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Microwave-mediated reductive amination-cyclization of 4-aryl-4-oxobutanoates: Facile synthesis of 3-methylidene-5-phenyl-2,3-dihydropyrrolidones

H SURYA PRAKASH RAO* and S P SENTHILKUMAR
Department of Chemistry, Pondicherry University, Pondicherry 605 014, India
e-mail: hspr@yahoo.com

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Abstract. Microwave-mediated three-component condensation of 4-aryl-4-oxobutanoates with ammonium formate furnishes 3-methylidene-5-phenyl-2,3-dihydropyrrolidones in good yield within 2 min. The pyrrolidone products were characterized on the basis of spectral data and X-ray crystal structure analysis. The reaction is found to be general and a variation in the ester and aryl moieties is possible. However, when alkylammonium formate is used only amide products are formed.

Keywords. Microwaves; three-component coupling; pyrrolidones; ammonium formate.

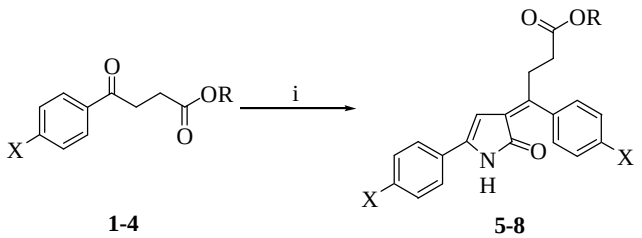
1. Introduction

Some tobacco alkaloids, which are primarily responsible for addictive properties, viz. nicotine,[1] nornicotine[2] and N-acetylnicotine,[3] incorporate 2-arylpyrrolidine structural motif. Surprisingly, in spite of their obvious importance, only a very few N-alkyl derivatives of nicotine are known. We planned to synthesize several variously N-alkylated derivatives of nicotine to evaluate biological activity. We reasoned that they could be easily generated from the reduction of corresponding N-alkyl-5-aryl-2-pyrrolidones, which could be readily generated by reductive amination of 4-aryl-4-oxobutanoates by applying our newly developed microwave mediated Leuckart reaction conditions.[4] In addition, appropriately hydroxy substituted N-alkyl-5-aryl-2-pyrrolidones could serve as precursors to ethanolamine based chiral auxiliaries. During the course of this targeted investigation, we found a facile microwave mediated synthesis of 3-methylidene-5-phenyl-2,3-dihydropyrrolidones and the results are described in this paper.

2. Results and discussion

When a solution of methyl-4-oxo-4-phenylbutanoate **1** in polyethylene glycol – 200 (PEG-200) was treated with ammonium formate under microwave irradiation at 370 W for 2 min, the reaction furnished an orange coloured methyl *Z*-4-(2-oxo-5-phenyl-2,3-dihydro-1*H*-3-pyrrolyliden)-4-phenylbutanoate **5** in 91% yield instead of 5-phenyl-2-pyrrolidone (scheme 1).

The structure of the three-component condensation product **5** was confirmed on the basis of spectral and analytical data. The UV spectrum showed l_{max} at 391 (log e = 4·66) due to extensive conjugation present in the molecule. The IR spectrum showed carbonyl absorption at n 1729 and 1681 cm^{-1} for ester and lactam functional groups, respectively. The ^1H NMR spectrum showed aliphatic and aro-



1-4 **5-8**

1, 5: X = H, R = CH_3; **2, 6**: X = H, R = CH_2CH_3; **3, 7**: X = Cl, R = CH_3; **4, 8**: X = R = H
Reagents and conditions: i. $HCOONH_4$, PEG-200, *mn*, 370 W, 2 min

Scheme 1.

*For correspondence

matic hydrogens in the ratio of 1 : 1·5. A peak at *d* 10·7 ppm as a broad singlet was due to the presence of NH and a sharp singlet at *d* 5·95 ppm was due to olefinic hydrogen. The presence of two triplets at *d* 3·67 (J = 8·2 Hz) ppm and *d* 2·53 (J = 8·0 Hz) ppm were due to two adjacent methylenes next to ester carbonyl group. The ^{13}C NMR spectrum showed seventeen signals out of which three were of aliphatic carbons, four were olefinic carbon atoms, eight aromatic carbons and one carbonyl group. The DEPT spectrum revealed the presence of one methyl, two methylene and seven methine carbons. The mass spectrum showed a molecular ion peak at 333, which was an additional support for the structure of the compound and showed the molecular formula to be $C_{21}H_{19}NO_3$. Finally the assigned structure was confirmed on the basis of single crystal X-ray determination[5] (figure 1) as **5** with the stereochemistry of double bond being *Z*. The crystal structure shows that **5** stabilizes in dimeric form through CH–O hydrogen bonding interactions.

