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Preparation of α- and β-substituted alanine derivatives by α-amidoalkylation or Michael addition reactions under heterogeneous catalysis assisted by microwave irradiation

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Abstract—Silica-supported Lewis acids are useful catalysts in conjunction with microwave irradiation for the synthesis of a range of alanine derivatives. Reaction of methyl α-acetamidoacrylate (**1**) with different heterocycles, such as furan (**2**), pyrrole (**3**), *N*-benzylpyrrole (**4**), indole (**5**) and pyrazole (**6**) and the carbocycle 1,3,5-trihydroxybenzene (**7**), led to several α-amino acid precursors. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

The development and application of new and practical methods for the preparation of structurally diverse amino acid derivatives is of fundamental importance due to the widespread use of these compounds in practically all areas of the physical and life sciences. Thus, non-naturally occurring amino acid derivatives constitute an increasingly important resource for new chemotherapeutic agents that include antibacterial compounds and enzyme inhibitors.[1] Some β-dialkylamino-α-alanines and β-(heteroaryl)-α-alanines are non-proteinogenic amino acids that are widely found in nature.[2] Moreover, aromatic amino acids, such as phenylglycine and arylglycine analogues, have found applications in the synthesis of penicillin and cephalosporin antibiotics.[3]

N-Acyl-α,β-didehydroamino acids have proven to be useful intermediates in the asymmetric and non-asymmetric synthesis of α-amino acids.[4] The potential value of the *N*-acyl-α,β-dehydroamino acid esters in synthetic chemistry is derived mainly from their ready availability and the intrinsic reactivity of their double bonds due to the presence both of acylamino and ester groups, which facilitate the nucleophilic attack at the α and β positions. In particular, alanine derivatives are known to behave as dienophiles,[5] dipolarophiles[6] and electrophiles[7] in Michael-type reactions. On the other hand, enamides such as methyl α-acetamidoacrylate can act as α-amidoalkylation reagents, most often after protonation at the terminal carbon atom.[8]

Here we would like to describe the ability of methyl α-acetamidoacrylate (**1**) to act as an electrophile in Lewis acid catalyzed α-acetamidoalkylation reactions with heterocycles such as furan, pyrrole, *N*-benzylpyrrole, indole and pyrazole to afford 2-methylglycine analogues. The results obtained depend very much on the reaction conditions and the Lewis acid used as the catalyst and a comparative study of the influence of the catalyst on the yield of the α-amino acid precursors will be showed.

The reactions were performed using homogeneous catalysis, although in these cases long reaction times were required. For this reason, we found it of interest to study the reaction of methyl α-acetamidoacrylate with different heterocycles and carbocycles using heterogeneous catalysis assisted by microwave irradiation under solvent-free conditions. In all cases, the catalysts were obtained by treatment of silica with $ZnCl_2$ [Si(Zn)],[9] Et_2AlCl [Si(Al)][10] or $TiCl_4$ [Si(Ti)].[11] The most important objectives of this work were:

1. To try to decrease the reaction times.
2. To avoid the use of the polluting homogeneous catalysts commonly used.
3. To study the chemo- and regioselectivity of the reaction (competition between α-amidoalkylation, Michael addition and Diels–Alder cycloaddition was observed).
4. To determine the reactivity of these alanine derivatives with aromatic systems.

Keywords: microwave irradiation; amino acid; nucleophile.

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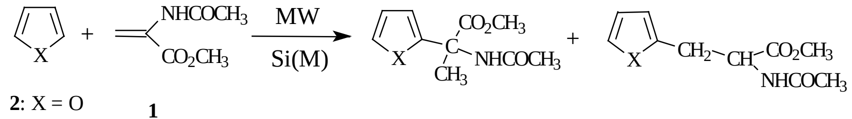


2: X = O
3: X = NH
1

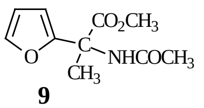
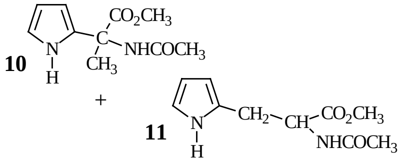
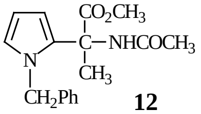
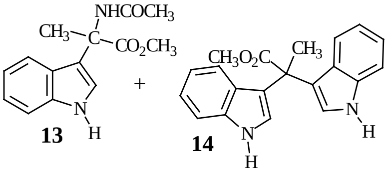
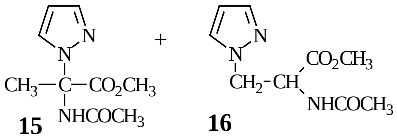
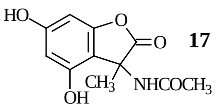
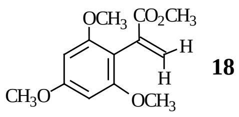
Scheme 1.

