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Journal of Organometallic Chemistry 662 (2002) 172–177

Journal of Organometallic Chemistry

www.elsevier.com/locate/jorganchem

Direct synthesis of unsaturated β-amino acids

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Received 26 July 2002; accepted 12 September 2002

Abstract

Zinc bromide promoted addition of trimethylsilyl butenoate lithium enolates to aromatic aldimines. The corresponding β-amino acids were obtained in moderate to good yields as *anti* isomers. The reaction was believed to proceed via the zinc enolates. A tentative explanation of the selectivity in favour of the *anti* isomers was proposed.

Keywords: Trimethylsilyl butenoates; Lithium enolates; Zinc bromide; Aldimines

1. Introduction

Interest in the synthesis of β-amino acids has increased enormously in the last decade due to their pharmacological and biological effects. Indeed, applications to β-lactam synthesis [1–5] and to the preparation of β-peptides [6–8] had led to growing attention to these compounds.

In connection with our work in this area, we wish to report here an interesting new synthesis of free unsaturated β-amino acids using unsaturated trimethylsilyl esters.

In a previous work, we have shown the ability of $ZnBr_2$ to promote exclusive γ-addition of unsaturated bis(trimethylsilyl)ketene acetals **1** to aldehydes [9,10] and to aldimines [11] affording the corresponding α,β-unsaturated-δ-hydroxy acids **2** and α,β-unsaturated-δ-aryl amino acids **3** (Scheme 1).

Recently, we have reported [12] an efficient direct synthesis of free unsaturated β-hydroxy acids **5** by α-coupling of unsaturated trimethylsilyl esters **4** (Scheme 2).

In the present paper, we report the successful application of these unsaturated trimethylsilyl esters to the direct synthesis of free unsaturated β-amino acids by an exclusive α-addition to aldimines.

2. Results and discussion

Surprisingly, when arylaldimines were added to unsaturated trimethylsilyl ester lithium enolates, the reaction did not work at all under varied reaction conditions (temperature, solvent, time and concentration). The weak reactivity of the imine functionality could explain these disappointing results. We tried to circumvent this problem by activation of the C=N double bond with Lewis acids, the strategy most commonly used in this field.

We first examined the reaction of trimethylsilyl butenoic ester **4a** with benzylidene aniline in the presence of several Lewis acids to determine the best catalyst for this reaction (Table 1).

From the results reported in Table 1, zinc bromide in THF can be considered as the most active Lewis acid (entry 12). When this reaction was tested with less than one equivalent (entry 13), lower chemical yield was obtained. Furthermore, an excess amount of $ZnBr_2$ did not increase the yield of the β-amino acid (entry 14). Last, we have found that it was more practical to add a

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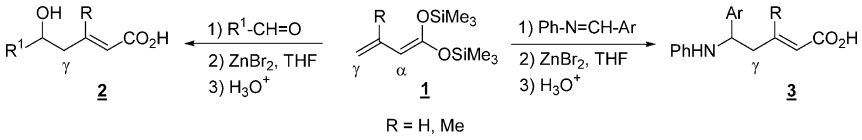
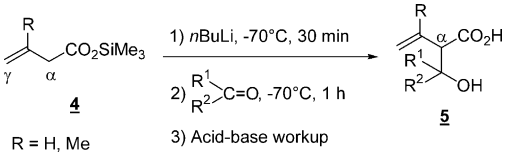
PII: S0022-328X(02)01905-8

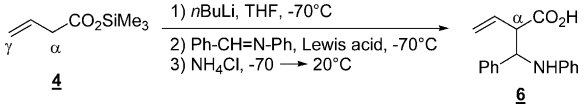


Scheme 1.



Scheme 2.

