Tetrahedron 70 (2014) 2449–2454

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Aza-Michael reaction: selective mono- versus bis-addition under environmentally-friendly conditions

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ARTICLE INFO

Article history:
Received 28 October 2013
Received in revised form 28 January 2014
Accepted 10 February 2014
Available online 18 February 2014

Keywords:
Aza-Michael reaction
Primary amines
Mono-addition
Bis-addition
Solvent-free
Acidic alumina

ABSTRACT

Aza-Michael reactions between primary amines and methyl propenoate have been investigated under environmentally-friendly solventless heterogeneous catalysis in order to obtain the mono- or the bis-adduct. The reaction conditions can be altered so as to maximise the yields of the required product with high selectivity.

1. Introduction

The aza-Michael reaction is one of the most important reactions in modern organic synthesis since a new carbon–nitrogen bond is formed.[1] It is characterized by 100% atom efficiency, uses cheap and easily available starting materials and provides an easy route to β-amino carbonyl derivatives, which are valuable building blocks for the synthesis of various nitrogen-containing biologically active compounds, antibiotics and other drugs.[2] Primary amines add to electron poor alkenes that are susceptible to nucleophilic attack to give secondary and tertiary derivatives. The first product formed, the mono-adduct, can react further to give the tertiary derivative, or bis-adduct, and to control the reaction's selectivity obtaining the desired product when using primary amines is not always an easy to achieve target. In fact most of the amines used in the literature were secondary amines, where there is no possibility of second addition, or primary aromatic amines, usually much less reactive nucleophiles,[3] and to the best of our knowledge no emphasis has been put on the production of either the mono-adduct or the bis-adduct when using primary amines, in spite of the great importance of this reaction.[4]

The most common methodologies to perform aza-Michael reactions require activation by harsh bases or strong acids, which are harmful to the environment and also give rise to undesirable by-products.[5] To efficiently catalyse the aza-Michael addition, in the past few years alternative methods[6] have been developed, such as microwave or ultrasound accelerated reactions,[7] use of Lewis acids,[8] ionic liquids,[9] silica-supported catalysts[10] and reactions in water.[11,7c,3d] However, despite some advantages, many of these methods use hazardous organic solvents, which is not desirable from a green chemistry point of view, require long reaction times, large excesses of reagents, the prior preparation of the task specific ionic liquid catalytic medium and of the alumina or silica-supported catalysts, and in many cases the catalyst has not been recoverable, which has limited industrial applications. Among heterogeneous catalysts, neutral and basic aluminas[12,7b,4d] were mostly reported as other catalysts' supports as well as silica, which often require a further work-up of the filtrate at the end of the reaction.[10b] While acidic alumina was reported as useful heterogeneous catalyst for classical C–C bond forming Michael additions only,[13] not for hetero-Michael reactions. Moreover several of these alternative methods have a finite scope of substrates and the reported yields were mainly observed for the mono-adducts only of secondary amines, whereas the reactions with primary amines were mostly not selective, affording mixtures of mono- and bis-adducts in almost equal amounts, or giving only bis-adducts when using a very large excess of Michael acceptors.

An important target of green chemistry is represented by elimination of volatile organic solvents making the syntheses simpler, saving energy and preventing solvent wastes, hazards, and toxicity.[14] The use of heterogeneous catalysts for organic reactions

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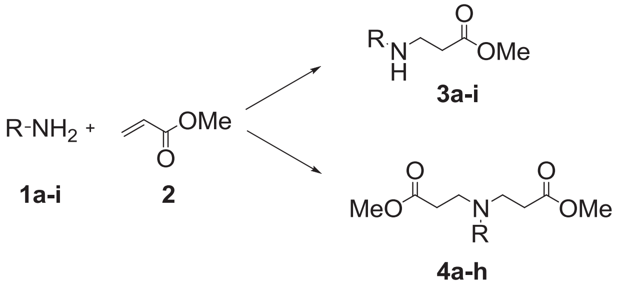
0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.02.021

is rapidly growing over homogeneous catalytic systems because of their several advantages like relative ease of extraction from the products, high stability and tolerance to harsh reaction conditions, ease of handling, reuse and environmental friendliness.[15] Thus heterogeneous catalysis and solventless conditions both show great potential for environmental pollution control and their combination represents a good way toward ideal synthesis.[16] In this context the development of efficient and operationally simple procedures for increasing selectivity of the aza-Michael mono- or bis-additions under environmentally-friendly conditions is highly appreciated.

In this study, the aza-Michael reactions between primary amines (**1**) and methyl propenoate (**2**) were investigated under solvent-free conditions and heterogeneous solid catalysis in order to efficiently obtain the mono-adduct (**3**) or the bis-adduct, (**4**) (Scheme 1).



Scheme 1. Mono- versus bis-addition product in aza-Michael reaction.

2. Results and discussion

In a preliminary study the aza-Michael reaction between pentan-1-amine (**1a**, $R{=}C_5H_{11}$) and methyl propenoate (**2**) was investigated as model reaction. The reaction was carried out at room temperature in the absence of any solvent and the conditions were initially altered using different ratios of reactants under no external catalysis and later testing two different heterogeneous solid catalysts, respectively, basic and acidic Al_2O_3, so as to maximise the yields of the required product. Tables 1 and 2 show the results of these preliminary studies.