The process described here, because of its procedural simplicity and the use of readily available chemicals, appears to be a promising and useful route to a wide variety of aromatic α-amino acids with potential therapeutic action.[12]

2. Results and discussion

Methyl α-acetamidoacrylate (**1**) reacted with heterocycles or carbocycles, such as **2–8**, under microwave irradiation within 10–30 min to afford the α- and/or β-substituted alanine derivatives **9–13**, **15–17**. This method provides access to aryl-substituted amino acid derivatives as well as to amino acids containing a β-tertiary carbon. The reactions were usually performed at atmospheric pressure in a focused microwave reactor with the exception of the reactions involving furan. In these cases, owing to the low boiling point of furan, a hermetically sealed Teflon vessel in a domestic oven or a modified Fisher–Porter reaction vessel

Table 1. Reactions of heterocyclic or carbocyclic derivatives with methyl α-acetamidoacrylate (**1**) using silica-supported Lewis acids as catalysts

Entry	Heterocycle (molar ratio)[a]	Catalyst[b]	Reaction conditions	Products	Yield (%)
1	Furan (**2**) (10:1)	Si(Zn)	15 min 150 W 50°C	 **9**	**9**: <3
2		Si(Al)	15 min 150 W 50°C		**9**: 16
3		Si(Ti)	15 min 150 W 50°C		**9**: 18
4	Pyrrole (**3**) (6:1)	Si(Zn)	15 min 270 W 100°C	 **10** + **11**	**11**: 70
5		Si(Al)	25 min 150 W 70°C		**10**: 51+**11**: 12
6		Si(Ti)	30 min 120 W 80°C		**10**: 32+**11**: 27
7[c]		Si(Zn)	15 min 100°C		**11**: 14
8	*N*-Benzyl-pyrrole (**4**) (1:2)	Si(Zn)	15 min 285 W 100°C	 **12**	**12**: <3
9		Si(Al)	10 min 240 W 70°C		**12**: 26
10		Si((Ti)	15 min 240 W 60°C		**12**: 44
11	Indole (**5**) (1:1)	Si(Zn)	15 min 270 W 100°C	 **13** + **14**	**14**: 37
12		Si(Al)	15 min 150 W 70°C		**13**: 39+**14**: 54
13		Si(Ti)	15 min 150 W 70°C		**13**: 18+**14**: 22
14		Si(Al)[d]	15 min 90 W 50°C		**13**: 50+**14**: 23
15[c]		Si(Al)[d]	15 min 50°C		**13**: 12
16	Pyrazole (**6**) (1:1)	Si(Zn)	10 min 240 W 80°C	 **15** + **16**	**15**+**16**:<3
17		Si(Al)	10 min 240 W 80°C		**15**: 17+**16**: 24
18		Si(Ti)	10 min 240 W 80°C		**15**: 7+**16**: 6
19		Si(Al)[e]	10 min 210 W 80°C		**15**: 7+**16**: 41
20	1,3,5-Trihydroxy-benzene (**7**) (1:3)	Si(Zn)	15 min 285W 100°C	 **17**	**17**: 41
21		Si(Al)	10 min 240W 60°C		**17**: 37
22		Si(Ti)	10 min 240W 60 °C		**17**: 46
23	1,3,5-Trimethoxy-benzene (**8**) (1:3)	Si(Zn)	20 min 240W 110°C	 **18**	**18**: 91
24		Si(Al)	15 min 270W 110°C		**18**: 23
25		Si(Ti)	15 min 270W 110°C		**18**: 32
26[c]		Si(Zn)	20 min 110°C		**18**: <3

[a] Molar ratio of heterocyclic or benzene derivative–methyl α-acetamidoacrylate.
[b] 0.5 g of Si(M) was used as catalyst.
[c] Thermal heating.
[d] In this reaction, a molar ratio indole–methyl α-acetamidoacrylate of 1:2 was used.
[e] In this reaction a molar ratio pyrazole–methyl α-acetamidoacrylate of 2:1 was used.

in a focused microwave reactor were used. The internal pressure in these reactions was always less than 3 bars.

Our study began with furan and pyrrole (Scheme 1) and was later extended to include other heterocyclic and carbocyclic systems. Molar ratios and temperatures were optimised and Table 1 shows the best results for each heterocyclic compound.

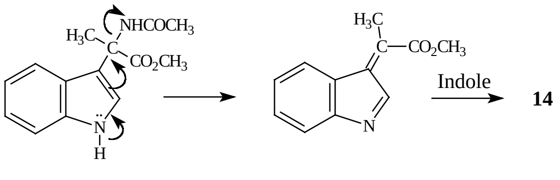
Reactions involving furan were performed in a focused microwave reactor (entries 1–3). Under these conditions, although nearly complete conversions were observed, yields were low because both reagents can decompose; furan by ring opening and the alanine derivative by polymerization. This decomposition has previously been observed in reactions of **1** with cyclopentadiene.[5b] Reducing the amount of catalyst did not overcome this decomposition. The use of small, closed Teflon vessels to avoid the evaporation of furan in a multimode microwave oven allowed us to increase the temperature, although yields were not improved under these conditions (data not shown). Under classical conditions at room temperature, using Si(Ti) as the catalyst, a yield of only 22% was obtained after 24 h.