Literature survey revealed that compound of the type **5** has a long history. At the turn of twentieth century, Klobb isolated an orange product from the reaction of ester **1** with ammonium acetate.[6] Fiesselmann and Ehmann have elaborately studied the reaction and assigned structure to acid derivative of **5**.[7] Treibs and co-workers studied further transformations of **5** for the synthesis of some nitrogen heterocycles.[8] Subsequently, Loev and co-workers synthesized several N-phenyl derivatives of **5**.[9] Soriano–Garcia and co-workers reported the crystal structure of its *E*-isomer.[10] However, mechanistic aspects of the transformation as well as complete characterization of **5** and its derivatives based on high resolution ^{1}H and ^{13}C NMR spectral data were not investigated.

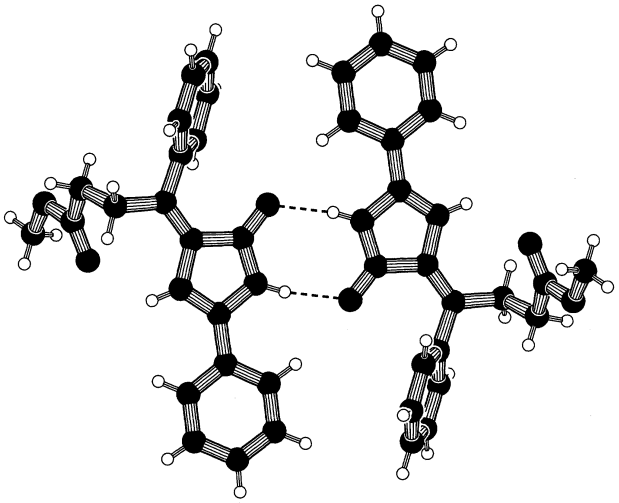


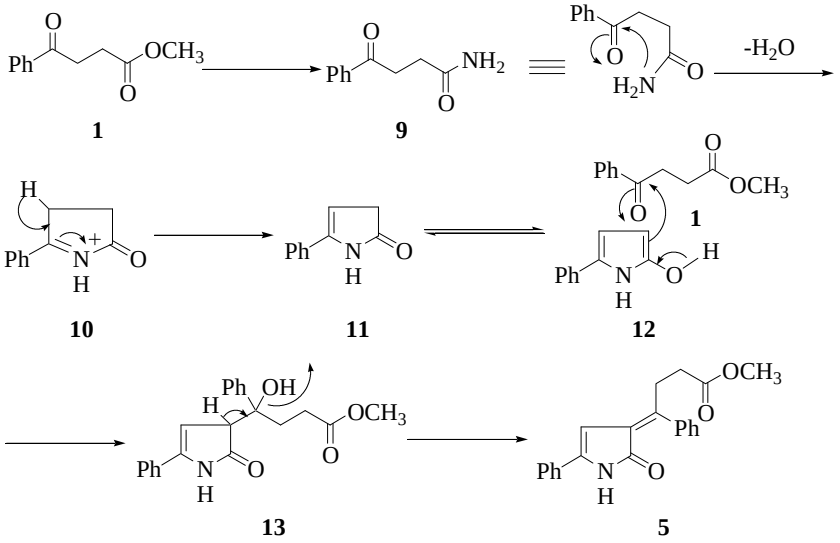
Figure 1. Crystal structure of methyl-4-(2-oxo-5-phenyl-2,3-dihydro-1*H*-3-pyrrolyliden)-4-phenylbutanoate (**5**).