Table 1
Influence of the Lewis acid on the formation of the unsaturated β-amino acid



Entry	Lewis acid [a]	Solvent	Yield (%) [b] **6**
1	None	THF	0
2	BF_3	Ether	16
3	$TiCl_4$	CH_2Cl_2	8
4	TMSOTf	THF	9
5	$Zn(OTf)_2$	THF	10
6	MgI_2	THF	Traces
7	$MgBr_2$	THF	Traces
8	ZnI_2	THF	20
9	$ZnCl_2$	THF	30
10	$ZnBr_2$	Toluene	22
11	$ZnBr_2$	Ether	31
12	$ZnBr_2$	THF	64
13	$ZnBr_2$ [c]	THF	35
14	$ZnBr_2$ [d]	THF	61
15	$ZnBr_2$ [e]	THF	69

[a] One equivalent of the Lewis acid was used unless otherwise noted.
[b] Estimated by ^{1}H-NMR on the crude reaction mixture with respect to nonreacted aldimine (molar percentage).
[c] 0.4 equivalent of $ZnBr_2$ was used.
[d] Two equivalents of $ZnBr_2$ were used.
[e] A solution of $ZnBr_2$ in THF was added at −70 °C to the trimethylsilyl ester lithium enolate.

THF solution of $ZnBr_2$ to the preformed trimethylsilyl ester lithium enolate; aldimine was then added (entry 15). In this case, zinc enolate was probably formed with activation of the C=N double bond (see Section 2.1).

We next investigated the scope and limitations of this new synthesis of β-amino acids. For this, the reaction has been performed with two trimethylsilyl butenoates **4** (R = H, Me) on a variety of structurally different aldimines. The results are summarized in Table 2.

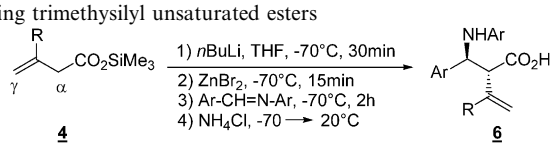
Several aldimines derived from aromatic aldehydes and anilines underwent addition reaction with trimethylsilyl but-3-enoate **4** (R = H) exclusively at the α-carbon to afford β-amino acids **6** in fairly good yields (entries a–e). An α,β-unsaturated aldimine gave only 1,2 adduct (entry f). This study was extended to trimethylsilyl 3-methylbut-3-enoate **4′** (R = Me) in order to confirm the synthetic utility of the method (entry g–j). In all the cases, β-amino acids resulting from only α-attack were obtained as an anti diastereoisomer. For the present addition reaction, aldimines derived from aromatic amines must be employed to obtain satisfactory yields. Attempts to improve the poor results obtained with aliphatic amines in changing the standard conditions (e.g. higher temperature) led to a complex mixture of α and γ attacks.

2.1. Reaction mechanism and stereochemistry

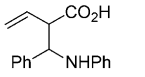
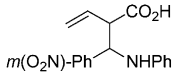
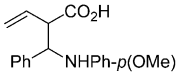
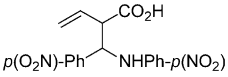
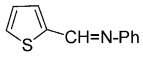
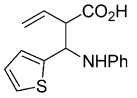
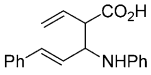
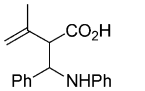
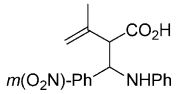
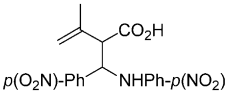
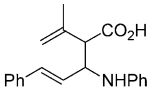
All the β-amino acids **6** prepared were obtained as powder, so no rigorous assignment by X-ray spectroscopy was possible and we sought another approach to determine the configuration of the diastereoisomers obtained. The crude β-amino acids were converted into their corresponding methyl esters **7** whose configurations had previously been determined [13] by ^{1}H-NMR: the chemical shifts of the α-hydrogens ($CHCO_2$) are larger for the *anti* β-amino acids than for the *syn* isomers and conversely those of the β-hydrogens (CHN) are larger for the *syn* than for the *anti* isomers. The vicinal coupling constants $J_{\alpha\beta}$ are less for the *syn* than for the *anti* isomers.