In reactions with pyrrole both α-amidoalkylation and Michael addition took place. Catalysts such as Si(Ti) or Si(Al) favoured the α-amidoalkylation product (entries 5 and 6) while the use of Si(Zn) exclusively gave the Michael addition product in 70% yield (entry 4). On using classical heating, i.e. in an oil bath under similar reaction conditions (time and temperature), product **11** was obtained in only 14% yield. However, with *N*-benzylpyrrole the only reaction observed was α-amidoalkylation. The best catalyst was Si(Ti) (entry 10), whereas Si(Zn) gave no reaction even at 100°C and Si(Al) gave only a low yield that did not increase with time (entries 8 and 9, respectively).

This reaction was extended to other benzocondensed heterocycles including indole (**5**) and azoles such as pyrazole (**6**) with the aim of obtaining tryptophan derivatives and β- and α-(1-pyrazolyl)alanine derivatives as synthetic precursors of anticonvulsant agents.[13]

Reactions with indole (Table 1, entries 11–15) afforded the bisindolyl derivative (**14**) as the main product. This product was obtained by elimination of acetamide and reaction with a second equivalent of indole (Scheme 2). The assistance of the indole system in the elimination of acetamide controls the formation of the symmetric dimer.

Product **14** predominates upon using a molar ratio of 1:1 and it was the only product obtained when Si(Zn) was used (entry 11). However, the best yields were obtained with Si(Al). Elimination of acetamide occurred to a lesser extent when the reaction was performed at 50°C and an increase in the amount of *N*-acetyl-α,β-didehydroalanine methyl ester used, under the same conditions, led to a 50% yield of the α-amidoalkylation product (**13**), which was the main product (entry 14). When we used similar conditions under thermal heating the yield decreased to 12%, a fact that demonstrates the activation of microwave irradiation.



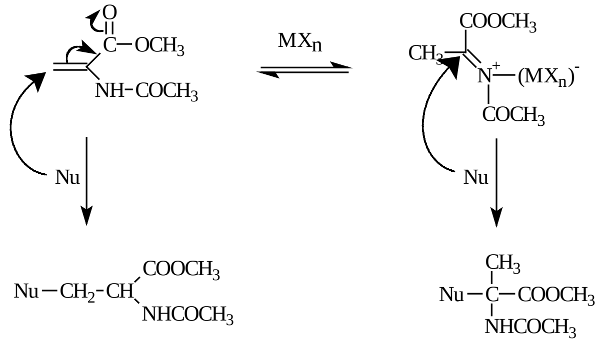
Scheme 2.

We performed the reaction with pyrazole under similar conditions (Table 1, entries 16–19) and in these cases addition at N-1 was observed. The selectivity depended on the reaction conditions and the Lewis acid used as a catalyst, although a mixture of α-amidoalkylation and Michael addition products was always obtained.

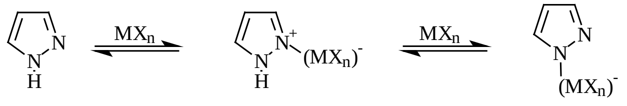
The competition between α-amidoalkylation and Michael addition reactions can be considered according to an enamine–imine equilibrium, which is activated by the presence of the Lewis acid (Scheme 3).

According to Scheme 3, the reaction of a good nucleophile with the electrophile, non-activated by co-ordination to an acid centre, takes place in the β-position. This behaviour is observed for heterocycles bearing sufficiently acidic NH groups which are able to react with aluminium and titanium Lewis acids to form a good nucleophile in an irreversible way (Scheme 4). For this reason, the Michael type reaction is not observed with the Zn-catalyst.

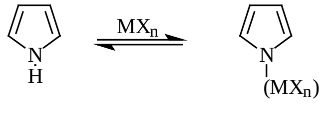
This equilibrium it is not possible in furan or *N*-substituted pyrrole derivatives due to the absence of NH, consequently only α-amidoalkylation is observed (Scheme 5).



Scheme 3.



Scheme 4.



Scheme 5.

Given that aromatic amino acids of the phenyl glycine type have found applications in the synthesis of semisynthetic penicillins and cephalosporins,[3] we attempted the reaction with carbocycles.

Phenol and anisole were the first starting materials investigated. However, the reaction did not occur in these cases and so more activated systems were tried. When this reaction was extended to more activated benzene derivatives like 1,3,5-trihydroxybenzene (Table 1, entries 20–22) and 1,3,5-trimethoxybenzene (Table 1, entries 23–26) the reaction did proceed.