Table 1
Improving the yield of the bis-adduct, $C_5H_{11}N(CH_2CH_2COOCH_3)_2$, **4a**

Entry	$C_5H_{11}NH_2$: $C_4H_6O_2$ **1a**:**2**	Catalyst	Reaction time (h)	Product	Yield[a] (%)
1	1.0:1.2		48	Bis-adduct	40
				Mono-adduct	14
2	1.0:2.2		24	Bis-adduct	31
				Mono-adduct	28
3	1.0:2.2	10 g basic Al_2O_3	24	Bis-adduct	60
				Mono-adduct	/
4	1.0:2.2	1 g basic Al_2O_3	24	Bis-adduct	54
				Mono-adduct	/
5	1.0:3.0		24	Bis-adduct	70
				Mono-adduct	24
6	1.0:3.0	2 g basic Al_2O_3	24	Bis-adduct	68
				Mono-adduct	/
7	1.0:2.2	2 g acid Al_2O_3	24	Bis-adduct	87
				Mono-adduct	/
8	1:2	2 g basic Al_2O_3	48	Bis-adduct	79
				Mono-adduct	14

/ not collected.
[a] Yield of pure isolated products.

All reactions were performed on a 0.01 mol scale of the limiting reagent, mixing together the two starting materials without any solvent and adding the solid catalyst when required. In the first reaction (entry 1, Table 1) the ratio of pentan-1-amine:methyl propenoate was 1.0:1.2. According to the stoichiometric equation this ratio should yield the mono-addition product, while 40% of the bis-adduct and 14% of the mono-adduct were obtained. This can be attributed to the fact that the initially produced mono-adduct is a secondary amine. Secondary amines are more basic than primary amines and thus the mono-adduct reacts faster than pentan-1-amine with methyl propenoate. A good yield was expected for bis-adduct when the ratio used was that of 1.0:2.2 (entry 2, Table 1) since two moles of methyl propenoate are required for its formation. However, a good yield was only obtained when the ratio used was that of 1.0:3.0 (entry 5, Table 1). In this latter scenario, the concentration of methyl propenoate present in the reaction mixture was relatively high and this favoured the formation of the bis-adduct. On the other side, in order to maximise the yield of the mono-addition product the amount of pentan-1-amine was then gradually increased in relation to the amount of methyl propenoate, and the yield of the mono-adduct increased from 14% (entry 1, Table 1) to 54% and 70% (entries 1 and 3, Table 2). This result was as expected since pentan-1-amine was present in a greater concentration than the mono-adduct in the reaction mixture.

Table 2
Improving the yield of the mono-adduct, $C_5H_{11}NH(CH_2CH_2COOCH_3)$, **3a**

Entry	$C_5H_{11}NH_2$: $C_4H_6O_2$ **1a**:**2**	Catalyst	Reaction time (h)	Product	Yield[a] (%)
1	2.2:1.0		24	Bis-Adduct	12
				Mono-adduct	54
2	2.2:1.0		6	Bis-adduct	18
				Mono-adduct	53
3	3.0:1.0		24	Bis-adduct	11
				Mono-adduct	70
4	2.2:1.0	1 g basic Al_2O_3	6	Bis-adduct	8
				Mono-adduct	62
5	3.0:1.0	1 g basic Al_2O_3	24	Bis-adduct	9
				Mono-adduct	59
6	1.0:1.0	2 g acid Al_2O_3	24	Bis-adduct	18
				Mono-adduct	63
7	1.0:1.0	2 g basic Al_2O_3	4	Bis-adduct	14
				Mono-adduct	53

[a] Yield of pure isolated products.

From this initial study summarized in Tables 1 and 2, it was observed that under neat conditions and without any catalyst added 70% yield for the bis-adduct was obtained when the ratio of **1a**:**2** was 1:3 (entry 5, Table 1), while the same good yield for the mono-adduct was obtained when this ratio was the opposite, 3:1 (entry 3, Table 2). Whereas under Al_2O_3 heterogeneous solid catalysis, the best results with nearly stoichiometric ratio of reactants were obtained when acidic Al_2O_3 (2 g, 200 mol %) was added as catalyst (respectively, 87% for the bis- and 63% for the mono-adduct, entry 7, Table 1 and entry 6, Table 2). The use of basic alumina had no significant effect on the yields obtained.

On the basis of these preliminary results we selected acidic alumina as the catalyst of choice. In a second series of experiments different amounts of the acidic and weakly acidic catalyst (100–300 mol %) were employed and increasing reaction temperatures were applied to further improve the selectivity obtained for the mono- or bis-addition reaction between hexan-1-amine (**1b**, $R{=}C_6H_{13}$) and methyl propenoate (**2**), chosen as second model reaction (Tables 3 and 4).

In order to maximize the yield for the mono-product **3b** the amount of **1b**:**2** was increased to 1.5:1 and 2:1, no major effect was evident although the reaction was complete in only 2.5 h (entry 2, Table 3). However in all the reactions conducted for improvement of the mono-adduct, the bis-adduct was also apparent. Although

Table 3
Optimization of the mono-adduct $C_6H_{13}NH(CH_2CH_2COOCH_3)$, **3b**

Entry	Ratio **1b**:**2**	Alumina catalyst (g)	Reaction time (h)	Temperature (°C)	Yield[a] (%) **3b**:**4b**
1	1.5:1	Acidic (2)	48	RT	62:20
2	2:1	Acidic (2)	2.5	RT	65:11
3	1:1	Acidic (2)	3	RT	72:17
4	1:1	Weakly acidic (2)	5	RT	70:15
5	2:1	Weakly acidic (2)	5	RT	51:7
6	1:1	Acidic (1)	26	RT	63:22
7	1:1	Acidic (3)	4	RT	73:18
8	1.5:1	Acidic (2)	2.5	50–60$^{(2.5)b}$	84:10

[a] Yield of pure isolated products.
[b] Heating time (h).