A tentative reaction mechanism and explanation of the stereoselectivity in favour of the *anti* isomer were shown in Scheme 3. It is very likely that trimethylsilyl butenoate zinc enolate was formed by addition of $ZnBr_2$ on the ester lithium enolate. Assuming that the reaction was under kinetic control (−70 °C), the stereochemical results could be rationalized in terms of six-membered cyclic transition states (Zimmerman–Traxler model). The major product could be deduced by evaluating steric interactions in such chairlike transition states shown in Scheme 3. Complexation of the nitrogen with the zinc atom was believed to be the initial interaction between zinc enolate and the C=N bond. Due to this chelation, the transition state A would be sterically preferred (the hydrogen of the aldimine eclip-

Table 2
Synthesis of unsaturated β-amino acids using trimethysilyl unsaturated esters



4 6

Entry	R	Imines	β-Amino Acids[a] 6	Yield (%)[b]
a	H	Ph-CH=N-Ph		69
b	H	*m*NO_2-Ph-CH=N-Ph		66
c	H	Ph-CH=N-Ph-*p*OMe		47
d	H	*p*NO_2-Ph-CH=N-Ph-*p*NO_2		74
e	H			55
f	H	Ph-CH=CH-CH=N-Ph		70
g	Me	Ph-CH=N-Ph		66
h	Me	*m*NO_2-Ph-CH=N-Ph		58
i	Me	*p*NO_2-Ph-CH=N-Ph-*p*NO_2		70
j	Me	Ph-CH=CH-CH=N-Ph		68

[a]. One diastereoisomer obtained (anti).

[b]. Isolated yield.

sing the bulky trimethylsilyl group) leading after hydrolysis to the *anti* isomer.

3. Conclusion

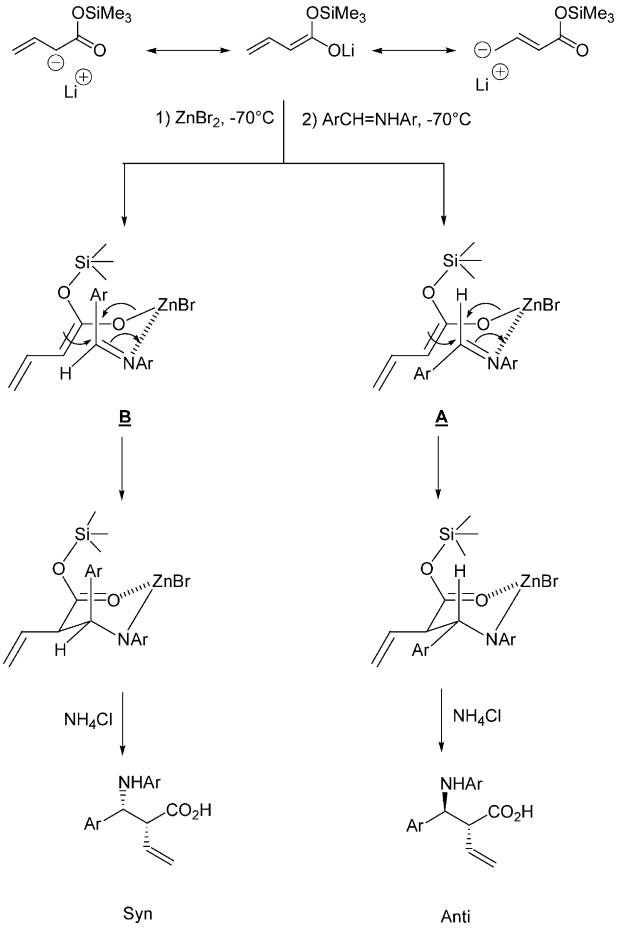
Our results demonstrate the practical utility of these trimethylsilyl butenoates as excellent reagents for direct synthesis of free unsaturated β-amino acids. Although the reaction works well, especially with aromatic aldimines, it still remains the only direct method to prepare free unsaturated β-amino acids uncontaminated by the γ-products.