For 1,3,5-trihydroxybenzene, the product obtained came from an α-amidoalkylation followed by a transesterification reaction, although the reversal reaction order is also possible. A similar product has been described by Ben-Ishai et al.,[14] who used glyoxylic acid derivatives as synthetic equivalents of glycine cations in reactions with aromatic compounds. On using the trihydroxy derivative as the starting material, the best results were obtained with a temperature of 60°C for Si(Al) or Si(Ti) (entries 21 and 22, respectively) and 100°C for Si(Zn) (entry 20). The best catalyst was Si(Ti), although the aromatic amino acid derivative was obtained only in moderate yields. An increase in the reaction time did not lead to an increase in the yields.

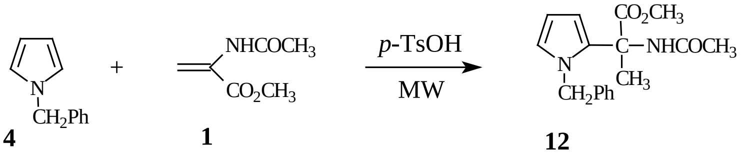
Finally, in the reactions between the trimethoxybenzene derivative and **1** using silica-supported Lewis acids as catalysts, the product obtained arises due to the α-amidoalkylation reaction and elimination of acetamide. We could not avoid this elimination in any case because this reaction must be favoured by the higher steric hindrance of methoxy groups and the higher temperature needed. Under these conditions the catalysts Si(Al) and Si(Ti) led to decomposition of the alanine ester derivative (entries 24 and 25), while use of the Si(Zn) catalyst led to 91% yield in 20 min (entry 23). Once again, the use of similar conditions (temperature and time) under thermal heating did not lead to any reaction.

An effective co-ordination between the Lewis acid and the alanine derivative (as is shown in Scheme 3) can be deduced by the fact that only α-amidoalkylation products were observed when a carbocycle such as a 1,3,5-trihydroxy- or trimethoxybenzene derivative was used.

The reactions reported here show that Si(M) systems are not sufficiently strong to produce the reaction to any great extent unless a very activated carbocyclic or heterocyclic compound is used. In order to increase the yields we employed, in some cases, other stronger acid catalysts such as a Brönsted acid (*p*-toluenesulfonic acid) or an ion exchange resin (Dowex) (Tables 2 and 3).

Thus, in the reaction of *N*-benzylpyrrole the yield increases to 68% when *p*-TsOH was used in catalytic amounts (Table 2, entry 2), nearly doubling the yield in comparison with that obtained with silica-supported catalysts (Table 1, entry 10). The best result was obtained using a temperature of 80°C and a reaction time of 15 min. Under thermal heating conditions the yield decreases to 30%.

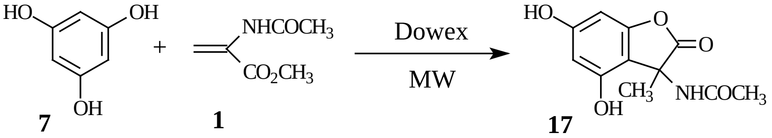
Table 2.



Entry[a]	Molar ratio **4**:**1**	*T* (°C)	Power (W)	Time (min)	Yield (%) **12**
1	1:1	80	60	15	25
2	1:2	80	30	15	68
3[b]	1:2	80	–	15	30

[a] In these reactions a catalytic amount of *p*-toluensulfonic acid (10 mg) was used.
[b] Thermal heating.

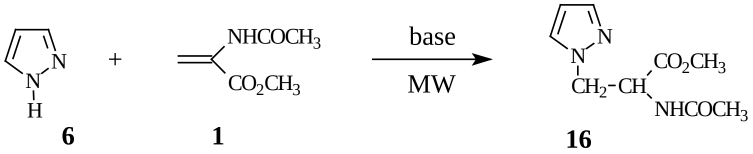
Table 3.



Entry[a]	Molar ratio **7**:**1**	*T* (°C)	Power (W)	Time (min)	Yield (%) **17**
1	1:3	60	30	10	<3
2	1:3	100	30	10	64
3[b]	1:3	100	–	10	<3

[a] In these reactions 0.2 g of Dowex was used as catalyst.
[b] Thermal heating.

Table 4.



Entry	Base[a]	Molar ratio 6:1	*T* (°C)	Power (W)	Time (min)	Yield (%) 16
1	$NaHCO_3$	1:1	120	150	10	42
2	$NaHCO_3$	1:1	120	150	10	50
3	Na_2CO_3	1:2	120	150	15	80
4[b]	Na_2CO_3	1:2	120	–	15	<3

[a] For these reactions 0.5 g of base was used.
[b] Thermal heating.

However, the use of *p*-TsOH with heterocycles such as furan or pyrrole, which are more sensitive to acidic conditions, led to decomposition of the reagents.

The reaction of 1,3,5-trihydroxybenzene produced a benzofuran derivative. This synthesis resembles the synthesis of coumarin derivatives described by us.[15] In consequence, we tested the use of a Dowex resin as catalyst.

With this resin the benzofuran derivative was obtained in 64% yield after 10 min. It can be seen that this yield is significantly higher than those obtained with silica-supported catalysts (Table 1, entries 20–22). Again thermal heating did not lead to any reaction (Table 3, entry 3).