Our present work showed that the three-component condensation involving two moles of methyl-4-oxo-4-phenylbutanoate and one mole of ammonium formate leading to the formation of pyrrolidone **5** takes place within two minutes under microwave irradiation. Conventional heating with ammonium acetate requires more than 7 h in methanol reflux. Thus, there is about 2×10^2 times rate enhancement. For reasons presently not clear, microwave mediated reactions appear to favour the formation of *Z*-isomer **5** rather than the more stable *E*-isomer. Moreover, unlike the microwave mediated reductive amination of 1,5-diketones, which lead to the formation of piperidine derivatives, the present reaction furnishes pyrrolidone derivatives of the type **5** from 4-phenyl-4-oxobutanoates.[11]

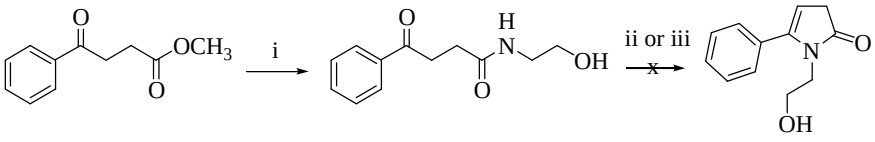
The mechanism for the formation of **5** is given in scheme 2. Decomposition of ammonium formate under high temperature releases ammonia and formic acid. Dehydrative condensation of ammonia with the carbonyl group of the ketoester **1** provides amide intermediate **9**. Subsequently, **9** undergoes intramolecular cyclization involving ester carbonyl to furnish 2-pyrrolidone derivative **11** via protonated imine **10**. The pyrrolidone derivative **11** may stabilize as **12** via keto-enol tautomerism. The enol **12** undergoes condensation with another molecule of ketoester **1** to give the pyrrolidone derivative **5** via an intermediate **13**.

This three-component condensation reaction was further extended to ethyl ester **2** as a follow-up on the mechanistic studies on the formation of the product **5**. The ketoester **2** also undergoes the condensation reaction in a similar fashion to give the pyrrolidone derivative 6 in about 88% as a mixture of isomers (scheme 1). Based on ^{13}C NMR spectral data the ratio of *Z*- and *E*-isomers is calculated to be 70 : 30.

The condensation reaction was next extended to 4-chloro-substituted ketoester **3**. This reaction also follows the same course and furnishes a mixture of isomers **7** in about 92% yield (scheme 1). Integration of the relevant signals in the ^{13}C NMR spectrum confirms *Z*- and *E*-ratio as 50 : 50.



Scheme 2.



Reagents and conditions: i. $HOCH_2CH_2NH_2$/HCOOH, PEG-200, *mn*, 370 W, 2 min; ii. P_2O_5/benzene or toluene, reflux; ii. Conc. H_2SO_4/DCM, rt.

Scheme 3.

The reaction was then attempted on 4-keto acid **4** with the intention to evaluate the role of an ester function in the condensation. We found that the reaction proceeds similar in a manner to that of the ester **1**. This reaction furnishes a mixture of geometrical isomeric acids **8** in about 54% yield (scheme 1.41). The ratio of *Z*- and *E*-isomer is found to be 70 : 30.

Next, the scope of the reaction was extended to the microwave mediated condensation of ketoester **1** with 2-hydroxyethylammonium formate with an intention to generate N-alkyl derivatives of 5-aryl-2-pyrrolidones. However, the reaction produces the amide, N-1-(2-hydroxyethyl)-4-oxo-4-phenylbutanamide **14** formed in 54% yield (scheme 3).

Structure of the amide **14** is assigned on the basis of IR, ^{1}H NMR and ^{13}C NMR spectral data. IR spectra show the presence of hydroxyl absorption at *n* 3460 cm^{-1} and amide carbonyl at *n* 1699 cm^{-1}. ^{1}H NMR spectra show a broad singlet at *d* 6·7 ppm revealing the presence of an NH group. The presence of four triplets *d* 2·60 (*J* = 6·5 Hz), *d* 3·34 (*J* = 6·5 Hz), *d* 3·38 (*J* = 5·18 Hz), *d* 3·67 (*J* = 5·06 Hz) ppm reveal the presence of four CH_2 groups in the molecule. ^{13}C NMR spectra show ten carbon signals out of which are two carbonyl, four aromatic and four aliphatic carbons.

Efforts towards the synthesis of 1-(2-hydroxyethyl)-5-phenyl-2-pyrrolidinone **15** from the cyclization of butanamide **14** with P_2O_5 in benzene or with conc. sulphuric acid in DCM did not yield desired results. Only extensive decomposition of the reaction mixture was noted (scheme 3).

