SYNTHESIS OF SUBSTITUTED AMIDES THROUGH ACTIVATED OXIMES AS COMPETITIVE BECKMANN REARRANGEMENT REACTION

N. Chandan
Department of Chemistry, Siddharth College of Arts, Science and Commerce, Fort Mumbai
nandkishorc@gmail.com

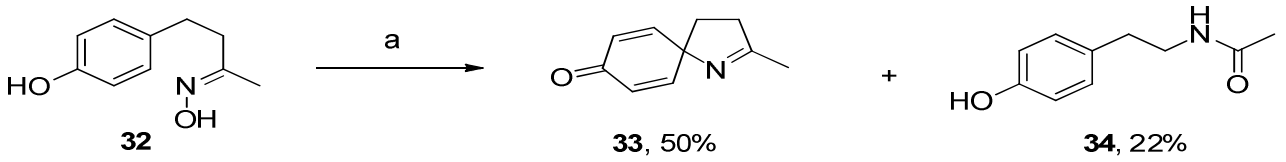
ABSTRACT

There are many amination methods have been reported but electrophilic amination of carbon nucleophiles is not usually used for the synthesis of heterocyclic compounds containing nitrogen. Oxime ethers or their derivatives (tosyl or mesyl) look to be possible substrates for electrophilic ring closure, initiated by attack of a nucleophilic carbon at the nitrogen atom. The methodology developed in our group for synthesis of 2,2,5-trisubstituted pyrrolidine was successfully calibrated with activated tosyl oxime or oxime ether nucleophilic cyclization, but when the substitution pattern changes with bulky groups the strategy competes with Beckmann rearrangement reaction. The precursor as activated oxime with was synthesised using α,β-unsaturated ketone as chalcone and activated malonic ester and malonamide, which was sterically hindered when subjected to basic condition instead cyclization products give exclusively Beckmann rearrangement products as substituted amidess. In this report verities of activated oximes underwent Beckmann rearrangement in effective manner to afford the corresponding amides in moderates to high yield.

Keywords: *Oxime, Oxime ether, tosyl, rearrangement, caprolactam, Beckmann etc.*

Introduction

The Beckmann rearrangement of ketoximes into amides is a significant reaction in synthesis organic chemistry. This rearrangement reaction has been extensively used to synthesised the ε-caprolactam and laurolactam starting material of many products in the industry.1,2 The Beckmann rearrangement of aldoximes and ketoximes to the corresponding amides under acidic conditions was naturally well-designed transformation and has been used to great success in the synthesis of natural products and pharmaceuticals alike3. Even though the reaction has clear usefulness in synthetic organic chemistry, the need for harsh reaction conditions limits its utility to carefully chosen substrates. In response to this problem, many groups have reported modifications of the reaction that allows the transformation to proceed under milder conditions. Whereas the oxime ethers or oxime derivatives (tosyl or mesyl) look to be a possible substrates for Beckmann rearrangement but it was target for electrophilic ring closure, initiated by attack of a nucleophilic carbon at the nitrogen atom.4,5 There are very few examples of this kind of reaction, because activated oximes and their derivatives always compete with well-known and faster rearrangement reactions called the Beckmann rearrangement6 and Neber reaction.7 However, Narasaka and Nakamura reported by ab initio calculation, that a ring closure reaction proceeding by the SN2 reaction mechanism onto the sp2 hybridised nitrogen atom of the oxime derivatives by the attack of nucleophilic carbon of an aromatic moiety should be energically feasible,8 for example when (E)-4-(4-hydroxyphenyl)butan-2-one oxime 32 was treated with protic acid CF3SO3H in the solvent dichloroethane, cyclisation product pyrroline 33 in 50% yield was obtained as a result of the nucleophilic carbon of aromatic ring attacking the sp2 nitrogen of the oxime, along with the competing Beckmann product 34, shown in Scheme 1. The cyclisation products were solvent and reagent dependant, since use of (n-Bu)4ReO4 gave complete conversion of oxime to cyclised pyrroline 33 without any Beckmann rearrangement product.8 In our report the changing the substrate substitution pattern and thermodynamic condition give exclusive substituted amide as the product through as Beckmann rearrangement competing reaction instead the cyclisation products.