Finally, a base-catalyzed (potassium hydrogen carbonate) conjugate addition of a purine derivative to methyl trifluoroacetylaminoacrylate in dimethyl sulfoxide has been described.[2d] This reaction opens the way for the use of bases, such as $NaHCO_3$ and Na_2CO_3, in the reaction with pyrazole in order to improve the synthesis of the β-substituted alanine derivative **16**.

As shown in Table 4, the best results were obtained at 120°C with Na_2CO_3 as the base. The pyrazole did not decompose under these conditions and so we increased the ratio of methyl α-acetamidoacrylate (**1**), a change that favoured the reaction and afforded a yield of 80% in 15 min. The use of sodium carbonate nearly doubled the yield over the best one obtained using Si(Al) as the catalyst (Table 4, entry 3 versus Table 1, entry 19). An increase in the reaction time did not give better results and these were similar when half the amount of catalyst was used (data not shown). It is important to bear in mind that the use of comparable conditions involving classical heating does not give any reaction.

Moreover, it is interesting to note that the synthesis of this product was reported by Pleixats et al.[7c] to require 144 h and gave 54% yield. The reaction time is reduced considerably with the method described here and also avoids the use of contaminating catalysts.

3. Conclusions

In conclusion, the synthesis of a range of alanine derivatives has been achieved using heterogeneous catalysts under microwave irradiation. The products are easily prepared by reaction of methyl α-acetamidoacrylate with heterocycles such as furan, pyrrole, *N*-benzylpyrrole, indole, pyrazole and benzene derivatives using silica-supported Lewis acids as catalysts. For *N*-benzylpyrrole (**4**) or trihydroxybenzene (**7**) the use of stronger acid catalysts, such as *p*-TsOH and Dowex resin, improves the yields over those obtained with silica gel catalysts. Similarly, for pyrazole (**6**) the best results were obtained by using bases such as sodium hydrogen carbonate or sodium carbonate. We therefore conclude that the type of catalyst used plays a crucial role in the conjugate addition.

Thus, the formation of the α- or β-substituted alanine derivative depends on the co-ordination of the Lewis acid with methyl α-acetamidoacrylate and the presence in the aromatic system of acidic NH groups. When the aromatic compound is reactive enough, the best catalyst is Si(Zn) because this does not produce decomposition of the reagents. With compounds of lower reactivity a stronger catalyst like Si(Ti) or Si(Al) is required. When competition between α-amidoalkylation and Michael addition reactions occurs, Si(Ti) and Si(Al) favour the first reaction whereas Si(Zn) favours the latter. With heterocycles like furan and *N*-benzylpyrrole and carbocyclic systems, only α-amidoalkylation occurs. Less reactive heterocycles did not react and three activating groups are required for carbocycles.

In all cases, the microwave irradiation produces some sort of activation in the reaction. The reaction times are very short in comparison to those described in the literature for these types of reaction. The effect of microwave irradiation is not exclusively an acceleration of the reaction, as some compounds did not react by classical heating in an oil bath under comparable reaction conditions (time and temperature).

Given that chiral *N*-acetyl-α,β-dehydroalanine esters can be easily prepared[16] and have proved to be successful in asymmetric reactions,[17] this method opens up a new route for acyclic stereoselection in α-amidoalkylation and Michael addition reactions.[18]

4. Experimental

4.1. General

All melting points were determined on a Gallenkamp apparatus and are uncorrected. ^1H- and ^{13}C-NMR spectra were recorded at 299.94 and 75.429 MHz, respectively, on a Varian Unity 300 spectrometer. Chemical shifts are reported in ppm (δ) using Me_4Si as standard, and coupling constants J are given in Hz. Total assignment was obtained by the acquisition of NOE-difference spectra and 2D NMR correlation experiments such as COSY and HETCOR. Column chromatography was carried out with SiO_2 (silica gel, Merck type 60, 230–400 mesh). Microwave irradiations were conducted in a focused microwave reactor (Prolabo MX350) with measurement and control of power and temperature by infrared detection. Catalysts modified with Lewis acids were obtained by treating silica gel with 1 M solutions of $ZnCl_2$, $AlEt_2Cl$ or $TiCl_4$ following the previously described method.[9–11] The silica contained 1.5 mmol of Zn g^{-1}, 1.4 mmol of Al g^{-1} and 1.2 mmol of Ti g^{-1}, respectively. For the Si(Zn) catalyst, activation for 2 h at 150°C under vacuum was necessary before use. Mass spectra were obtained on a VG Autospec instrument (70 eV). Elemental analyses were determined on a Perkin–Elmer PE 2400 CHN apparatus. Reagents were purchased from commercial suppliers or prepared by literature methods.