Table 4
Optimization of the bis-adduct $C_6H_{13}N(CH_2CH_2COOCH_3)_2$, **4b**

Entry	Ratio **1b**:**2**	Alumina catalyst (g)	Reaction time (h)	Temperature (°C)[b]	Yield[a] (%) **3b**:**4b**
1	1:2.2	Acidic (2)	97	RT	/:84
2	1:2	Acidic (2)	144	RT	/:80
3	1:2.2	Acidic (2)	23	RT	/:88
4	1:2	Acidic (2)	48	RT	5:90
5	1:2	Acidic (2)	48	50–60$^{(8)}$	/:84
6	1:2	Acidic (2)	51	70–80$^{(15)}$; 100–110$^{(3)}$	/:73
7	1:2	Acidic (2)	5.5	100–110$^{(5.5)}$	/:90
8	1:2	Acidic (1)	6	100–110$^{(6)}$	/:80

/ not collected.
[a] Yield of pure isolated products.
[b] Heating time (h).

weakly acidic alumina catalyst produced similar results to that of acidic alumina, a difference in the reaction times was evident, those of acidic alumina being much shorter. Also, a change in the amount of catalyst used was done and it was found that an increase in the amount of catalyst does not significantly affect the yield of the product, whereas a decrease affects the rate and the yield of the reaction in a negative way (entries 7, and 6, Table 3). A great improvement was finally observed for the mono-product **3b** when heating at 50–60 °C was applied, recording increased yield and greatly reduced reaction time (84%, entry 8, Table 3). According to the results shown in Table 3 the best conditions for production of the mono-adduct were using the 1.5:1 mol ratio of amine to acceptor, with 0.2 g of acidic alumina per mmol of substrate as the catalyst, and increasing the temperature to reflux values.

Following the initial promising results obtained for the bis-product the mole ratio of **1b**:**2** was only slightly decreased to 1:2, obtaining the same good results and showing that the slight excess of **2** in the mixture did not affect the yield of product **4b** as well as longer reaction time. In this case weakly acidic alumina was not utilized as it had shown that for the mono-adduct no improvement was observed. Monitoring the temperature effect on the bis-product **4b** it was determined that heating the reaction at 50–60 °C increased the rate of reaction (entry 5, Table 4) as observed through GC analysis, as after 8 h of heating the reaction proceeded much faster than without heating; however the reaction still reached finalization after 48 overall hours. Furthermore (entry 6, Table 4) heating at 70–80 °C for 15 h did not make a significant difference and only increasing the temperature up to 100–110 °C greatly affected the rate of reaction (entry 7, Table 4), reducing the reaction time to only 5.5 h. It was concluded that the best conditions observed in bis-addition optimization were the 1:2 stoichiometric ratio of amine to acceptor, the use of 0.2 g of acidic alumina per mmol of substrate and heating to reflux.

To explore the efficiency and more general validity of this procedure for the selective mono- or bis-aza-Michael addition, different aliphatic and aromatic amines were reacted with methyl propenoate, under the corresponding best reaction conditions found. When using other aliphatic amines (Tables 5 and 6) the results were similar to those obtained with the model reactions with high selectivities, high yields and no side reactions. Whereas cyclohexylamine produced mono-adduct in high yields but bis-adduct in substantially lower yields, which can be associated with the increased steric hindrance of the product. On the other hand aromatic amines are very weak nucleophile, and hence addition is much more difficult to occur. Furthermore, the following bis-addition is even more difficult for steric reasons, and thus the capability of forming any bis-adduct is even smaller.[3] Under our conditions the mono-adducts of the primary aromatic amines were produced in quantitative yields, except for 4-nitroaniline (**1h**), in which the bis-adducts were formed in low yields, even with an excess of **2**. A secondary aromatic amine (**1i**), which can only produce the mono-adduct, was also tested, and it was not produced in high yields as obtained with the primary aromatic amines, this result can again be attributed to the increased steric hindrance.

Table 5
Mono-addition of aliphatic and aromatic amines, **1c**–**i**, and **2**

Entry	R	Reaction time (h)	Temperature (°C)	Yields[a] (%) **3**:**4**
1	n-C_3H_7 **1c**	2	40–45	79:11
2	n-C_4H_9 **1d**	3	70–80	80:11
3	c-C_6H_{11} **1e**	1.5	100–110	95:3
4	Ph **1f**	3	100–110	97:1
5	p-C_2H_5–C_6H_4 **1g**	3	100–110	87:5
6	p-NO_2–C_6H_4 **1h**	3	100–110	Trace[b]
7	$PhNHCH_3$ **1i**[c]	3.5	100–110	81[d]

[a] Yield of pure isolated products.
[b] Approximate GC yield 1.7:0.7 (of **3**:**4**).
[c] Secondary amine used.
[d] Mono-adduct **3i** only possible product.

Table 6
Bis-addition of aliphatic and aromatic amines, **1c**–**h**, and **2**

Entry	R	Reaction time (h)	Temperature (°C)$^{(\text{heating time,h})}$	Yields[a] (%) **3**:**4**
1	n-C_3H_7 **1c**	6	40–45$^{(6)}$	/:88
2	n-C_4H_9 **1d**	6.5	70–80$^{(6.5)}$	/:93
3	c-C_6H_{11} **1e**	27	100–110$^{(8.5)}$	42:51
4	Ph **1f**	22.5	100–110$^{(9)}$	98:1
5[b]	p-C_2H_5–C_6H_4 **1g**	27	100–110$^{(8)}$	98:1
6[b]	p-NO_2–C_6H_4 **1h**	4	100–110$^{(9)}$	Trace[c]

[a] Yield of pure isolated products.
[b] 2.5 equiv acceptor was used.
[c] Approximate GC yield 3.2:1.2 (of **3**:**4**).