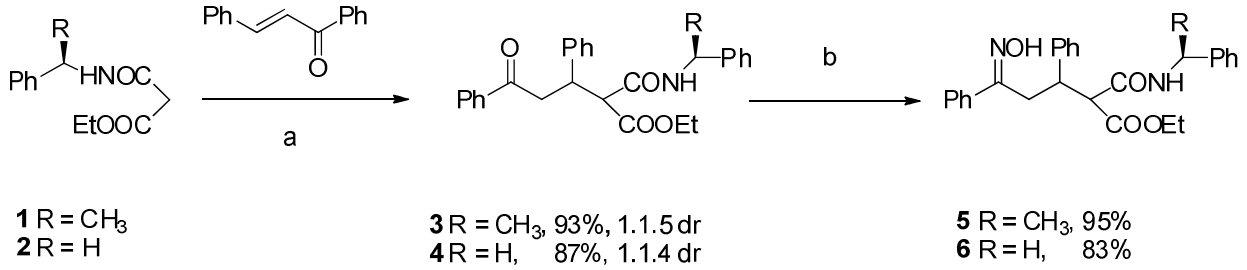


Reagents and conditions (a) CF_3SO_3H, dichloroethane [8]

Scheme-1: Competing Beckmann rearrangement reaction.

Result and Discussions

The novel rout to synthesised 2,2,5-trisubstituted pyrrolidines through nucleophilic substitution at activated oxime[9] was already developed as methodology to get the core of many natural products. While on framing the different substitution patter we have tried different substrates. To configure different functionality on the 2-position of the polysubstituted pyrrolidine, we used malonamide as an active methylene. Two different malonamides, (*S*)-ethyl 3-oxo-3-(1-phenylethylamino) propanoate **1** and ethyl 3-(benzylamino)-3-oxopropanoate **2**, were reacted with the aromatic chalcone in presence of anhydrous K_2CO_3 in dry CH_2Cl_2 heated to reflux for 15 hr afforded the corresponding Michael adducts **3** and **4** in very high yields of 93 and 87% respectively. The adducts **3** and **4** were readily converted into oxime by treatment with $NH_2OH.HCl$, Et_3N in EtOH (reflux for 7 hr) and afforded oxime **5** and **6** in very high yields of 95 and 83% (Scheme-**2**).



1 R = CH_3
2 R = H

3 R = CH_3, 93%, 1.1.5 dr
4 R = H, 87%, 1.1.4 dr

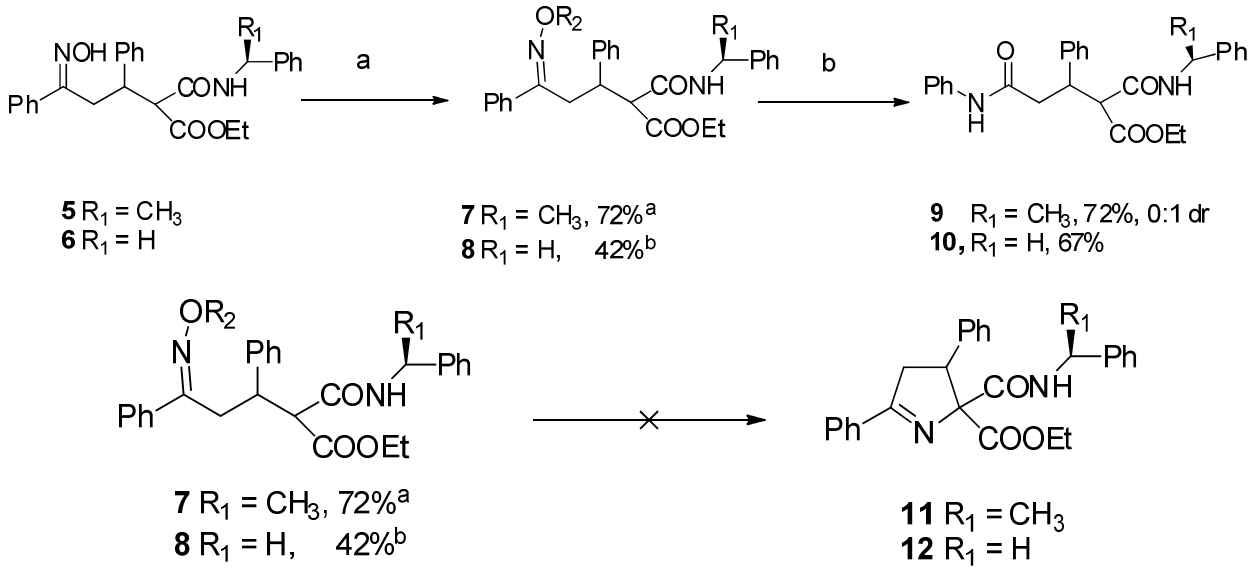
5 R = CH_3, 95%
6 R = H, 83%

Reagents and conditions (a) anhydrous K_2CO_3, CH_2Cl_2, reflux, 15 hr; (b) $NH_2OH.HCl$, Et_3N, reflux 7 hr.