Thus, in this investigation we have shown that microwave-mediated three component coupling of ketoester **1** with ammonium formate takes place readily to yield pyrrolidone ester **5** within 2 min. The reaction is general for ester and aryl moieties. However, changes in ammonium formate lead to formation of amide only. Presently we are investigating incorporating the orange-coloured product of the type **5** on a polymer matrix to study physicochemical properties of the resulting product.

3. Experimental

3.1 *General*

The progress of all the reactions was monitored by TLC (TLC silica gel; Qualigens or TLC alumina: SRL, India) using hexanes/ethyl acetate mixture as an eluent. Column chromatography was accomplished on silica gel (100–200 mesh, Acme synthetic chemicals) using hexanes/ethyl acetate mixture as an eluent. IR spectra were recorded as solutions of KBr or neat using an ABB Bomem MB-104 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or $CDCl_3 : CCl_4$ (1 : 1) using a JEOL 400 MHz, Varian 300 MHz or Bruker 300 MHz NMR spectrometer. The mass spectra were recorded on a Finnigan MAT 8230 or JEOL DX-303 mass spectrometer. The elemental analysis was carried out on an Elementar vario EL (Germany) apparatus. The microwave reactions were carried out using BPL-Sanyo (India), mono-made, multi power; power source: 230 V, 50 Hz, microwave frequency: 2450 MHz microwave oven. The starting materials **1–4** were prepared by following the literature procedure.[12]

3.2 *General procedure for reductive amination-cyclization of methyl-4-oxo-4-phenylbutanoate (**1**) under microwave irradiation*

Methyl-4-oxo-4-phenylbutanoate, compound **1** (682 mg, 3·75 mmol) was dissolved in 6 mL PEG-200, ammonium formate (895 mg, 15 mmol) was added and the solution was subjected to microwave irradiation at 370 W for 2 min. The reaction was monitored by TLC and showed the formation of a product. The reaction mixture was cooled to room temperature, dissolved in 30 mL dichloromethane (DCM) and poured over ice-cooled water. The organic layer was separated and washed water (3×15 mL) to remove excess PEG-200 present in the reaction mixture. The organic layer was then washed with brine solution (2×10 mL) and dried over anhydrous Na_2SO_4. The DCM solution was concentrated under *vacuo* and the resulting mixture was subjected to column chromatography (silica gel 100–200 mesh) using 15% EtOAc-hexanes as eluent to give **5** (586 mg, 91%).

3.2a *Methyl-4-(2-oxo-5-phenyl-2,3-dihydro-1H-3-pyrrolyliden)-4-phenylbutanoate* (**5**): An orange-coloured solid; m.p. 136–138°C; R_f = 0·18 (10% EtOAc-hexanes); UV (MeOH) l_{max} 391 (log e = 4·66); IR (KBr) n 699, 756, 903, 1168, 1279, 1448, 1681, 1729, 3191 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$/CCl_4, 1 : 1) d 2·53 (*t*, J = 8·0 Hz, 2H), 3·61 (*s*, 3H), 3·67 (*t*, J = 8·2 Hz, 2H), 5·95 (*s*, 1H), 7·25–7·43 (*m*, 8H), 7·64 (*d*, J = 8·1 Hz, 2H), 10·7 (*br s*, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$/CCl_4, 1 : 1) d 28·70, 32·62, 51·42, 99·16, 125·15, 128·55, 128·64, 128·83, 128·90, 129·01, 130·07, 130·97, 141·12, 141·53, 151·96, 171·29, 172·75 ppm; LRMS 333 (10%, M^+), 301 (5%), 273 (49%), 144 (100%), 116 (39%), 89 (44%), 63 (25%); Analysis: Calcd. for $C_{21}H_{19}NO_3$: C, 75·13; H, 4·88; N, 4·04%. Found: C, 75·10; H, 4·90; N, 4·01%.