4. Experimental

4.1. General

All experiments of non-aqueous reactions were carried out under a nitrogen atmosphere using freshly distilled anhydrous solvents. Trimethylchlorosilane was distilled over magnesium. Unless otherwise noted, catalysts and starting materials were purchased from commercial sources and used as received. 3-Methylbut-3-enoic acid was prepared according to the method of Gaudemar [14].

^{1}H- and ^{13}C-NMR spectra were recorded at 250 MHz using $CDCl_3$ or acetone-d_6 as solvent. Chemical shifts



Scheme 3.

were given in ppm (J in Hertz) relative to chloroform or acetone. Melting points are uncorrected. Flash column chromatography was carried out on Merck grade 60 silica gel (230–400 mesh). Silica gel F254 (0.5 mm Merck) was used for preparative thin-layer chromatography (TLC).

4.2. Preparation of aldimines

Starting aldimines were easily prepared from the corresponding aromatic aldehydes and anilines in pentane [15].

4.3. Preparation of zinc bromide

Anhydrous $ZnBr_2$ was prepared by heating ground zinc (3.6 g, 55 mmol) and 1,2-dibromoethane (9.5 g, 50 mmol) in tetrahydrofuran (THF, 100 ml) for 16 h at reflux. The resulting solution was allowed to cool slowly to room temperature (r.t.). The remaining excess zinc was removed by filtration. Complete evaporation of solvent under high vacuum gave pure $ZnBr_2$ as a white powder.

4.4. Trimethylsilylation of but-3-enoic acids

These unsaturated acids were trimethylsilylated using trimethylchlorosilane and pyridine in anhydrous Et_2O by usual way.

4.5. Synthesis of unsaturated β-amino acids. General procedure

To n-butyllithium (1.6 M hexane solution, 7.5 ml, 12 mmol) was added a solution of trimethylsilyl ester (10 mmol) in anhydrous THF (10 ml) at −70 °C under nitrogen. After stirring for 30 min, a THF solution of $ZnBr_2$ (0.5 M, 10 ml) was added at the same temperature and stirred for 15 min. A solution of aldimine (10 mmol) in THF (10 ml) was slowly added at −70 °C and then stirred for two additional hours. Aqueous 0.1 M HCl was added at −70 °C and the flask was allowed to warm to r.t. The mixture was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent in vacuo afforded crude β-amino acids **6** that were purified by chromatography with CH_2Cl_2–MeOH (19:1) as eluent.

4.5.1. (Phenyl-phenylamino-methyl)-but-3-enoic acid (**6a**)

White solid; m.p. = 141 °C.

^{1}H-NMR (250 MHz, acetone-d_6) δ 7.43–7.39 (m, 2H, Ph), 7.24–7.12 (m, 4H, Ph), 6.96–6.90 (m, 2H, Ph), 6.56–6.45 (m, 3H, Ph, NH), 5.97 (ddd, 1H, J = 16.9, 10.4, 8.5, CH=), 5.19–5.12 (m, 2H, CH_2=), 4.74 (d, 1H, J = 8.5 Hz, CHN), 3.44 (t, 1H, J = 8.5 Hz, CHCOOH).

^{13}C-NMR (62.9 MHz, acetone-d_6) δ 173.1, 148.9, 143.1, 135.4, 130.0, 129.4, 128.8, 128.4, 120.0, 118.1, 114.7, 60.2, 59.0.

IR (KBr, cm^{-1}) 3390 (NH), 3400–3200 (OH), 1720 (C=O). MS (APCI-, MeCN) m/z 266 [M−H$^-$]. Anal. Calc. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.26; H, 6.40; N, 5.23%.

4.5.2. [(3-Nitro-phenyl)-phenylamino-methyl]-but-3-enoic acid (**6b**)

Orange solid; m.p. = 150 °C.