Finally the catalyst recycling was examined. One of the fundamentals in green chemistry is the decrease in use of the catalyst. It is dependent on the recycling of the catalyst and its reuse for several cycles. During our study the catalyst from entry 4 Table 4, which was used in the production of the bis-adduct **4b**, was recovered by simple filtration, washed with diethyl ether and then dried under vacuum in a desiccator. It was reused, under same conditions, without any special activation for two consecutive cycles (entries 2 and 3, Table 7) producing a yield of 83% and 74% of **4b**, respectively.

3. Conclusions

The aza-Michael reaction is one of the most widely used reactions in modern organic synthesis and a powerful tool for

Table 7
The % yields obtained for **4b** using recycled acidic alumina catalyst

Entry	Ratio **1b**:**2**	Acidic alumina catalyst (mol %)	Reaction time (h)	Yield[a] (%) **4b**
1	1:2	200	48	90%
2	1:2	200[b]	68	83%
3	1:2	200[c]	72	74%

[a] Yield of pure isolated products.
[b] Catalyst recycled from entry 1.
[c] Catalyst recycled from entry 2.

building C–N bonds following green chemistry principles. Our results show that aza-Michael reactions between primary amines and methyl propenoate can be controlled in order to obtain in high yields the required product, which is the secondary or the tertiary derivative, as result of a selective mono- or a double-addition. Moreover the reaction can be performed under green environmentally-friendly conditions, using nearly stoichiometric ratio of reactants and with a simple work-up procedure. In fact the best results for both adducts were obtained under solvent-free conditions and heterogeneous acidic catalysis, so acidic Al_2O_3 could be proposed as an alternative efficient solid heterogeneous catalyst for selective aza-Michael reactions, with the advantage of no need of catalyst preparation or activation, as required by mostly of the supported solid catalysts, no promotions of side reactions like the polymerization of the starting electron poor alkene, and small amounts required (only 0.2 g per mmol of substrate). It shows a high catalytic activity in solvent-free green conditions, can be easily separated minimizing product losses and can be easily recycled at least two times, without re-activation and any significant loss of activity; in addition, the catalyst is easily commercially available. More applications of aza-Michael reactions promoted by acidic alumina are under development in our laboratories.

4. Experimental

4.1. General

All commercially available chemicals and reagents were purchased from Aldrich and used without further purification. Acidic (Scharlau, grain size: 0.05–0.2 mm, 70–290 mesh ASTM, pH 4.5, activity degree 1), weakly acidic (Sigma–Aldrich, ~150 mesh, pH ~6.0) and basic (Acros, Brockmann I, 50–200 μm, pH 9–10) alumina were used without any activation. IR spectra were recorded on a Shimadzu IRAffinity-1 FTIR Spectrometer, calibrated against a 1602 cm^{-1} polystyrene absorbance spectrum. Samples were either analysed as a thin film or in a Nujol™ mull, between sodium chloride discs. The ^1H and ^{13}C NMR spectra were recorded on Bruker AM250 NMR spectrometer fitted with a dual probe at frequencies of 250 MHz and 62.9 MHz for ^1H and ^{13}C NMR, respectively. Samples were dissolved in deuterated chloroform (with TMS). Mass spectra (EI) were recorded with a Thermo Finnigan Trace DSQ quadropole mass spectrometer together with a Thermo Finnigan Trace GC Ultra equipped with a 25 m by 0.22 mm BP1 (100% dimethlypolysiloxane stationary phase) column. Microanalyses were performed with a CHNS-O analyzer Model EA 1108 from Fisons Instruments. Reaction monitoring was done by TLC and GC analysis. Gas chromatography was carried out on a Shimadzu GC-2010 *plus* gas chromatograph equipped with a flame ionisation detector and HiCap 5 GC column with dimensions of 0.32 mm (internal diameter)×30 m (length)×0.25 μm (film thickness), using nitrogen as carrier gas. Most of the synthesised compounds are known and their spectroscopic data are in agreement with those reported in the literature.

4.2. Procedure A: general procedure followed for the preparation of mono-adducts, 3

The amine **1** (15 mmol) and methyl propenoate **2** (10 mmol) were pipetted into a round bottomed flask equipped with a magnetic bar and a reflux condenser. Acidic alumina (2 g, 200 mol %) was then introduced in the flask at room temperature by means of a plastic funnel. The mixture was heated to reflux by using an oil bath. The reaction was followed by TLC and GC analysis. On completion the mixture was allowed to cool to room temperature. The mixture was then filtered through a filter paper and the catalyst rinsed with diethyl ether. The filtrate was concentrated by rotary evaporation and then purification of the mono-adduct was done using gravity column chromatography on silica gel. For aliphatic amines, the bis-adduct side product was primarily eluted using 75:25 of hexane and ethyl acetate. As soon as the bis-adduct was eluted, the eluent's polarity was increased to 50:50 of hexane and ethyl acetate to elute the remaining mono-adduct. On the other hand, for aromatic amines, the mono-adduct was the first to elute out of the column, and was eluted using only 80:20 of hexane and ethyl acetate, respectively. The yields of the purified adducts **3** were finally recorded and characterisation was done using IR and NMR spectroscopy.

4.3. Procedure B: general procedure followed for the preparation of bis-adducts, 4

Procedure A was followed with the difference being that 20 mmol of the Michael acceptor **2** and 10 mmol of the amine **1** were utilized, while keeping all of the other conditions the same. At the end of the reaction the products in the mixture were then separated by column chromatography on silica gel. The bis-adducts produced from aliphatic amines were eluted using 75:25 of hexanes and ethyl acetate, respectively. In the case of aromatic amines, the mono-adduct and the amine were first eluted using 80:20 of hexanes and ethyl acetate, and then the bis-adduct was eluted using ethyl acetate only. The product **4** was weighed and characterized by IR and NMR analysis.