3.3 *Reductive amination-cyclization of ethyl-4-oxo-4-phenylbutanoate (**2**) with ammonium formate*

Following the general procedure described above, the reaction of ethyl-4-oxo-4-phenylbutanoate **2** (957 mg, 4·65 mmol) and ammonium formate (1·17 g, 18·6 mmol) in 8 mL PEG-200 resulted in ethyl 4-(2-oxo-5-phenyl-2, 3-dihydro-1*H*-3-pyrrolyliden)-4-phenylbutanoate **6**, which was purified by column chromatography.

3.3a *Ethyl-4-(2-oxo-5-phenyl-2,3-dihydro-1H-3-pyrrolyliden)-4-phenylbutanoate* (**6**): An orange-coloured solid; Yield 707 mg, (88%); m.p. 140–142°C; R_f = 0·18 (10% EtOAc-hexanes); UV (MeOH) l_{max} 391 (log e = 4·34); IR (KBr) n 698, 757, 903, 1045, 1177, 1281, 1451, 1592, 1684, 1730, 2985, 3070, 3176 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) d 1·18 (*t*, 3H), 1·24 (*t*, J = 8·0 Hz, 2H), 2·42 (*t*, 2H), 2·51 (*t*, J = 8·0 Hz, 2H), 3·07 (*t*, J = 8·0 Hz, 2H), 3·65 (*t*, J = 8·0 Hz, 2H), 4·04 (*q*, 2H), 4·08 (*q*, 2H), 5·96 (*s*, 1H), 6·29 (*s*, 1H), 7·34–7·52 (*m*, 20H), 9.60 (*br s*, 1H), 9·87 (*br s*, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) d 14·15, 14·19, 28·30, 30·93, 32·63, 32·72, 32·76, 60·39, 60·69, 97·92, 99·62, 124·95, 128·06, 128·16, 128·37, 128·64, 128·94, 129·04, 129·21, 129·85, 130·40, 130·42, 138·48, 140·58, 140·65, 141·89, 152·69, 170·80, 172·80, 172·81 ppm; LRMS 347 (34%, M^+), 301 (16%), 273 (100%), 260 (8%), 244 (20%), 230 (8%), 104 (14%); Analysis: Calcd. for $C_{22}H_{21}NO_3$: C, 76·03; H, 6·08; N, 4·03%. Found: C, 76·06; H, 6·04; N, 4·07%.

3.4 *Reductive amination-cyclization of methyl-4-(4-chlorophenyl)-4-oxobutanoate (**3**) with ammonium formate*

Following the general procedure described above, the reaction of methyl-4-(4-chlorophenyl)-4-oxobut-

anoate **3** (307 mg, 1·36 mmol) and ammonium formate (343 mg, 5·44 mmol) in 4 mL PEG-200 furnished methyl-4-(4-chlorophenyl)-4-[5-(4-chlorophenyl)-2-oxo-2, 3-dihydro-1*H*-3-pyrrolyliden]butanoate **7** which was purified by column chromatography.

3.4a *Methyl-4-(4-chlorophenyl)-4-[5-(4-chlorophenyl)-2-oxo-2, 3-dihydro-1H-3-pyrrolyliden]butanoate* (**7**): An orange-coloured solid; Yield: 244 mg (93%); m.p. 216–218°C; R_f = 0·19 (10% EtOAc-hexanes); UV (MeOH) l_{max} 400 (log *e* = 4·23); IR (KBr) *n* 686, 768, 833, 899, 1008, 1091, 1164, 1284, 1436, 1490, 1591, 1683, 1735, 3088, 3173 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *d* 2·41 (*t*, *J* = 7·8 Hz, 2H), 2·49 (*t*, *J* = 8·0 Hz, 2H), 2·49 (*t*, *J* = 8·0 Hz, 2H), 3·02 (*t*, *J* = 7·8 Hz, 2H), 3·57 (*s*, 3H), 3·59 (*s*, 3H), 5·89 (*s*, 1H), 6·24 (*s*, 1H), 7·26–7·49 (*m*, 16H), 9·73 (*s*, 1H), 10·09 (*s*, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) *d* 28·34, 32·26, 32·41, 32·48, 51·71, 51·86, 97·99, 99·50, 126·02, 126·20, 128·08, 128·10, 128·35, 128·85, 129·17, 129·21, 129·91, 130·02, 130·66, 130·71, 134·25, 134·86, 135·11, 135·28, 136·62, 140·16, 141·33, 149·09, 151·40, 169·50, 170·61, 172·65, 173·00 ppm; LRMS 405 (6%, M^+ + 4), 403 (28%, M^+ + 2), 401 (38%, M^+), 369 (21%), 345 (28%), 343 (69%), 341(100%), 307 (29%), 247 (24%), 233 (24%), 138 (56%), 113 (12%), 111 (34%), 85 (38%), 57 (94%); Analysis: Calcd. for $C_{21}H_{17}Cl_2NO_3$: C, 62.71; H, 4.26; N, 3.48%. Found: C, 62.75; H, 4.29; N, 3.52%.