^{1}H-NMR (250 MHz, acetone-d_6) δ 8.32 (m, 1H, Ar), 8.06–8.02 (m, 1H, Ar), 7.91–7.88 (m, 1H, Ar), 7.58–7.51 (m, 1H, Ar), 6.99–6.92 (m, 2H, Ar), 6.60–6.46 (m, 3H, Ar, NH), 6.01 (dt, 1H, J = 17.5, 9.5 Hz, CH=), 5.22–5.16 (m, 2H, CH_2=), 4.95 (d, 1H, J = 8.5 Hz, CHN), 3.53 (t, 1H, J = 8.5 Hz, CHCOOH).

^{13}C-NMR (62.9 MHz, acetone-d_6) δ 172.9, 149.7, 148.3, 146.0, 135.6, 134.8, 130.7, 130.2, 123.5, 120.7, 118.6, 114.7, 59.6, 58.6.

IR (KBr, cm^{-1}) 3390 (NH), 3400–3200 (OH), 1720 (C=O). MS (APCI-, MeCN) m/z 311 [M−H$^-$]. Anal. Calc. for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.29; H, 5.18; N, 8.97%.

*4.5.3. [(4-Methoxyphenylamino)-phenyl-methyl]-but-3-enoic acid (**6c**)*

White solid; m.p. = 137 °C.

^{1}H-NMR (250 MHz, acetone-d_6) δ 7.50–7.46 (m, 2H, Ar), 7.32–7.17 (m, 3H, Ar), 6.67–6.57 (m, 4H, Ar), 6.06 (dt, 1H, J = 17.6, 9.3 Hz, CH=), 5.24–5.17 (m, 2H, CH_2=), 4.76 (d, 1H, J = 8.5 Hz, CHN), 3.63 (s, 3H, OMe), 3.48 (t, 1H, J = 8.5 Hz, CHCOOH).

^{13}C-NMR (62.9 MHz, acetone-d_6) δ 173.2, 153.3, 143.3, 142.9, 135.5, 129.3, 128.8, 128.3, 119.9, 116.1, 115.6, 61.1, 59.1, 56.1.

IR (KBr, cm^{-1}) 3390 (NH), 3400–3200 (OH), 1720 (C=O). MS (APCI-, MeCN) m/z 296 [M−H$^-$]. Anal. Calc. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.82; H, 6.42; N, 4.72%.

*4.5.4. [(4-Nitro-phenyl)-(4-nitro-phenylamino)-methyl]-but-3-enoic acid (**6d**)*

Yellow solid; m.p. = 167 °C.

^{1}H-NMR (250 MHz, acetone-d_6) δ 8.17–8.14 (m, 2H, Ar), 7.93–7.90 (m, 2H, Ar), 7.79–7.74 (m, 2H, Ar), 6.79–6.72 (m, 3H, Ar, NH), 5.86–5.71 (m, 1H, CH=), 5.20–5.01 (m, 3H, CH_2=, CHN), 3.59 (t, 1H, J = 9.0 Hz, CHCOOH).

^{13}C-NMR (62.9 MHz, acetone-d_6) δ 172.8, 153.6, 148.7, 148.4, 139.0, 133.6, 129.7, 126.6, 124.3, 120.6, 113.1, 59.0, 57.3.

IR (KBr, cm^{-1}) 3390 (NH), 3400–3200 (OH), 1720 (C=O). MS (APCI-, MeCN) m/z 356 [M−H$^-$]. Anal. Calc. for $C_{17}H_{15}N_3O_6$: C, 57.14; H, 4.23; N, 11.76. Found: C, 57.16; H, 4.22; N, 11.77%.

*4.5.5. [Phenylamino-(2-thienyl)methyl]-but-3-enoic acid (**6e**)*

Orange liquid.

^{1}H-NMR (250 MHz, acetone-d_6) δ 7.21–6.58 (m, 9H, Ar, NH), 5.83 (dt, 1H, J = 16.9, 9.5 Hz, CH=), 5.34–5.27 (m, 2H, CH_2=), 5.00 (d, 1H, J = 8.3 Hz, CHN), 3.48 (t, 1H, J = 8.3 Hz, CHCOOH).

