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Fast, easy, solvent-free, microwave-promoted Michael addition of anilines to α,β-unsaturated alkenes: synthesis of *N*-aryl functionalized β-amino esters and acids

Kristen M. Amore, Nicholas E. Leadbeater,* Tyson A. Miller and Jason R. Schmink

Department of Chemistry, University of Connecticut, 55 North Eagleville Road, Storrs, CT 06269-3060, USA

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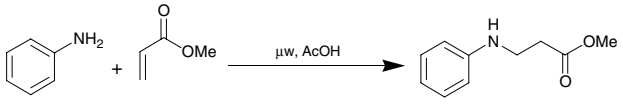
Abstract—The rapid, simple, microwave-promoted synthesis of *N*-aryl functionalized β-amino esters using Michael addition reactions is presented. Reactions are performed neat at 200 °C for 20 min and are catalyzed by acetic acid. The esters can be easily hydrolyzed to the corresponding *N*-aryl functionalized β-amino acids.

The preparation of β-amino acids and their derivatives is seeing increasing research interest due to their applications in medicinal chemistry and their biological activity.[1,2] They undergo no or little degradation by peptidases. Nonpeptidic β-amino acids are found in β-lactam-antibiotics, HIV-protease inhibitors, and enzyme inhibitors. A number of synthetic approaches have been used for the preparation of racemic β-amino acids.[3] Examples include hydrolysis of β-amino nitriles, homologation of α-amino acids, Michael-type additions to double bonds, Knoevenagel-type condensations of an aldehyde and malonic acid in the presence of ammonium acetate, amidomethylation of aryl acetic or malonic esters, oxidation of amino alcohols or ring opening of β-lactams. Our interest in the area came about from a desire to prepare *N*-aryl functionalized substrates (**1**). We wanted to use the Michael addition reaction of anilines to α,β-unsaturated alkenes as our synthetic pathway. While Michael addition reactions of amines to α,β-unsaturated substrates are well known,[4] we found few previous reports in the literature using anilines as substrates. In addition, yields were generally low. Acetic acid has been used as a catalyst for the reaction of aniline with methyl acrylate.[5–7] The reaction times are long (8–22 h) and the yields are moderate at best. A solvent-free protocol has been developed using silica as a solid support for the reaction of a range of amines and a few anilines with electron-deficient alkenes. In the case of the anilines, reactions are run for between 9 and 12 h.[8] Lewis acid catalysis has been used for the reaction of aniline with methyl acrylate or acrylonitrile giving the desired Michael adducts in 45% and 33% yields, respectively.[9] Lithium perchlorate can be used as a promoter; while this works well for amines, yields using anilines are low.[10] Barluenga et al. have used an aminomercuration–demercuration route with yields between 39% and 47%.[11] Transition metal catalysis can be used to make

Table 1. Optimization of conditions for the Michael reaction[a]



(2)

Entry	Temperature (°C)	Time (min)	Yield (%)
1	140	30	48
2	170	30	82
3	170	10	57
4	200	10	75
5	215	10	75
6	230	10	73
7	200	20	81
8[b]	200	20	23

[a] Reactions were performed using 15 mmol aniline, 15 mmol methyl acrylate, and 10 mol % acetic acid. An initial microwave irradiation power of 300 W was used, the temperature being ramped from rt to the desired temperature and held there for the allotted time. The reaction mixture was stirred throughout the microwave heating.
[b] Performed in the absence of acetic acid.