Scheme-2 : Synthesis of Michael adduct and Ketoxime for malonamides.

The oxime **5** was treated with Na-metal in EtOH, followed by the addition of 2,4-dinitrofluorobenzene and gave oxime ether **7** in a good yield of 72%. The oxime ether **7** was then subjected to the ring closure conditions, (NaH in dry THF heated to reflux for 30 min) and gave the Beckmann rearranged product as amide **9** in a good yield of 72% instead the cyclised 2,2,5-trisubstituted pyrroline **11** as a single diastereomer, probably is due the bulk of the substituents. The Beckmann rearranged product amide **9** was crystalline; hence the structure was confirmed by X-ray single crystal analysis as shown in Figure-**1**. Different reaction conditions were tried; anhydrous $CsCO_3$ in dry CH_2Cl_2 heated to reflux for 30 min gave no pyrroline **11**, but instead amide as Beckmann rearranged product was the only product found. When DBU in CH_2Cl_2 was used, no trace of pyrroline **11** was isolated and again the Beckmann rearrangement was the major product (Scheme-3). The oxime **6** was treated with *p*-toluenesulfonyl chloride and base (Et_3N in CH_2Cl_2, stirred for 5 hr at rt) and afforded the tosyl oxime **8** in 42% in yield but no cyclised product was found. The tosyl oxime **8** was then treated with the ring closure conditions; NaH in dry THF was heated to reflux for 30 min and gave 67% of amide **10** as Beckmann rearranged product, whereas no trace of cyclised pyrroline **12**, we have tried with oxime ether of oxime **6** and tried with different bases like NaH, $CsCO_3$ and DBU but we end up with amide as the product. It was

also observed that oxime when converted tosyl oxime or oxime ether and if the reaction stirred with heating at 50^{0C} for 5 hrs time the product directly as amide with tosyl oxime and oxime ether was also found as Beckmann product.



Reagents and conditions (a) i) Na-metal, EtOH, 2,4-dinitrofluorobenzene, rt; ii) *p*TsCl, Et_3N, CH_2Cl_2, 0 °C to rt; (b) i) NaH, THF, reflux, 30 min; ii) anhydrous $CsCO_3$, CH_2Cl_2, reflux, 30 min; iii) DBU, CH_2Cl_2, 0 °C to rt.

Scheme-3: synthesis of Amide through Beckmann rearrangement.

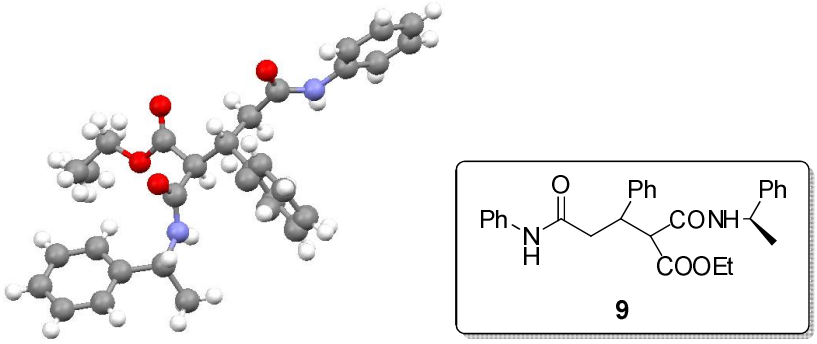
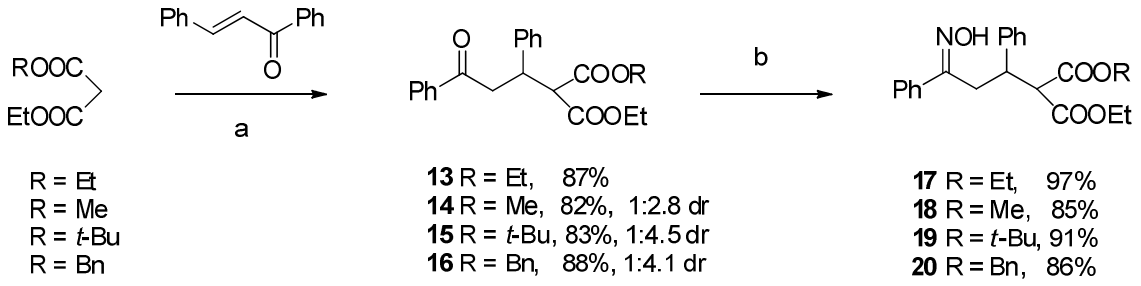


