e**	18	76
6		 **2e**	**3f**	18	70
7		 **2a**	**3g**	24	65
8		 **2a**	–	36	–[b]
9		 **2a**	–	36	–[b]
10		 **2a**	–	36	–[b]

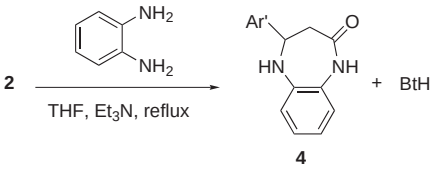
[a] Isolated yields based on *N*-cinnamoylbenzotriazoles used.
[b] No reaction.

between aniline and *N*-cinnamoylbenzotriazole (**2a**) based on ^{1}H NMR, ^{13}C NMR, IR and elemental analysis.

It can be seen from Table 1 that aniline and aromatic amines with electron-donating groups attached to the aromatic rings gave better yields (entries 1, 2, 4, 6) than those with electron-withdrawing groups (entries 7, 8), however, no product was obtained with *p*-nitroaniline. *N*-Phenylaniline and *N*-ethylaniline failed to give 1,4-addtition adducts either, where the steric hindrance may play an important role in preventing the reaction to take place (Table 1, entries 9, 10). On the other hand, *ortho*-substituents such as chloro did not impede the addition reaction (entry 2).

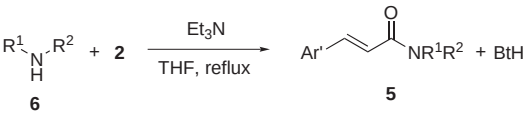
Although successful aromatic amine-mediated Michael addition was known,[9] the Michael acceptors involved were usually limited to such α,β-ethylenic compounds as acrylonitrile and acrylate. On the other hand, cinnamates usually afforded Michael products in poor yields.[3b] Taking into consideration that the nucleophiles are aromatic amines and that our α,β-unsaturated carbonyl compounds are β-aryl substituted, the yields of β-amino *N*-acylbenzotriazoles obtained here are quite satisfactory. In addition, since *N*-acylbenzotriazoles are effective N-, C-, S-, and O-acylating agents,[6c] the β-amino *N*-acylbenzotriazoles thus formed may be useful organic intermediates towards the synthesis of a variety of biologically active β-amino acid derivatives.

This significance of this aromatic amine-mediated Michael addition to *N*-cinnamoylbenzotriazoles can be manifested by using *o*-phenylenediamine as the nucleophile, where 1,4-aza-Michael additions followed by acylation at the carboxyl end afforded 1,3,4,5-tetrahydro-4-aryl-1,5-benzodiazepine-2-ones **4** in satisfactory yields (Scheme 2 and Table 2). Such compounds may have potential biological activities.[10] Although condensation reaction between *o*-phenylenediamine with crotonic acid to give tetrahydro-4-methyl-1,5-benzodiazepine-2-one had been reported,[11] similar condensation of *o*-phenylenediamine with cinnamic acids afforded 2-styrylbenzimidazoles[12] instead of 1,3,4,5-tetrahydro-4-aryl-1,5-benzodiazepine-2-ones. Hence, our present method produced 1,3,4,5-tetrahydro-4-aryl-1,5-benzodiazepine-2-ones in good yields under mild reaction conditions.



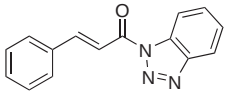
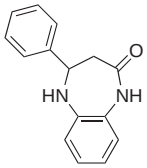
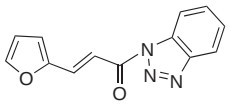
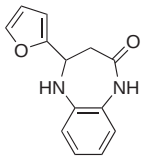
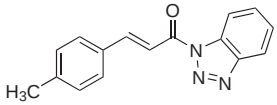
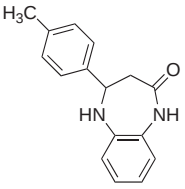
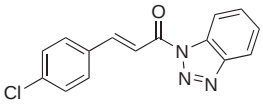
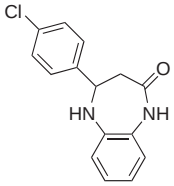
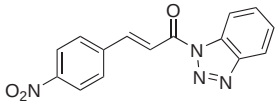
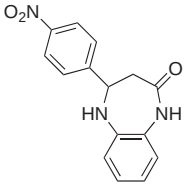
Scheme 2

It is interesting to note that when cyclohexylamine, an aliphatic amine, was used as the substrate, the corresponding cinnamide **5** was obtained in excellent yield (91%), which was formed from the 1,2-attack of the amine on the amide carbonyl group followed by elimination of the benzotriazoyl anion. Other primary and secondary aliphatic amines **6** gave similar results (Scheme 3, Table 3). No 1,4-addition products were detected and clean N-acylation was observed in all cases with aliphatic amines, therefore showing very high regioselectivity. Furthermore, it was noted that *N*-cinnamoylbenzotriazoles bearing an electron-withdrawing group (*p*-nitro-, *p*-chloro-) reacted with less hindered aliphatic primary amines (e.g., *n*-propylamine) in shorter time and gave better yields.