^{13}C-NMR (62.9 MHz, acetone-d_6) δ 176.8, 159.0, 146.8, 145.8, 132.4, 129.6, 127.3, 125.3, 121.8, 119.0, 114.7, 56.1, 52.5.

IR (KBr, cm^{-1}) 3390 (NH), 3400–3200 (OH), 1720 (C=O). MS (APCI-, MeCN) m/z 272 [M−H$^-$]. Anal. Calc. for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12. Found: C, 65.86; H, 5.51; N, 5.12%.

*4.5.6. Phenyl-3-phenylamino-2-vinyl-pent-4-enoic acid (**6f**)*

Orange solid; m.p. = 150 °C.

^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.23–7.00 (m, 8H, Ph), 6.65–6.46 (m, 4H, Ph, PhCH=, NH), 6.10 (dd, 1H, J = 16.7, 6.7 Hz, CH=), 5.89 (m, 1H, CH=), 5.23–5.16 (m, 2H, CH_2=), 4.40 (m, 1H, CHN), 3.30 (t, 1H, J = 6.7 Hz, CHCOOH).

^{13}C-NMR (62.9 MHz, $CDCl_3$) δ 178.4, 147.4, 147.3, 137.1, 133.8, 129.7, 129.6, 128.9, 128.6, 127.9, 126.9, 126.8, 118.5, 115.7, 114.6, 58.3, 57.2.

IR (KBr, cm^{-1}) 3400 (NH), 3400–3200 (OH), 1720 (C=O). MS (APCI-, MeCN) m/z 292 [M−H$^-$]. Anal. Calc. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.91; H, 6.51; N, 4.75%.

*4.5.7. (Phenyl-phenylamino-methyl)-3-methylbut-3-enoic acid (**6g**)*

White solid; m.p. = 156 °C.

^{1}H-NMR (250 MHz, acetone-d_6) δ 7.39–7.35 (m, 2H, Ph), 7.12–7.00 (m, 3H, Ph), 6.85–6.78 (m, 2H, Ph), 6.46–6.33 (m, 3H, Ph), 4.98 (s, 1H, CH_2=), 4.88 (s, 1H, CH_2=), 4.65 (d, 1H, J = 11.1 Hz, CHN), 3.42 (d, 1H, J = 11.1 Hz, CHCOOH), 1.68 (s, 3H, Me).

^{13}C-NMR (62.9 MHz, acetone-d_6) δ 172.5, 147.6, 142.6, 141.3, 128.8, 128.0, 127.9, 127.1, 116.7, 116.1, 113.1, 61.3, 56.4, 18.1.

IR (KBr, cm^{-1}) 3390 (NH), 3400–3200 (OH), 1720 (C=O). MS (APCI-, MeCN) m/z 280 [M−H$^-$]. Anal. Calc. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.84; H, 6.80; N, 4.98%.

*4.5.8. [(3-Nitro-phenyl)-phenylamino-methyl]-3-methylbut-3-enoic acid (**6h**)*

Red solid; m.p. = 167 °C.

^{1}H-NMR (250 MHz, acetone-d_6) δ 8.40–8.39 (m, 1H, Ar), 8.04–7.95 (m, 2H, Ar), 7.56–7.49 (m, 1H, Ar), 6.98–6.92 (m, 2H, Ar), 6.61–6.44 (m, 3H, Ar), 5.13 (s, 1H, CH_2=), 5.03 (s, 1H, CH_2=), 4.95 (d, 1H, J = 11.1 Hz, CH=), 3.61 (d, 1H, J = 11.1 Hz, CHCOOH), 1.81 (s, 3H, Me).

^{13}C-NMR (62.9 MHz, acetone-d_6) δ 173.3, 149.7, 148.3, 146.6, 141.9, 136.0, 130.6, 130.2, 123.8, 123.5, 118.5, 117.9, 114.4, 62.0, 57.2, 19.4.