4.2. General procedure

A mixture of methyl α-acetamidoacrylate (**1**) (1.0 mmol), the appropriate heterocyclic (**2–6**) or benzene (**7–8**) derivative (0.33–10 mmol) and 0.5 g of silica-supported Lewis acid (by dissolving the mixture in 10 mL of CH_2Cl_2 followed by evaporation of the solvent) was exposed to microwave irradiation in a focused microwave reactor for the time and power indicated in Table 1. For reactions with other solid catalysts, such as *p*-toluenesulfonic acid, Dowex 50WX2-200 or a base ($NaHCO_3$, Na_2CO_3), amounts of 0.01, 0.2 and 0.5 g, respectively, were used (Tables 2–4). In all reactions, the products were isolated by addition of 75 mL of CH_2Cl_2 (except for reactions of compound **7** where CH_3CN was used) and the catalyst was then separated by filtration. The solvent was removed under reduced pressure and the crude reaction mixtures were analysed by ^1H NMR spectroscopy on samples in $CDCl_3$ or DMSO-d_6. Yields were determined by ^1H NMR spectroscopy using CH_2Br_2 (δ=4.93 ppm) or CH_3NO_2 (δ=4.32 ppm) as an internal standard. The products were purified by column chromatography of the crude reaction mixture on silica gel. All compounds were characterised by analytical methods and ^1H- and ^{13}C NMR spectroscopy, using mono- and two-dimensional techniques. The new compounds exhibit NMR spectroscopic properties consistent with their structures and gave satisfactory molecular weight determinations (mass spectrometry).

4.2.1. *N*-Acetyl-α-(2-furanyl)alanine methyl ester (9). The furan derivative was purified by column chromatography on silica gel using hexane–ethyl acetate=3:1 as eluent (isolated product **9**, mp 92–93°C[7b]). Yields were determined by integration of the ^1H NMR signal of the methyl ester group (δ=3.76 ppm) using CH_2Br_2 as an internal standard. ^1H NMR ($CDCl_3$, δ): 1.97 (s, 3H, CH_3), 2.02 (s, 3H, $COCH_3$), 3.76 (s, 3H, OCH_3), 6.36–6.37 (m, 2H, 3-H and 4-H), 6.60 (bs, 1H, NH), 7.36–7.37 (m, 1H, 5-H). ^{13}C NMR ($CDCl_3$, δ): 21.7 ($COCH_3$), 23.5 (CH_3), 53.1 (OCH_3), 58.9 (α-C), 107.4 (3-C), 110.7 (4-C), 142.2 (5-C), 152.6 (2-C), 168.9 and 171.5 (2×CO).

4.2.2. *N*-Acetyl-α-(2-pyrrolyl)alanine methyl ester (10) and *N*-acetyl-β-(2-pyrrolyl)alanine methyl ester (11). The pyrrole derivatives were purified by column chromatography on silica gel using hexane–ethyl acetate=1:6 as eluent, the elution order was: product **11** (yellow oil) followed by compound **10** (mp 100–103°C, purified by washing the solid with hexane). Yields were determined by integration of the ^1H NMR signal of the NH acetamide proton (δ=2.00 ppm) for compound **10** and the signal due to the CH_2 group (δ=3.17 ppm) for compound **13**, both using CH_3NO_2 as an internal standard.

***N*-Acetyl-α-(2-pyrrolyl)alanine methyl ester (10).** MS (EI) *m/z* 210.1 (M^+). ^1H NMR ($CDCl_3$, δ): 1.91 (s, 3H, CH_3), 2.00 (s, 3H, $COCH_3$), 3.77 (s, 3H, OCH_3), 6.11–6.12 (m, 2H, 3-H and 4-H), 6.26 (bs, 1H, NHCO), 6.74–6.75 (m, 1H, 5-H), 9.41 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, δ): 22.6 (CH_3), 23.3 ($COCH_3$), 53.1 (OCH_3), 57.6 (α-C), 106.2 and 107.4 (3-C, 4-C), 118.7 (5-C), 131.0 (2-C), 170.5 and 172.7 (2×CO). Anal. calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found C, 57.35; H, 6.85; N, 13.1.

***N*-Acetyl-β-(2-pyrrolyl)alanine methyl ester (11).** MS (EI) *m/z* 210.1 (M^+). ^1H NMR ($CDCl_3$, δ): 2.08 (s, 3H, $COCH_3$), 3.17 (d, J=5.4 Hz, 2H, CH_2), 3.77 (s, 3H, OCH_3), 4.80 (dt, J=5.4, 7.4 Hz, 1H, CH), 5.89–5.90 (m, 1H, 3-H), 6.10–6.12 (m, 1H, 4-H), 6.40 (d, J=7.4 Hz, 1H, NHCO), 6.69–6.71 (m, 1H, 5-H), 8.58 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, δ): 23.2 ($COCH_3$), 30.1 (CH_2), 52.6 (CH), 52.7 (OCH_3), 107.4 (3-C), 108.4 (4-C), 117.8 (5-C), 125.5 (2-C), 171.4 and 172.0 (2×CO). Anal. calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found C, 57.25; H, 6.8; N, 13.25.