Scheme 3

Table 2 Preparation of 1,3,4,5-Tetrahydro-4-aryl-1,5-benzodiazepine-2-ones from *o*-Phenylenediamine and *N*-Cinnamoylbenzotriazoles

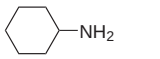
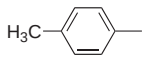
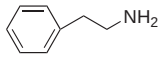
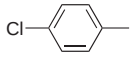
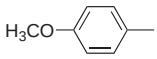
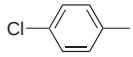
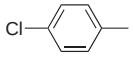
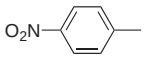
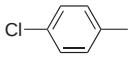
Entry	*N*-Cinnamoylbenzotriazoles **2**	Products	Reaction time (h)	Yield (%)[a]
1	 **2a**	 **4a**	1	85
2	 **2c**	 **4b**	12	76
3	 **2d**	 **4c**	12	76
4	 **2e**	 **4d**	10	81
5	 **2f**	 **4e**	2	83

[a] Isolated yields based on *N*-cinnamoylbenzotriazoles.

According to the literature, Michael addition of aliphatic amine prefers to occur at lower temperature but is unfavorable at temperature above 50 °C.[5] Another research also found that aliphatic amines reacted with cinnamate producing good yields of Michael products at room temperature, whereas the corresponding α,β-unsaturated amides were obtained at 60 °C.[2f] To clarify whether the reaction course is also temperature-dependent in our case, the reaction between *n*-propylamine and *p*-chloro-*N*-cinnamoylbenzotriazole (**2e**) was carried out at room temperature (Table 3, entry 5). It was found that the same cinnamide **5d** was produced in excellent yields in slightly longer reaction time. Similar observation was also found between *n*-propylamine and *p*-nitro-*N*-cinnamoylbenzotriazole (**2f**) at room temperature (Table 3, entry 6). Hence, the regiochemistry of the reaction is not dependent on the reaction temperature.

It is noteworthy that the reaction outcome[13] between amines and α,β-unsaturated *N*-acylbenzotriazoles is in contrast to similar reactions between amines and other α,β-unsaturated carbonyl compounds. For example, both aliphatic and aromatic amines undergo 1,4-addition to α,β-unsaturated esters,[3k,9b,f] However, they react with cinnamyl chlorides via exclusive 1,2-addition pathway to afford cinnamides.[14] The differential reactivity exhibited by aromatic and aliphatic amines toward *N*-cinnamoylbenzotriazoles here is therefore very interesting. A tentative explanation may be that aromatic amines behave more like a soft base since the unshared electron pair on the nitrogen atom readily delocalizes to the phenyl ring, whereas aliphatic amines are comparably harder with the unshared electron pair localized on the nitrogen atom. According to soft–hard acid–base theory, soft bases like aromatic amines tend to attack soft acid centers (i.e. the β-position of *N*-cinnamoylbenzotriazole), while hard bases

Table 3 Reactions of Aliphatic Amines with *N*-Cinnamoylbenzotriazoles

Entry	Alkyl amines **6**	Ar′ of **2**	Products	Reaction time	Yield (%)[a]
1		 **2d**	**5a**	6 h	91
2		 **2e**	**5b**	2.5 h	86
3	*n*-$C_3H_7NH_2$	 **2g**	**5c**	1.5	91
4	*n*-$C_4H_9NH_2$	 **2e**	**5d**	10 min	95
5	*n*-$C_4H_9NH_2$	 **2e**	**5d**	30 min[b]	95
6	*n*-$C_3H_7NH_2$	 **2f**	**5e**	10 min[b]	95
7		 **2a**	**5f**	3 h	88
8		 **2a**	**5g**	3 h	83
9	$(C_2H_5)_2NH$	 **2e**	**5h**	3 h	80

[a] Isolated yields based on *N*-cinnamoylbenzotriazoles.
[b] The run was carried out at r.t.

such as aliphatic amines have a higher affinity to hard acid positions (i.e. the carboxyl end of *N*-cinnamoylbenzotriazole).