IR (KBr, cm^{-1}) 3390 (NH), 3400–3200 (OH), 1720 (C=O). MS (APCI-, MeCN) m/z 325 [M−H$^-$]. Anal. Calc. for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.19; H, 5.55; N, 8.58%.

*4.5.9. [(4-Nitro-phenyl)-(4-nitro-phenylamino)-methyl]-3-methylbut-3-enoic acid (**6i**)*

Yellow solid; m.p. = 186 °C.

^{1}H-NMR (250 MHz, acetone-d_6) δ 8.06–8.02 (m, 2H, Ar), 7.84–7.80 (m, 2H, Ar), 7.74–7.71 (m, 2H, Ar), 6.71–6.68 (m, 2H, Ar), 5.18 (d, 1H, J = 9.5 Hz, CHN), 4.82 (s, 1H, CH_2=), 4.71 (s, 1H, CH_2=), 3.60 (d, 1H, J = 9.5 Hz, CHCOOH), 1.58 (s, 3H, Me).

^{13}C-NMR (62.9 MHz, acetone-d_6) δ 173.4, 154.2, 149.8, 148.6, 141.3, 139.1, 130.2, 127.0, 124.6, 117.3, 113.2, 60.6, 58.5, 21.9.

IR (KBr, cm^{-1}) 3390 (NH), 3400–3200 (OH), 1720 (C=O). MS (APCI-, MeCN) m/z 370 [M−H$^-$]. Anal. Calc. for $C_{18}H_{17}N_3O_6$: C, 58.22; H, 4.61; N, 11.32. Found: C, 58.34; H, 4.60; N, 11.33%.

*4.5.10. Isopropenyl-5-phenyl-3-phenylamino-pent-4-enoic acid (**6j**)*

Orange solid; m.p. = 167 °C.

^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.25–6.97 (m, 8H, Ph), 6.64–6.60 (m, 3H, Ph, NH), 6.48 (d, 1H, $J = 15.9$ Hz, PhCH=), 6.03 (dd, 1H, $J = 15.9$, 7.4 Hz, CH=), 4.97 (s, 1H, CH_2=), 4.92 (s, 1H, CH_2=), 4.42 (t, 1H, $J = 7.4$ Hz, CHN), 3.29 (d, 1H, $J = 7.4$ Hz, CHCOOH), 1.78 (s, 3H, Me).

^{13}C-NMR (62.9 MHz, $CDCl_3$) δ 177.2, 147.1, 140.1, 137.1, 131.9, 129.5, 128.9, 128.8, 128.7, 127.8, 126.9, 126.8, 118.5, 116.9, 114.8, 59.2, 56.5, 21.5.

IR (KBr, cm^{-1}) 3400 (NH), 3400–3200 (OH), 1720 (C=O). MS (APCI-, MeCN) *m/z* 306 [$M-H^-$]. Anal. Calc. for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.12; H, 6.90; N, 4.57%.

*4.5.11. Methyl 2-(phenyl-phenylamino-methyl)-but-3-enoate (**7a**)*

Yellow liquid.

^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.34–7.02 (m, 8H, Ph), 6.62–6.44 (m, 3H, Ph, NH), 5.90 (ddd, 1H, $J =$ 17.1, 10.2, 9.6 Hz, CH=), 5.24–5.14 (m, 2H, CH_2=), 4.57 (d, 1H, $J = 8.6$ Hz, CHN), 3.43 (s, 3H, Me), 3.32 (t, 1H, $J = 8.6$ Hz, CHCOOH).

^{13}C-NMR (62.9 MHz, $CDCl_3$) δ 171.5, 145.9, 140.3, 131.9, 128.0, 127.4, 126.6, 125.9, 119.4, 116.9, 112.6, 58.3, 57.3, 50.8.

MS (APCI-, MeCN) *m/z* 280 [$M-H^-$]. Anal. Calc. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.82; H, 6.80; N, 4.98%.

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