* Corresponding author. Tel.: +1 860 486 5076; fax: +1 860 486 2981; e-mail: nicholas.leadbeater@uconn.edu

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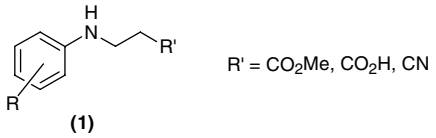
compounds containing an *N*-aryl functionalized β-amino ester or acid unit. A cationic (diphosphine)palladium(II) complex has been used for the hydroamination reaction between aniline and methyl acrylate or acrylonitrile.[12] Copper iodide, in conjunction with an aminoalcohol ligand, has been used for aryl amination reactions between bromobenzene and β-amino acids.[13]

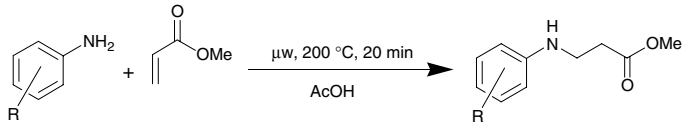
Microwave irradiation is a useful heating technique because it can enhance the rate of reactions and in many cases improve the product yields compared to traditional heating methods.[14–16] Microwave heating has been used as a tool in a range of Michael reactions with success,[17,18] but not for the addition of anilines to α,β-unsaturated alkenes. We therefore decided to probe this reaction.

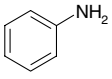
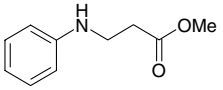
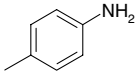
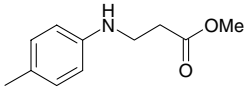
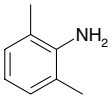
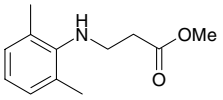
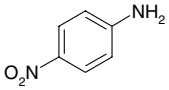
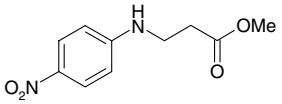
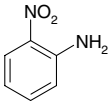
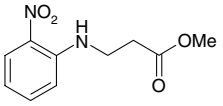
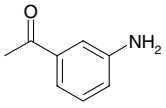
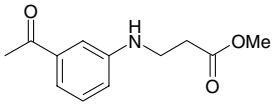
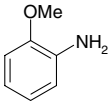
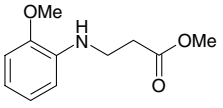
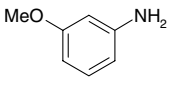
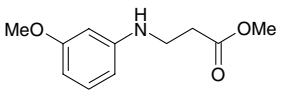
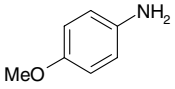
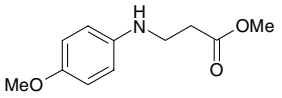
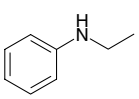
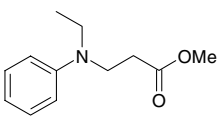


(1)

As our starting point, we focused on the acid-catalyzed addition of aniline to methyl acrylate. The results are

Table 2. Michael addition of anilines to methyl acrylate[a]



Entry	Aniline	Product	Yield (%)
1			81
2			79
3			29
4			56
5			4
6			34
7			70
8			79
9			76
10			43

[a] Reactions were performed using 15 mmol aniline, 15 mmol methyl acrylate, and 10 mol % acetic acid. An initial microwave irradiation power of 150 W was used, the temperature being ramped from rt to 200 °C and held at this temperature until a total time of 20 min had elapsed. The reaction mixture was stirred throughout the microwave heating.

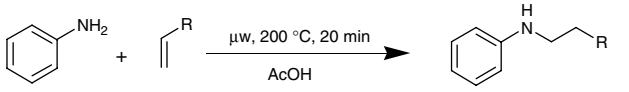
shown in Table 1.[19] Working on a 15 mmol scale, heating a 1:1 mixture of the substrates with 10 mol % acetic acid at 140 °C for 30 min resulted in a 48% yield of the desired product (**2**) (Table 1, entry 1). Increasing the reaction temperature to 170 °C led to an increase in the product yield to 82% (Table 1, entry 2). We wanted to reduce the reaction time but found that, working at 170 °C, moving from heating for 30 min to just 10 min resulted in a decrease in yield to 57% (Table 1, entry 3). Increasing the temperature while maintaining the shorter reaction time (10 min) had a beneficial effect. Performing the reaction at 200 °C resulted in a 75% yield (Table 1, entry 4) and there was no advantage in increasing the temperature further (Table 1, entries 5 and 6). Finally, working at 200 °C we determined the best reaction time to be 20 min (Table 1, entry 7). Performing the reaction in the absence of the acid catalyst resulted in a drop in yield to 23% (Table 1, entry 8). If greater than 10 mol % of acetic acid was used, significant quantities of *N*-phenylacetamide were formed as a by-product.