4.4. Product identification

*4.4.1. Methyl 3-(pentylamino)propanoate (**3a**).*[17] Colourless oil. IR (neat, cm^{-1}): ν=3323, 2954, 2927, 2858, 1732, 1436, 1460, 1363, 1128, 1064, 1014, 839. ^1H NMR ($CDCl_3$, 250 MHz): δ 0.90 (t, J=6.7 Hz, 3H), 1.23–1.34 (m, 4H), 1.42–1.53 (m, 2H), 1.60 (br s, 1H), 2.58 (dt, J=6.7 and 7.3 Hz, 4H), 2.89 (t, J=6.7 Hz, 2H), 3.68 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm) 14.0, 22.6, 29.5, 29.8, 34.0, 45.0, 50.0, 52.0, 173.2.

*4.4.2. Methyl 3-[(3-methoxy-3-oxopropyl)(pentyl)amino]propanoate (**4a**).* Colourless oil. IR (neat, cm^{-1}): ν=2953, 2858, 1750, 1436, 1355, 1128, 1093, 1049, 840. ^1H NMR ($CDCl_3$, 250 MHz): δ 0.88 (t, J=6.7 Hz, 3H, Me), 1.18–1.48 (m, 6H, $(CH_2)_3$Me), 2.36–2.47 (m, 6H, CH_2CO, CH_2N), 2.76 (t, J=7.3 Hz, 4H, CH_2N), 3.68 (s, 6H, O*Me*). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm) 14.1, 22.6, 27.0, 29.7, 32.8, 49.2, 52.0, 53.8, 173.2. MS (EI): m/z (%)=259 (6) $[M]^+$, 202 (100), 186 (62), 160 (26), 130 (44), 84 (26). Anal. Calcd for $C_{13}H_{25}NO_4$ (259.343): C, 60.21; H, 9.72; N, 5.4; O, 24.68. Found: C, 60.37; H, 9.51; N, 5.31; O, 24.89.

*4.4.3. Methyl 3-(hexylamino)propanoate (**3b**).*[18,2e] Yellow oil. IR (neat, cm^{-1}): ν=3325, 2922, 1734, 1436, 1363, 1174, 1016, 840, 725. ^1H NMR ($CDCl_3$, 250 MHz) δ 0.88 (t, J=6.7 Hz, 3H), 1.22–1.38 (m, 6H), 1.41–1.57 (m, 3H), 2.53 (t, J=6.1 Hz, 2H), 2.60 (t, J=7.3 Hz, 2H), 2.88 (t, J=6.1 Hz, 2H), 3.70 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm) 14.1, 22.6, 27.0, 30.1, 31.8, 34.6, 45.1, 49.9, 51.6, 173.3.

*4.4.4. Methyl 3-[hexyl(3-methoxy-3-oxopropyl)amino]propanoate (**4b**).*[2g] Colourless oil. IR (neat, cm^{-1}): ν=2929, 1735, 1436, 1355, 1174, 1041, 842. ^{1}H NMR (CDCl3, 250 MHz): δ 0.88 (t, J=6.7 Hz, 3H), 1.18–1.48 (m, 8H), 2.40 (t, J=7.3 Hz, 2H), 2.44 (t, J=7.3 Hz, 4H), 2.76 (t, J=7.3 Hz, 4H), 3.68 (s, 6H). ^{13}C NMR (CDCl3, 62.9 MHz) δ (ppm) 14.1, 22.7, 27.0, 27.1, 31.8, 32.6, 49.3, 51.5, 53.9, 173.1.

*4.4.5. Methyl 3-(propylamino)propanoate (**3c**).*[18] Pale yellow oil. IR (neat, cm^{-1}): ν=3325, 2956, 1735, 1436, 1363, 1178, 1012, 839, 750. ^{1}H NMR (CDCl$_3$, 250 MHz): δ 0.92 (t, J=7.3 Hz, 3H), 1.50 (sextet, J=7.3 Hz, 2H), 1.50 (s, 1H, N–H), 2.53 (t, J=6.1 Hz, 2H), 2.58 (t, J=7.3 Hz, 2H), 2.89 (t, J=6.1 Hz, 2H), 3.69 (s, 3H).

*4.4.6. Methyl 3-[(3-methoxy-3-oxopropyl)(propyl)amino]propanoate (**4c**).*[19] Colourless oil. IR (neat, cm^{-1}): ν=2954, 1737, 1436, 1373, 1174, 1047, 842. ^{1}H NMR (CDCl$_3$, 250 MHz): δ 0.85 (t, J=7.3 Hz, 3H), 1.44 (sextet, J=7.3 Hz, 2H), 2.37 (t, J=7.3 Hz, 2H), 2.45 (t, J=7.3 Hz, 4H), 2.77 (t, J=7.3 Hz, 4H), 3.68 (s, 6H).

*4.4.7. Methyl 3-(butylamino)propanoate (**3d**).*[18,11a] Pale yellow oil. IR (neat, cm^{-1}): ν=3325, 2954, 1735, 1436, 1361, 1176, 1058, 734. ^{1}H NMR (CDCl$_3$, 250 MHz): δ 0.92 (t, J=7.3 Hz, 3H), 1.34 (sextet, J=7.3 Hz, 2H), 1.47 (quintet, J=7.3 Hz, 2H), 1.58 (s, 1H, N–H), 2.53 (t, J=6.7 Hz, 2H), 2.61 (t, J=7.3 Hz, 2H), 2.89 (t, J=6.7 Hz, 2H), 3.69 (s, 3H).