Fig-1: X-ray crystal structure for product **9**

The same competing Beckmann rearrangement for the synthesis of amide was observed for the malonic esters and chalcone (aromatic α,β-unsaturated ketone) adduct, when it was applied to the newly developed methodology. The required substrates were synthesised by conjugate addition of diethyl malonate, ethyl methyl malonate, *t*-butyl ethyl malonate and benzyl ethyl malonate with chalcone in presence of anhydrous K_2CO_3 in dry CH_2Cl_2 heated to reflux for 15 hr; this afforded the corresponding adducts[10,11] **13**, **14**, **15** and **16** in high yields of 87, 82, 83 and 88% with diastereoselectivity ratio for **14**, **15** and **16** is 1:2.8, 1:4.5 and 1:4.1 respectively (Scheme-**4**). The isolation of all adducts was very straightforward and there was no double Michael addition product formation. The resultant adducts **13**, **14**, **15** and **16** were subjected to $NH_2OH.HCl$ with base (Et_3N in EtOH heated to reflux for 7 hr) and gave corresponding oximes **17**, **18**, **19** and **20** again in very high yields of 97, 85, 91 and 86% respectively (Scheme **4**).



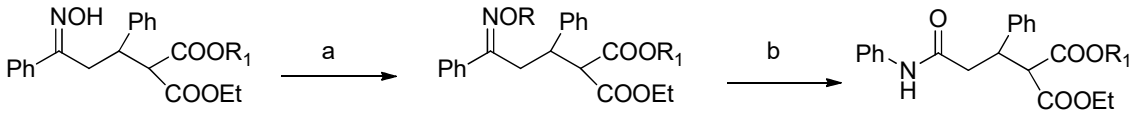
R = Et
R = Me
R = *t*-Bu
R = Bn

13 R = Et, 87%
14 R = Me, 82%, 1:2.8 dr
15 R = *t*-Bu, 83%, 1:4.5 dr
16 R = Bn, 88%, 1:4.1 dr

17 R = Et, 97%
18 R = Me, 85%
19 R = *t*-Bu, 91%
20 R = Bn, 86%

Reagents and conditions a) anhydrous K_2CO_3, CH_2Cl_2, reflux; b) $NH_2OH.HCl$, Et_3N, EtOH reflux, 7 hr.

Scheme-4: Synthesis of Michael adduct and Ketoxime for malonic esters.



R = Et
R = Me
R = *t*-Bu
R = Bn

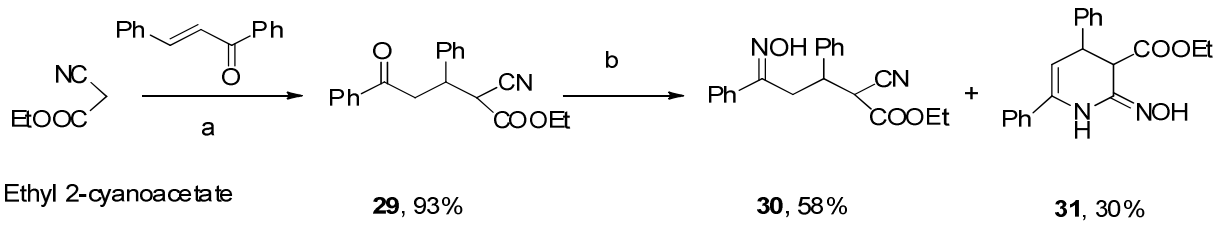
21 R = Et, 78%
22 R = Me, 77%
23 R = *t*-Bu, 75%
24 R = Bn, 72%

25 R = Et, 67%
26 R = Me, 74%
27 R = *t*-Bu, 65%
28 R = Bn, 69%

Reagents and conditions (a) *p*TsCl, Et_3N, CH_2Cl_2, 0 °C to rt; b) NaH, THF Reflux 30min

Scheme-5: Beckmann rearrangement reaction competes with cyclization.