4.2.3. *N*-Acetyl-α-(*N*-benzylpyrrol-2-yl)alanine methyl ester (12). The pyrrole derivative was purified by column chromatography on silica gel using hexane–ethyl acetate=3:1 as eluent (isolated product **12**, mp 116–118°C from chloroform–hexane). Yields were determined by integration of the ^1H NMR signal of the methyl ester group (δ=3.55 ppm) using CH_3NO_2 as an internal standard.

MS (EI) *m/z* 300.1 (M^+). ^1H NMR ($CDCl_3$, δ): 1.48 (s, 3H, $COCH_3$), 2.02 (s, 3H, CH_3), 3.55 (s, 3H, OCH_3), 5.11 (d, J=16.9 Hz, 1H, CH_2), 5.35 (d, J=16.9 Hz, 1H, CH_2), 6.31 (dd, J=2.8, 3.7 Hz, 1H, 4-H), 6.26 (bs, 1H, NH), 6.39 (dd, J=1.8, 3.7 Hz, 1H, 3-H), 6.67 (dd, J=1.8, 2.8 Hz, 1H, 5-H), 6.88 (d, J=7.1 Hz, 2H, *o*-Ph), 7.24–7.34 (m, 3H, Ph). ^{13}C NMR ($CDCl_3$, δ): 23.1 (CH_3), 23.3 ($COCH_3$), 50.9 (CH_2), 53.1 (OCH_3), 58.1 (α-C), 107.6 (4-C), 110.3 (3-C), 125.1 (5-C), 125.4 (*o*-Ph), 127.2 (*p*-Ph), 128.9 (*m*-Ph), 129.6 (2-C), 139.1 (*ipso*-Ph), 168.5 and 173.1 (2×CO). Anal. calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found C, 68.10; H, 6.75; N, 9.45.

4.2.4. *N*-Acetyl-α-(3-indolyl)alanine methyl ester (13) and methyl 2,2-(bisindol-3-yl)propanoate (14). The indole derivatives were purified by column chromatography on silica gel using hexane–ethyl acetate=3:1 as eluent. The elution order was: product **14** (mp 88–91°C, purified by washing the solid with hexane) followed by compound **13** (mp 199–202°C, purified by washing the solid with hexane). Yields were determined by integration of the ^{1}H NMR signal of the NH proton (δ=6.73 ppm) for compound **14** and signal of the 4-H proton (δ=7.50 ppm) for compound **13** using CH_3NO_2 (δ=4.32 ppm) as an internal standard.

***N*-Acetyl-α-(3-indolyl)alanine methyl ester (13).** MS (EI) *m/z* 260.1 (M$^+$). ^{1}H NMR ($CDCl_3$, δ): 2.00 (s, 3H, $COCH_3$), 2.11 (s, 3H, CH_3), 3.68 (s, 3H, OCH_3), 6.73 (s, 1H, NHCO), 7.11 (d, J=2.7 Hz, 1H, 2-H), 7.13 (dt, J=1.2, 7.8 Hz, 1H, 5-H), 7.20 (dt, J=1.2, 7.8 Hz, 1H, 6-H), 7.35 (dd, J=1.2, 7.8 Hz, 1H, 7-H), 7.76 (dd, J=1.2, 7.8 Hz, 1H, 4-H), 8.60 (bs, 1H, NH). ^{13}C NMR ($CDCl_3$, δ): 22.3 (CH_3), 23.7 ($COCH_3$), 52.9 (OCH_3), 58.6 (α-C), 111.7 (7-C), 119.8 (3-C and 5-C), 119.9 (4-C), 122.2 (6-C), 123.2 (2-C), 124.5 (9-C), 136.7 (8-C), 169.3 and 173.4 (2×CO). Anal. calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found C, 64.73; H, 6.30; N, 10.60.

Methyl 2,2-(bisindol-3-yl)propanoate (14). MS (EI) *m/z* 318.2 (M$^+$). ^{1}H NMR ($CDCl_3$, δ): 2.11 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 6.88 (d, J=2.4 Hz, 2H, 2-H), 7.00 (dd, J=7.6, 8.0 Hz, 2H, 5-H), 7.15 (t, J=7.6 Hz, 2H, 6-H), 7.32 (d, J=7.6 Hz, 2H, 7-H), 7.50 (d, J=8.0 Hz, 2H, 4-H), 7.96 (bs, 2H, NH). ^{13}C NMR ($CDCl_3$, δ): 25.9 (CH_3), 46.2 (α-C), 52.2 (OCH_3), 111.2 (7-C), 119.0 (3-C), 119.2 (5-C), 121.2 (4-C), 121.7 (6-C), 122.9 (2-C), 126.0 (9-C), 136.7 (8-C), 175.9 (CO). Anal. calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found C, 75.61; H, 5.85; N, 8.68.