*4.4.8. Methyl 3-[butyl(3-methoxy-3-oxopropyl)amino]propanoate (**4d**).*[20] Colourless oil. IR (neat, cm^{-1}): ν=2954, 1728, 1436, 1373, 1174, 1045, 842. ^{1}H NMR (CDCl$_3$, 250 MHz): δ 0.90 (t, J=7.3 Hz, 3H), 1.28 (sextet, J=6.1 Hz, 2H), 1.40 (quintet, J=6.7 Hz, 2H), 2.40 (t, J=7.3 Hz, 2H), 2.45 (t, J=7.3 Hz, 4H), 2.77 (t, J=7.3 Hz, 4H), 3.68 (s, 6H).

*4.4.9. Methyl 3-(cyclohexylamino)propanoate (**3e**).*[17,11a] Yellow oil. IR (neat, cm^{-1}): ν=3319, 2926, 1735, 1436, 1363, 1170, 1045, 846, 750. ^{1}H NMR (CDCl$_3$, 250 MHz): δ 0.95–1.22 (m, 4H), 1.42 (s, 1H), 1.54–1.95 (m, 6H), 2.42 (dt, J=3.7 Hz, J=2.4 Hz, 1H), 2.52 (t, J=6.7 Hz, 2H), 2.91 (t, J=6.7 Hz, 2H), 3.69 (s, 3H).

*4.4.10. Methyl 3-[cyclohexyl(3-methoxy-3-oxopropyl)amino]propanoate (**4e**).*[5c,8c] Pale pink oil. IR (neat, cm^{-1}): ν=2927, 1730, 1435, 1357, 1174, 1047, 840. ^{1}H NMR (CDCl$_3$, 250 MHz): δ 1.0–1.30 (m, 4H), 1.85–1.55 (m, 6H), 2.38–2.30 (m, 1H), 2.42 (t, J=7.3 Hz, 4H), 2.78 (t, J=7.3 Hz, 4H), 3.65 (s, 6H).

*4.4.11. Methyl 3-anilinopropanoate (**3f**).*[3d] White solid. IR (Nujol, cm^{-1}): ν=3396, 1741, 1602, 1506, 1174, 746. ^{1}H NMR (CDCl$_3$, 250 MHz): δ 2.63 (t, J=6.7 Hz, 2H), 3.46 (t, J=6.7 Hz, 2H), 3.70 (s, 3H), 4.02 (broad s, 1H), 6.63 (d, J=7.9 Hz, 2H), 6.73 (t, J=7.3 Hz, 1H), 7.20 (t, J=8.5 Hz, 2H). ^{13}C NMR (CDCl$_3$, 62.9 MHz) δ (ppm) 33.7, 39.4, 51.7, 113.0, 117.7, 129.3, 147.6, 172.8.

*4.4.12. Methyl 3-[(3-methoxy-3-oxopropyl)anilino]propanoate (**4f**).*[3d] White solid. IR (Nujol, cm^{-1}): ν=3030, 2954, 1734, 1600, 1506, 1373, 1199, 908, 734. ^{1}H NMR (CDCl$_3$, 250 MHz): δ 2.59 (t, J=7.3 Hz, 2H), 2.63 (t, J=7.3 Hz, 2H), 3.64 (t, J=7.3 Hz, 2H), 3.65 (t, J=7.3 Hz, 2H), 3.68 (s, 6H), 6.77 (d, J=8.6, 2H), 6.80 (t, J=7.3 Hz, 1H), 7.26 (t, J=6.7 Hz, 2H).

*4.4.13. Methyl 3-(4-ethylanilino)propanoate (**3g**).* Brown oil. IR (neat, cm^{-1}): ν=3396, 3016, 2958, 1732, 1616, 1517, 1436, 1367, 1174, 1047, 823. ^{1}H NMR (CDCl$_3$, 250 MHz): δ 1.19 (t, J=7.3 Hz, 3H, Me), 2.54 (q, J=7.3 Hz, 2H, CH_2Me), 2.62 (t, J=6.7 Hz, 2H, CH_2CO), 3.44 (t, J=6.7 Hz, 2H, CH_2N), 3.70 (s, 3H, O*Me*), 3.91 (broad s, 1H, N*H*), 6.58 (d, J=8.5 Hz, 2H, Ph), 7.03 (d, J=8.5 Hz, 2H, Ph). ^{13}C NMR (CDCl$_3$, 62.9 MHz) δ (ppm) 15.9, 27.9, 33.8, 39.8, 51.7, 113.3, 128.6, 133.7, 145.5, 172.9. MS (EI): m/z (%)=207 (54) [M]$^+$, 192 (27), 134 (100), 118 (30). Anal. Calcd for $C_{12}H_{17}NO_2$ (207.269): C, 69.54; H, 8.27; N, 6.76; O, 15.44. Found: C, 69.72; H, 8.11; N, 6.88; O, 15.31.

*4.4.14. Methyl 3-[4-ethyl(3-methoxy-3-oxopropyl)anilino]propanoate (**4g**).* Brown oil. IR (neat, cm^{-1}): ν=2960, 1737, 1610, 1516, 1456, 1375, 1172, 1076, 819. ^{1}H NMR (CDCl$_3$, 250 MHz): δ 1.21 (t, J=7.3 Hz, 3H, Me), 2.5–2.7 (m, 2H, CH_2Me), 2.57 (t, J=7.3 Hz, 4H, CH_2CO), 3.5–3.6 (m, 4H, CH_2N), 3.67 (s, 6H, O*Me*), 6.82 (d, J=8.5 Hz, 2H, Ph), 7.14 (d, J=8.5 Hz, 2H, Ph). ^{13}C NMR (CDCl$_3$, 62.9 MHz) δ (ppm) 15.9, 27.8, 32.4, 47.2, 51.7, 113.3, 128.8, 133.2, 144.9, 172.6. MS (EI): m/z (%)=293 (38) [M]$^+$, 262 (10), 220 (100), 178 (16) 148 (16), 118 (14). Anal. Calcd for $C_{16}H_{23}NO_4$ (293.360): C, 65.51; H, 7.90; N, 4.77; O, 21.81. Found: C, 65.36; H, 7.61; N, 4.90; O, 21.69.