In the similar way the oximes **17, 18, 19** and **20** was converted into the required substrate as tosyl oximes **21, 22, 23** and **24** by the treatment with *p*-toluenesulfonyl chloride and base (Et_3N in CH_2Cl_2) where traces of rearrangement product was also found. The tosyl oximes **21, 22, 23** and **24** was then reflux to 30 min with NaH/$CsCO_3$/DBU give the good yield of amides with 67, 74, 65 and 69% instead the pyrroline. In a similar way, oximes **18, 19** and **20** could not be converted into the corresponding oxime ether because 2,4-dinitrofluorobenzene with Na-metal in EtOH causes transesterification of the methyl, *t*-Butyl and benzyl group with an ethyl group. To avoid the transesterification of oximes we preferred to treat with *p*-toluenesulfonyl chloride and base (Et_3N in CH_2Cl_2) and methanesulfonyl chloride[12] with pyridine in CH_2Cl_2 at 0 °C to rt. To get a cyano functional group at the 2-position of pyrroline in attempt of cyclization reaction, we used ethyl 2-cyanoacetate as the active methylene-containing compound; on conjugate addition with the aromatic chalcone in presence of anhydrous K_2CO_3 in dry CH_2Cl_2 heated to reflux for 15 hr the corresponding product **29** was obtained in very high yield of 93%. The adduct **29** was treated with $NH_2OH.HCl$ and Et_3N in EtOH heated to reflux for 5 hr and afforded the oxime **30** in 58% as well as the by-product six-membered nitrogen containing heterocycle compound **31** in 30% yield (Scheme **6**), the yield of the heterocyclic compound varies when reaction mixture kept refluxed for 12 hrs the yield increases to 70% as crystalline solid mass. The oxime **30** was converted to tosyl oxime but when treated with base under refluxed condition it neither converted into Beckmann rearrangement product as amide or cyclization product as pyrroline. Whereas we ended up with new novel rout to synthesised six member highly substituted heterocyclic compounds as ethyl 2-(hydroxyimino)-4,6-diphenyl-1,2,3,4-tetrahydropyridine-3-carboxylate. The structure of **31** was confirmed by X-ray single crystal structure (Figure-**2**).



Ethyl 2-cyanoacetate **29**, 93% **30**, 58% **31**, 30%

Reagents and conditions (a) anhydrous K_2CO_3, CH_2Cl_2, reflux, 15 hr; (b) $NH_2OH.HCl$, Et_3N, reflux, 5 hr.

Scheme-6: Synthesis of Heterocyclic compound

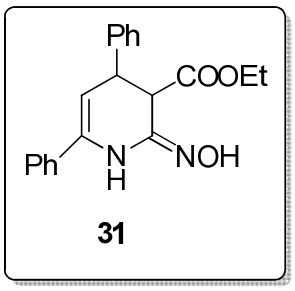


Fig-2: X-ray Crystal structure for six-member heterocycle **31**.

Conclusions

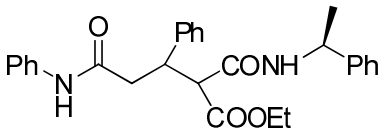
In summary, we have developed a mild and effective methodology to synthesise the highly substituted amides system through the competitive reaction as Beckmann rearrangement of ketoximes/tosyloxime/oxime ether. This methodology was developed as the by-product formed in the attempt of nucleophilc ring closer of tosyloxime/oxime ether in basic condition on reflux expecting the substituted pyrrolidines but leading to the corresponding amides in moderate to high yields.

Experimental

General Procedure

To a solution of oxime ether or tosyl oxime (1.0 eq.) in dry THF at room temperature, dispersion of NaH (3.0 eq. 60% dispersion in mineral oil) was added and heated to reflux for 30 min to 1 hr and the progress of the reaction was monitored by TLC. After completion of the reaction, saturated NH_4Cl was added and the product Beckmann rearranged as amide was extracted by EtOAc. The extracts were dried over Na_2SO_4, concentration of reaction mixture gave the crude product which was purified by flash column chromatography (eluting with EtOAc : petrol) to afford amide product.