4.2.5. *N*-Acetyl-α-(1-pyrazolyl)alanine methyl ester (15) and *N*-acetyl-β-(1-pyrazolyl)alanine methyl ester (16). The pyrazole derivatives were purified by column chromatography on silica gel using hexane–ethyl acetate=1:1 as eluent. The elution order was: product **15** (mp 121–123°C, chloroform–hexane) followed by compound **16** (mp. 92–94°C,[7c] chloroform–diethyl ether). Yields were determined by integration of the ^{1}H NMR signal of the methyl group (δ=2.28 ppm) for compound **15** and the signal due to the 4-H proton (δ=6.24 ppm) for compound **16** using CH_3NO_2 as an internal standard.

***N*-Acetyl-α-(1-pyrazolyl)alanine methyl ester (15).** MS (EI) *m/z* 211.1 (M$^+$). ^{1}H NMR ($CDCl_3$, δ): 2.00 (s, 3H, $COCH_3$), 2.28 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 6.28 (dd, J=1.6, 2.4 Hz, 1H, 4-H), 7.26 (bs, 1H, NH), 7.53 (d, J=1.6 Hz, 1H, 3-H), 7.83 (d, J=2.4 Hz, 1H, 5-H). ^{13}C NMR ($CDCl_3$, δ): 22.1 (CH_3), 23.8 ($COCH_3$), 53.9 (OCH_3), 73.2 (α-C), 105.5 (4-C), 129.4 (5-C), 139.9 (3-C), 169.5 and 169.7 (2×CO). Anal. calcd for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.89. Found C, 51.36; H, 6.35; N, 19.70.

***N*-Acetyl-β-(1-pyrazolyl)alanine methyl ester (16).** ^{1}H NMR ($CDCl_3$, δ): 2.04 (s, 3H, $COCH_3$), 3.75 (s, 3H, OCH_3), 4.52 (dd, J=3.8, 14.2 Hz, 1H, CH_2), 4.67 (dd, J=3.8, 14.2 Hz, 1H, CH_2), 4.93 (dt, J=3.8, 7.3 Hz, 1H, CH), 6.24 (t, J=2.2 Hz, 1H, 4-H), 6.67 (d, J=7.3 Hz, 1H, NH), 7.32 (d, J=2.2 Hz, 1H, 5-H), 7.51 (d, J=2.2 Hz, 1H, 3-H). ^{13}C NMR ($CDCl_3$, δ): 23.1 ($COCH_3$), 52.1 (CH_2), 52.8 (OCH_3), 52.9 (CH), 105.8 (4-C), 130.5 (5-C), 140.4 (3-C), 169.9 and 170.0 (2×CO).

4.2.6. 3-Acetamido-4,6-dihydroxy-3-methyl-2-benzofuranone (17). The benzofuranone **17** was purified by column chromatography on silica gel using hexane–ethyl acetate=1:6 as eluent. Yields were determined by integration of the ^{1}H NMR signal of the methyl group (δ=1.49 ppm) using CH_2Br_2 as an internal standard. MS (EI) *m/z* 237.1 (M$^+$). ^{1}H NMR (DMSO, δ): 1.49 (s, 3H, CH_3), 1.77 (s, 3H, $COCH_3$), 5.98 and 6.51 (2×d, J=1.9 Hz, 2H, 5-H and 7-H), 8.88 (s, 1H, NH), 9.67 (bs, 2H, OH). ^{13}C NMR (DMSO, δ): 21.4 ($COCH_3$), 21.7 (CH_3), 55.5 (3-C), 89.9 and 98.3 (5-C and 7-C), 105.7 (9-C), 154.1 and 154.2 (4-C and 6-C), 158.8 (8-C), 168.3 and 176.3 (2×CO). Anal. calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found C, 55.85; H, 4.72; N, 5.8.

4.2.7. Methyl 2-(2′,4′,6′-trimethoxyphenyl)acrylate (18). The styrene derivative was purified by column chromatography on silica gel using hexane–ethyl acetate=3:1 as eluent (isolated product **18**, mp 78–80°C, hexane). Yields were determined by integration of the ^{1}H NMR signal of the 3′-H and 5′-H protons (δ=6.16 ppm) using CH_2Br_2 as an internal standard. MS (EI) *m/z* 252.2 (M$^+$). ^{1}H NMR ($CDCl_3$, δ): 3.72 (s, 3H, $COOCH_3$), 3.76 (s, 6H, 2′-OCH_3 and 6′-OCH_3), 3.82 (s, 3H, 4′-OCH_3), 5.74 (d, J=2.0 Hz, 1H, H_{trans}), 6.16 (s, 2H, 3′-H and 5′-H), 6.50 (d, J=2.0 Hz, 1H, H_{cis}). ^{13}C NMR ($CDCl_3$, δ): 51.9 ($COOCH_3$), 55.3 and 55.8 (4′-C, 2′-C and 6′-C), 90.8 (3′-C and 5′-C), 107.9 (1′-C), 128.9 (3-C), 133.4 (2-C), 158.5 (2′-C and 6′-C), 161.1 (4′-C), 168.3 (CO). Anal. calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. Found C, 62.05; H, 6.37.

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