*4.4.15. Methyl 3-(methylanilino)propanoate (**3i**).*[3d] Brown-yellow oil. IR (neat, cm^{-1}): ν=3026, 2949, 1734, 1600, 1502, 1435, 1363, 1172, 1045, 837. ^{1}H NMR (CDCl$_3$, 25 MHz): δ 2.58 (t, J=7.3 Hz, 2H), 2.93 (s, 3H), 3.67 (s, 3H), 3.68 (t, J=7.3 Hz, 2H), 6.73 (t, J=6.7 Hz, 1H), 6.74 (d, J=8.5 Hz, 2H), 7.25 (t, J=7.9 Hz, 2H).

Acknowledgements

The Authors thank the University of Malta for financial support.

References and notes

1. (a) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337–2347; (b) Dugger, R. W.; Ragan, J. A.; Brown Ripin, D. H. *Org. Process Res. Dev.* **2005**, *9*, 253–258; (c) Harrison-Marchand, A.; Chataigner, I.; Maddaluno, J. In *Science of Synthesis*; Georg Thieme: New York, NY, 2005; Vol. 26, p 1225; (d) Krishna, P. R.; Sreeshailam, A.; Srinivas, R. *Tetrahedron* **2009**, *65*, 9657–9672.
2. (a) Ballini, R.; Bazán, N. A.; Bosica, G.; Plamieri, A. *Tetrahedron Lett.* **2008**, *49*, 3865–3867; (b) Rulev, A. Y. *Russ. Chem. Rev.* **2011**, *80*, 197–218; (c) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, UK, 1992; p 114; (d) Xu, L.-W.; Xia, C. G. *Eur. J. Org. Chem.* **2005**, 633–639; (e) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narsaiah, A. V. *Chem. Lett.* **2003**, 988–989; (f) Cardillo, G.; Tomassini, C. *Chem. Soc. Rev.* **1996**, *25*, 117–128; (g) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; De Pue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391–1407.
3. (a) Ding, R.; Katebzadeh, K.; Roman, L.; Bergquist, K.; Lindstrom, U. M. *J. Org. Chem.* **2006**, *71*, 352–355; (b) Yeom, C.; Kim, M. J.; Kim, B. M. *Tetrahedron* **2007**, *63*, 904–909; (c) Cao, Y.-J.; Lai, Y.-J.; Wang, X.; Li, Y.-J.; Xiao, W.-J. *Tetrahedron Lett.* **2007**, *48*, 21–24; (d) De, K.; Legros, J.; Crousse, B.; Bonnet-Delpon, D. *J. Org. Chem.* **2009**, *74*, 6260–6265.
4. (a) Monsalve, L. N.; Gillanders, F.; Baldessari, A. *Eur. J. Org. Chem.* **2012**, *6*, 1164–1170; (b) Medina, F.; Michon, C.; Agbossou-Niedercorn, F. *Eur. J. Org. Chem.* **2012**, *31*, 6218–6227; (c) Medina, F.; Michon, C.; Agbossou-Niedercorn, F. *C. R. Chim.* **2013**, *16*, 311–317; (d) Ai, X.; Wang, X.; Liu, J.-M.; Ge, Z.-M.; Cheng, T.-M.; Li, R.-T. *Tetrahedron* **2010**, *66*, 5373–5377.
5. (a) Jenner, G. *Tetrahedron Lett.* **1995**, *36*, 233–236; (b) Chan, P. W. H.; Cottrel, I. F.; Moloney, M. G. *Tetrahedron Lett.* **1997**, *38*, 5891–5894; (c) Shaikh, N. S.; Deshpande, V. H.; Bedekar, A. V. *Tetrahedron* **2001**, *57*, 9045–9048; (d) Azizi, N.; Saidi, M. R. *Tetrahedron* **2004**, *60*, 383–387; (e) Kobayashi, S.; Karumoto, K.; Sugiura, M. *Org. Lett.* **2002**, *4*, 1319–1322; (f) Bartoli, G.; Bosco, M.; Marcantoni, E.; Petrini, M.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2001**, *66*, 9052–9055; (g) Reboule, I.; Gil, R.; Collin, J. *Tetrahedron Lett.* **2005**, *46*, 7761–7764.
6. (a) Yadav, J. S.; Reddy, A. R.; Rao, Y. G.; Narsaiah, A. V.; Reddy, B. V. S. *Synthesis* **2007**, 3447–3450; (b) Khan, A. T.; Parvin, T.; Gazi, S.; Choudhury, L. *Tetrahedron Lett.* **2007**, *48*, 3805–3808; (c) Das, B.; Chowdhury, N. *J. Mol. Catal. A: Chem.* **2007**, *263*, 212–215; (d) Hou, X.; Hemit, H.; Yong, J.; Nie, L.; Aisa, H. *Synth. Commun.* **2010**, *40*, 973–979.
7. (a) Duan, Z.; Xuan, X.; Li, T.; Yang, C.; Wu, Y. *Tetrahedron Lett.* **2006**, *47*, 5433–5436; (b) Saikia, M.; Kakati, D.; Joseph, M. S.; Sarma, J. C. *Lett. Org. Chem.* **2009**, *6*, 654–658; (c) Labade, V. B.; Pawar, S. S.; Shingare, M. S. *Monatsh. Chem.* **2011**, *142*, 1055–1059; (d) Wei, T.; Hua, M.; Shi, H.; Liu, Y.; Zhang, Y. *J. Chem. Res.* **2010**, 452–454.
8. (a) Bartoli, G.; Bartolacci, M.; Giuliani, A.; Marcantoni, E.; Massacesi, M.; Torregiani, E. *J. Org. Chem.* **2005**, *70*, 169–174; (b) Choudhary, V. R.; Dumbre, D. K.; Patil, S. K. *RSC Adv.* **2012**, *2*, 7061–7065; (c) Mao, X.-X.; Shen, Y.-M.; Wang, J.; Xia, Q.-H. *Kinet. Catal.* **2011**, *52*, 525–528; (d) Vijender, M.; Kishore, P.; Satyanarayana, B. *Synth. Commun.* **2007**, *37*, 589–592.
9. (a) Xu, J.-M.; Wu, Q.; Zhang, Q.-Y.; Zhang, F.; Lin, X.-F. *Eur. J. Org. Chem.* **2007**, 1798–1802; (b) Ying, A.; Zheng, M.; Xu, H.; Qiu, F.; Ge, C. *Res. Chem. Intermed.* **2011**, *37*, 883–890; (c) Chen, X.; Li, X.; Song, H.; Qian, Y.; Wang, F. *Tetrahedron Lett.* **2011**, *52*, 3588–3591; (d) Ying, A.-G.; Wang, L.-M.; Deng, H.-X.; Chen, J.-H.; Chen, X.-Z.; Ye, W.-D. *ARKIVOC* **2009**, *xi*, 288–298; (e) Xu, J.-M.; Qian, C.; Liu, B.-K.; Wu, Q.; Lin, X.-F. *Tetrahedron* **2007**, *63*, 986–990; (f) Yang, L.; Xu, L.-W.; Zhou, W.; Li, L.; Xia, C.-G. *Tetrahedron Lett.* **2006**, *47*, 7723–7726.