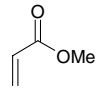
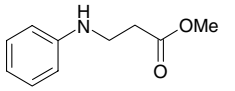
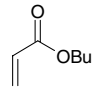
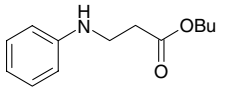
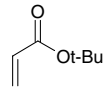
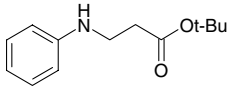
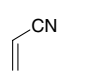
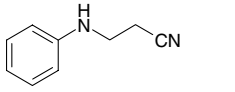
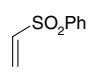
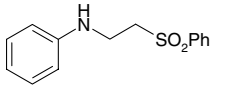
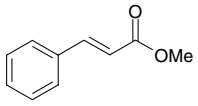
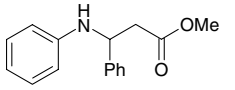
We screened a range of aniline substrates in the Michael addition to methyl acrylate.[20] The results are shown in Table 2. Our optimization data showed that the product yield obtained running the reaction at 200 °C for 20 min was almost identical to that achieved at 170 °C for 30 min. We opted for using a shorter reaction time at a slightly higher temperature (Table 1, entry 7) and used these conditions for screening. Anilines bearing electron-withdrawing groups (Table 2, entries 4–6) react less well than those containing electron-donating groups (Table 2, entries 7 and 8). The reaction is sensitive to the position of the substituent on the aromatic ring of the aniline; ortho-substituted examples (Table 2, entries 3, 5, and 7) reacting less well than their meta- or para-substituted analogs (Table 2, entries 2, 4, and 8). An example of an aniline bearing an *N*-alkyl group was screened (Table 2, entry 10) and the yield found to be significantly lower than in the case of the free aniline (Table 2, entry 1), suggesting that the steric problems extend to substituents on the nitrogen.

We next screened a range of α,β-unsaturated alkenes in the reaction with aniline. The results are shown in Table 3. While *n*-butyl acrylate worked well as a substrate (Table 3, entry 2), in the case of the *t*-butyl analog, significant decomposition occurred during the course of the reaction (Table 3, entry 3). The reaction of aniline with acrylonitrile and phenyl vinyl sulfone gave good yields of the desired product in each case (Table 3, entries 4 and 5). The reaction with the more sterically crowded methyl cinnamate was not successful indicating a limitation of the methodology (Table 3, entry 6).

Microwave heating can be used to facilitate hydrolysis reactions. To this end, we wanted to show that the esters could be readily converted to the corresponding amino acids. We chose as an example, the adduct formed from aniline and methyl acrylate (**2**) and tried to prepare β-amino acid **3**.

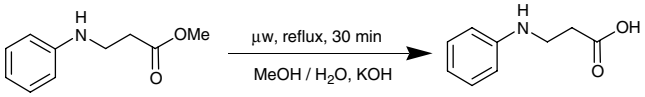
Table 3. Michael addition of aniline to α,β-unsaturated alkenes[a]



Entry	Alkene	Product	Yield (%)
1			81
2			83
3			0[b]
4			60
5			96
6			0

[a] Reactions were using 15 mmol aniline, 15 mmol alkene, and 10 mol % acetic acid. An initial microwave irradiation power of 300 W was used, the temperature being ramped from rt to 200 °C and held at this temperature until a total time of 20 min had elapsed. The reaction mixture was stirred throughout the microwave heating.

[b] Decomposition observed.