In conclusion, *N*-cinnamoylbenzotriazoles are good Michael acceptors as well as effective acylating agents depending on the structures of reacting amine partners. With aromatic amines, Michael additions predominate and β-amino *N*-acylbenzotriazoles were obtained in good yields; with *o*-phenylenediamine, Michael addition followed by acylation afforded 1,3,4,5-tetrahydro-4-aryl-1,5-benzodiazepine-2-ones in satisfactory yields. For aliphatic amines, excellent yields of cinnamides could be prepared.[15] This good control of regioselectivity is extremely valuable in organic synthesis. The reaction between other nucleophiles and *N*-cinnamoylbenzotriazoles are now underway in our laboratory.

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(13) **Typical Experimental Procedure.**
A mixture of aromatic or aliphatic amine (1.1 mmol), *N*-cinnamoybenzotriazole (1 mmol) and Et_3N (1 mL) was refluxed in dry THF (10 mL) for the indicated time (monitored by TLC). Removal of THF and Et_3N under reduced pressure afforded a residue, which was separated by preparative TLC on silica gel with EtOAc and cyclohexane (1:6) as eluent to afford β-amino *N*-acylbenzotriazoles. Alternatively, Et_2O was added to the reaction mixture,

followed by washing with sat. Na_2CO_3 solution, drying with anhyd $MgSO_4$ and removal of the solvent under reduced pressure. The residue solidified and was recrystallized from EtOH or other appropriate solvent to afford pure α,β-unsaturated amides.

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(15) **Physical Data of Selected Compounds.**

1-{(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-3-phenyl-3-phenylamino}propan-1-one (3a).

Mp 167–169 °C. IR: ν_{max} = 3299 (NH), 3257, 3138, 3085, 1682 (C=O), 1602, 1548 (Ar) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, 1 H, *J* = 8.2 Hz, ArH), 7.97 (br, 1 H, NH), 7.23–7.46 (m, 12 H, ArH), 7.03–7.06 (m, 1 H, ArH), 6.45 (dd, 1 H, *J* = 5.2, 10.0 Hz, CH), 4.09 (dd, 1 H, *J* = 10.0, 15.2 Hz, CH), 3.46 (dd, 1 H, *J* = 5.20, 15.2 Hz, CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 146.0, 138.7, 137.7, 129.1, 129.0, 128.9, 128.6, 127.7, 126.6, 124.5, 124.4, 120.2, 119.6, 110.1, 56.0, 43.6. Anal. Calcd for $C_{21}H_{18}N_4O$: C, 73.67; H, 5.30; N, 16.36. Found: C, 73.36; H, 5.36; N, 16.28.

1,3,4,5-Tetrahydro-4-aryl-1,5-benzodiazepine-2-one (4a).

Decomposed beyond 83 °C. IR: ν_{max} = 3345 (NH), 3178, 3060, 2958, 2904, 1666 (C=O), 1596 (Ar) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.92 (s, 2 H, ArH, NH), 7.30–7.45 (m, 5 H, ArH), 7.07–7.09 (m, 1 H, ArH), 6.94–6.96 (m, 1 H, ArH), 6.85 (d, 1 H, *J* = 8.0 Hz, ArH), 5.04 (dd, 1 H, *J* = 4.0, 12.0 Hz, CH), 3.85 (br, 1 H, NH), 2.91 (dd, 1 H, *J* = 12.0, 4 Hz, CH), 2.78 (dd, 1 H, *J* = 12.0, 4.0 Hz, CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 144.2, 138.5, 129.0, 128.2, 127.7, 126.3, 126.1, 122.6, 121.6, 121.2, 63.5, 41.8. Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.38; H, 5.97; N, 11.69.

***(E)*-*N*-Cyclohexyl-3-*p*-tolylacrylamide (5a).**

Mp 166–167 °C. IR: ν_{max} = 3288 (NH), 3072, 3025, 2927, 2853, 1660 (C=O), 1618, 1553 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (1 H, d, *J* = 15.6 Hz, C=CH), 7.39 (2 H, d, *J* = 8.0 Hz, ArH), 7.16 (2 H, d, *J* = 8.0 Hz, ArH), 6.31 (1 H, d, *J* = 15.6 Hz, C=CH), 5.44 (1 H, br d, *J* = 6.1 Hz, NH), 3.90–3.92 (1 H, m, CH), 2.36 (3 H, s, CH_3); the following peaks all result from cyclohexyl: 1.97–2.00 (2 H, m), 1.72–1.75 (2 H, m), 1.36–1.43 (2 H, m), 1.14–1.25 (4 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 140.6, 139.8, 132.2, 129.5, 127.7, 120.1, 48.3, 33.3, 25.6, 24.9, 21.4. Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.66; H, 8.81; N, 5.71.