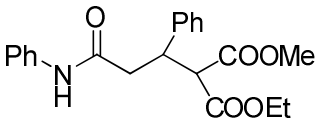
(±)Ethyl 5-oxo-3-phenyl-5-(phenylamino)-2-(1-phenylethylcarbamoyl) pentanoate, 9[15-17]



Following the general procedure tosyl oxime/oxime ether **7** (139 mg, 0.22 mmol) in dry THF (10 mL) was added NaH (16mg, 0.66 mol, 60%) and heated to reflux for 30 min, to give crude product which was purified by flash column chromatography and isolated instead ring closure pyrroline, the Beckman rearrangement product **9** (262 mg, 78%) as a yellow crystal m.p. = 236-238 °C; R_f = 0.43 (EtOAc : petrol, 2:1); υ_{max}(film)/cm^{-1} 3311, 3205, 3064, 2980, 1737, 1678, 1654, 1601, 1548, 1364, 1263, 1180, 1082, 990, 860, 753; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.29 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.37 (3H, d, *J* 6.9 Hz, CH_3CHNH), 2.60 (1H, dd, *J* 13.3, 5.5 Hz CH*H*CHPh), 3.14 (1H, dd, *J* 13.3, 10.1 Hz C*H*HCHPh), 3.75 (1H, d, *J* 6.1 Hz, CHPhC*H*), 3.87 (1H, m, C*H*PhCH), 4.18 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.12 (1H, m, CH_3CHNH), 6.90-7.36 (15H, m, 3 x Ar*H*), 7.56 (1H, d, *J* 7.9 Hz, CH_3CHNH), 9.04 (1H, s, CON*H*); δ_C(100 MHz; $CDCl_3$; Me_4Si) 13.7, 14.1 (OCH_2CH_3), 21.2, 21.4 (CH_3CHNH), 41.3, 41.7 (CH_2CHPh), 44.5 (*C*HPhCH), 48.6

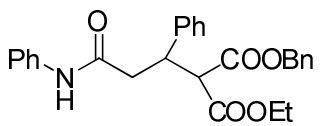
(CH_3CHNH), 53.7 (CHPh*C*H), 61.5 (OCH_2CH_3), 119.4, 123.6, 126.0, 127.1, 127.2, 127.5, 128.1, 128.2, 128.3, 128.5 (3 x Ar*C*), 137.8, 138.6, 142.0 (3 x quaternary Ar*C*), 165.8 (*C*ONH), 169.3 (*C*ONH), 171.1 (*C*OO); m/z (ESI^+) 481 ($[M+Na]^+$, 100%), 459 ($[M+H]^+$, 95%), 457 ($[M-H]^-$, 95%), HRMS (ESI^+) $C_{28}H_{30}N_2NaO_4^+$ ($[M+Na]^+$) requires 481.2098; found 481.2102.

(±)1-Ethyl 3-methyl 2-(3-oxo-1-phenyl-3-(phenylamino)propyl)malonate, 26[13,14]



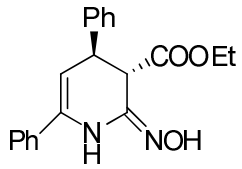
Following the general procedure to a solution of tosyl oxime **22** (124 mg, 0.33 mmol) in dry THF (10 mL) was added NaH (64 mg, 0.99 mol, 60%) and heated to reflux for 30 min to give crude product which was purified by flash column chromatography to afford amide **26** (91 mg, 74%) as a semisolid; m.p. = 154-156 °C; R_f = 0.26 (EtOAc : petrol, 1:1); υ_{max}(film)/cm^{-1} 3309, 3076, 2977, 1734, 1661, 1600, 1543, 1310, 1151, 757, 699; δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.99, 1.26 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.76, 2.92 (2H, m, PhCHCH_2), 3.49, 3.76 (3H, s, OCH_3), 3.87, 3.90 (1H, d, *J* 9.1 Hz, C*H*CHPh), 4.00 (1H, m, CHC*H*Ph), 3.94, 4.23 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 7.07 (1H, bs, N*H*), 7.29-7.35 (10H, m, 2 × Ar*H*); δ_C(100 MHz; $CDCl_3$; Me_4Si) 13.6, 13.9 (OCH_2CH_3), 41.7, 41.9 (CHCHPh), 42.1, 42.2 (COCH_2), 52.4, 52.7 (OCH_3), 56.8, 56.9 (*C*HCHPh), 61.5, 61.8 (OCH_2CH_3), 119.7-128.0 (Ar*C*), 137.6, 140.0 (quaternary Ar*C*), 167.5, 168.1, 168.6, 168.9, 172.3 (2 × *C*OO, *C*ONH); m/z (ESI^+), 761 ($[2M+Na]^+$, 100%), 368 ($[M-H]^-$, 100%); HRMS (ESI^+) $C_{21}H_{23}NNaO_5^+$ ($[M+Na]^+$) requires 392.1468; found 392.1471.