(2) **(3)**

The ester, in a 1:1 MeOH/H_2O solution containing potassium hydroxide, was heated to reflux for 30 min in an open vessel using microwave irradiation. After reaction, the amino acid product was obtained by adjusting the pH to the isoelectric point followed by an aqueous/organic extraction. The pure β-amino acid (**3**) was obtained in a 90% yield; this corresponding to 74% over both steps.[21]

In summary, we present a rapid, simple, microwave-promoted synthesis of *N*-aryl functionalized β-amino esters using Michael addition reactions is presented. The reactions are performed neat at 200 °C for 20 min and are catalyzed by acetic acid. The esters can be easily hydrolyzed to the corresponding *N*-aryl functionalized β-amino acids. Other chemistry could be performed at the carbonyl or CN functionality of the reaction products. In this regard, the methodology could be seen as an alternative to Buchwald–Hartwig couplings for the preparation of certain *N*-aryl substituted compounds.

Acknowledgments

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19. Reactions were conducted using a commercially available monomode microwave unit (CEM Discover™). The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0 to 300 W. Syntheses of the Michael adducts were performed in glass vessels (capacity 10 mL) sealed with a septum. The pressure was controlled by a load cell connected to the vessel. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. Hydrolysis reactions were performed in a 100 mL round-bottom flask. The apparatus was equipped with an opening in the top (attenuator) through which a glass tube could be placed connecting the flask in the microwave cavity with a reflux condenser located outside the cavity. All reactions were stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel.
20. *Typical procedure for the Michael addition reaction: Preparation of 3-phenylaminopropanoate* (**2**). In a 10 mL glass tube were placed aniline (1.395 g, 1.36 mL, 15.0 mmol), methyl acrylate (1.2915 g, 1.35 mL, 15.0 mmol), acetic acid (0.090 g, 0.086 mL, 1.5 mmol), and a magnetic stir bar. The vessel was sealed with a septum and placed into the microwave cavity where it was sealed with a pressure lock. Using an initial microwave power of 300, the reaction mixture was heated from rt to 200 °C where it was held by modulating microwave power for a total reaction time of 20 min. Upon completion, the reaction mixture was cooled to room temperature, the tube opened and the crude product characterized by comparison of NMR data with that in the literature. ^{1}H NMR ($CDCl_3$): δ 7.18 (t, 2H, $J = 7.5$ Hz), δ 6.70 (t, 1H, $J = 7.3$ Hz), δ 6.62 (d, 2H, $J = 7.7$ Hz), δ 4.00 (br, 1H), δ 3.70 (s, 3H), δ 3.46 (t, 2H, $J = 6.4$ Hz), δ 2.63 (t, 2H, $J = 6.4$ Hz).
21. *Typical procedure for the hydrolysis of the Michael adduct: Preparation of 3-phenylaminopropanoic acid* (**3**). In a 100 mL round-bottom flask were placed methanol (30 mL), water (30 mL), potassium hydroxide (4.489 g, 80.0 mmol), and the entire contents of the reaction mixture from the synthesis of **2**. Using an initial microwave power of 200 W, the reaction mixture was heated from rt to reflux (87 °C), where it was held by modulating microwave power for a total reaction time of 30 min. Upon completion, the solution was allowed to cool, poured into a separatory funnel, and the pH adjusted to 6.0 using HCl and $NaHCO_3$. The aqueous phase was extracted with four 20 mL portions of diethyl ether. The organic extracts were combined, washed with brine, dried over $MgSO_4$, whereupon the solvent was removed in vacuo, leaving the crude product. This product (500 mg) was purified using flash chromatography, an 80:20:0.1 DCM/MeOH/Et_3N mixture used as the eluent. The white solid recovered was characterized as **3** by the comparison of NMR data with that in the literature (379 mg, 2.31 mmol; 74% overall yield for the two steps). ^{1}H NMR (d_6-DMSO): δ 7.22 (t, 2H, $J = 7.4$ Hz), δ 6.77 (t, 1H, $J = 7.4$ Hz), δ 6.67 (d, 2H, $J = 7.6$ Hz), δ 3.50 (t, 2H, $J = 6.3$ Hz), δ 2.70 (t, 2H, $J = 6.3$ Hz).