10. (a) Saidi, M. R.; Pourshojaei, Y.; Aryanasab, F. *Synth. Commun.* **2009**, *39*, 1109–1119; (b) Wang, Y.; Yuan, Y.-Q.; Guo, S.-R. *Molecules* **2009**, *14*, 4779–4789; (c) Mukherjee, C.; Misra, A. *Lett. Org. Chem.* **2007**, *4*, 54–59.
11. (a) Ranu, B. C.; Banerjee, S. *Tetrahedron Lett.* **2007**, *48*, 141–143; (b) Loh, T. P.; Wie, L. L. *Synlett* **1998**, 975–976; (c) Polshettiwar, V.; Varma, R. S. *Tetrahedron Lett.* **2007**, *48*, 8735–8738; (d) Matveeva, E. V.; Petrovskii, P. V.; Odinets, I. L. *Tetrahedron Lett.* **2008**, *49*, 6129–6133; (e) Matveeva, E. V.; Petrovskii, P. V.; Klemenkova, Z. S.; Bondarenko, N. A.; Odinets, I. L. *C. R. Chim.* **2010**, *13*, 964–970.
12. Yang, L.; Xu, L.-W.; Xia, C.-G. *Tetrahedron Lett.* **2005**, *46*, 3279–3282.
13. Ballini, R.; Maggi, R.; Palmieri, A.; Sartori, G. *Synthesis* **2007**, *19*, 3017–3020.
14. (a) Tanaka, K. *Solvent-free Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2003; (b) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025–1074; (c) Ranu, B. C.; Dey, S. S.; Hajra, A. *ARKIVOC* **2002**, *7*, 76–81.
15. (a) Sheldon, R. A.; Dakka, J. *Catal. Today* **1994**, *19*, 215–245; (b) Hoelderich, W. F.; Heitmann, G. *Catal. Today* **1997**, *38*, 227–233; (c) McKillop, A.; Young, D. W. *Synthesis* **1979**, 401–422; (d) Noritaka, M.; Misono, M. *Chem. Rev.* **1998**, *98*, 199–217; (e) Maitlis, P. M.; Long, H. C.; Quyoum, R.; Turner, M. L.; Wang, Z.-Q. *Chem. Commun.* **1996**, 1–8; (f) Clark, J. H. *Pure Appl. Chem.* **2001**, *73*, 103–111.
16. (a) Wender, P. A.; Handy, S. L.; Wright, D. L. *Chem. Ind.* **1997**, 765–769; (b) *Chemistry of Waste Minimisation*; Clark, J. H., Ed.; Chapman and Hall: London, UK, 1995; (c) Sheldon, R. A. *Chem. Ind.* **1997**, 12–15; (d) Clark, J. H.; Macquarrie, D. J. *Chem. Soc. Rev.* **1996**, *25*, 303–310; (e) Hall, N. *Science* **1994**, *266*, 32–34; (f) Corma, A. *Chem. Rev.* **1995**, *95*, 559–614; (g) Arends, I. W. C. E.; Sheldon, R. A.; Wallan, M.; Schuchardt, U. *Angew. Chem., Int. Ed.* **1997**, *36*, 1144–1163.
17. Biggs, D. F.; Coutts, R. T.; Selley, M. L.; Towill, A. *J. Pharm. Sci.* **1972**, *61*, 1739–1745.
18. Coutts, R. T.; Hubbard, J. W.; Midha, K. K.; Prasad, K. *J. Pharm. Sci.* **1971**, *60*, 28–33.
19. Preobrashenskii. *Zh. Obshch. Khim.* **1957**, *27*, 3162–3166.
20. Chaudhuri, M. K.; Hussain, S.; Kantam, M. L.; Neelima, B. *Tetrahedron Lett.* **2005**, *46*, 8329–8331.