(±)1-Benzyl 3-ethyl 2-(3-oxo-1-phenyl-3-(phenylamino)propyl)malonate, 28[18-21]



Following the general procedure to a solution of tosyl oxime **24** (105 mg, 0.24 mmol) in dry THF (10 mL) was added NaH (51 mg, 0.70 mol, 60%) and heated to reflux for 30 min to give crude product which was purified by flash column chromatography to afford amide **28** (91 mg, 74%) as a semisolid; m.p. = 162-164 °C; R_f = 0.39 (EtOAc : petrol, 1:4); υ_{max}(film)/cm^{-1} 3430, 3033, 2970, 1732, 1542, 1443, 1378, 12534, 1148, 697; δ_H(400 MHz; $CDCl_3$; Me_4Si) 0.95 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.72 (2H, m, PhCHCH_2), 3.89 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 3.92 (1H, d, *J* 4.9 Hz, C*H*CHPh), 4.01 (1H, m, CHC*H*Ph), 5.26 (2H, s, CH_2Ph), 7.16 (1H, s, N*H*), 7.26-7.33 (15H, m, 3 × Ar*H*); δ_C(100 MHz; $CDCl_3$; Me_4Si) 13.0 (OCH_2CH_3), 41.2 (PhCH*C*H$_2$), 41.6 (CH*C*HPh), 56.4 (*C*HCHPh), 60.9 (OCH_2CH_3), 66.7 (*C*H$_2$Ph), 119.1, 123.5, 126.8, 127.3, 127.6, 127.7, 127.9, 128.0, 128.2, 128.3 (Ar*C*), 134.5, 136.9, 139.4 (quaternary Ar*C*), 166.7, 167.7, 167.9 (*C*ONH, 2 × *C*OO); m/z (ESI^+), 913 ($[2M+Na]^+$, 100%), 468 ($[M+Na]^+$, 65%), 444 ($[M-H]^-$, 20%); HRMS (ESI^+) $C_{27}H_{27}NNaO_5^+$ ($[M+Na]^+$) requires 468.1781; found 468.1782.

(±) (3*S*,4*R*)-ethyl 2-(hydroxyimino)-4,6-diphenyl-1,2,3,4-tetrahydropyridine-3-carbo- -xylate, 31



When **29** (1.12 g, 3.48 mmol) was treated with $NH_2OH.HCl$ (264 mg, 3.83 mmol), TEA (342 mg, 1.2 mmol) in EtOH (30 mL) heated to reflux, pyridine was isolated as a by-product which was purified by recrystalisation to afford pyridine **31** (355 mg, 30%) as a pale yellow crystals; m.p. = 92-94 °C; R_f = 0.30 (EtOAc : petrol, 4:6); υ_{max}(film)/cm^{-1} 3423, 3074, 2985, 1735, 1607, 1476, 1248, 1026, 910, 762, 698; δ_H(400 MHz; $CDCl_3$; Me_4Si) 1.16 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.06 (1H, bs, O*H*), 3.57 (1H, d, *J* 7.1 Hz, (C3)*H*), 4.14 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.22 (1H, dd, *J* 7.1, 4.6 Hz, (C4)*H*), 5.29 (1H, d, *J* 4.6 Hz, (C5)*H*), 7.22-7.54 (10H, m, 2 x Ar*H*), 8.06 (1H, bs, N*H*); δ_C(100 MHz; $CDCl_3$; Me_4Si) 14.1 (OCH_2CH_3), 41.8 (*C*4), 49.7 (*C*3), 61.5 (OCH_2CH_3), 102 (*C*5), 125.4-128.9 (Ar*C*), 135.6, 136.5 (quaternary Ar*C*), 141.5 (*C*5), 145.9 (*C*2), 169.7 (*C*OO); m/z (ESI^+) 335 ($[M-Na]^-$, 35%), HRMS (ESI^+) $C_{20}H_{19}N_2O_3^-$ ($[M-Na]^-$) requires 335.1401; found 335.1401.

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