3.5 *Reductive amination-cyclization of 4-oxo-4-phenylbutanoic acid (**4**) with ammonium formate*

Following the general procedure described above, the reaction of 4-oxo-4-phenylbutanoic acid **4** (700 mg, 3·93 mmol) and ammonium formate (990 mg, 15·7 mmol) in 6 mL PEG-200 yielded 4-(2-oxo-5-phenyl-2,3-dihydro-1*H*-3-pyrrolyliden)-4-phenylbutanoic acid **8** which was purified by column chromatography.

3.5a *4-(2-Oxo-5-phenyl-2,3-dihydro-1H-3-pyrrolyliden)-4-phenylbutanoic acid* (**8**): An orange solid; Yield 340 mg, (54%); m.p. 222–224°C; R_f = 0·23 (10% EtOAc-hexanes); UV (MeOH) l_{max} 391 (log *e* = 4·16); IR (KBr) *n* 698, 766, 906, 1160, 1212, 1278, 1427, 1446, 1493, 1599, 1683, 1706, 3062, 3169 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + drop of DMSO-d_6) *d* 2·39 (*t*, *J* = 12·33 Hz, 2H), 3·0 (*br s*, 1H), 3·58 (*t*, *J* = 12·35 Hz, 2H), 5·90 (*d*, *J* = 3·3 Hz, 1H), 7·31–7·44 (*m*, 6H), 7·54–7·64 (*m*, 4H), 10·08 (*br s*, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$ + drop of DMSO-d_6) *d* 27·28, 32·09, 98·58, 127·89, 128·34 (2C), 129·61, 129·93, 140·25, 140·71, 150·44, 169·72, 174·07 ppm; LRMS 319 (54%, M^+), 273 (100%), 230 (33%), 182 (53%), 127 (72%), 89 (88%), 57 (52%); Analysis: Calcd. for $C_{20}H_{17}NO_3$: C, 75·22; H, 5·35; N, 4·39%. Found: C, 75·26; H, 5·38; N, 4·43%.

3.6 *Reductive amination-cyclization of methyl-4-oxo-4-phenylbutanoate (**1**) with 2-aminoethyl-ammonium formate*

2-Amino-1-ethanol (634 mg, 10·4 mmol) was taken in a clean 10 mL conical flask that was kept in ice-salt mixture and formic acid (479 mg, 10·4 mmol) was added drop by drop till the effervescence ceased. To this solution 4 mL PEG-200 was added followed by methyl-4-oxo-4-phenylbutanoate **1** (199 mg, 1·04 mmol). The contents of the flask were exposed to microwave irradiation at 370 W for 2 min. After completion of the reaction (TLC) the reaction mixture was cooled to room temperature, diluted with 30 mL DCM and poured over ice-cooled water. The organic layer was separated and washed with water (3 × 15 mL), brine solution (2 × 10 mL) and dried over anhydrous Na_2SO_4. The DCM solution was concentrated under *vacuo* and the resulting mixture was subjected to column chromatography (silica gel 100–200 mesh) using 20% EtOAc-hexanes as an eluent to furnish amide **14**.

3.6a *N-1-(2-Hydroxyethyl)-4-oxo-4-phenylbutanamide* (**14**): Yield: 140·1 (54%); R_f = 0·21 (10% EtOAc-hexanes); IR (neat) *n* 696, 761, 992, 1072, 1176, 1208, 1413, 1448, 1543, 1699, 2882, 2928, 3460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *d* 2·60 (*t*, *J* = 6·5 Hz, 2H), 3·34 (*t*, *J* = 6·5 Hz, 2H), 3·38 (*t*, *J* = 5·18 Hz, 2H), 3·67 (*t*, *J* = 5·06 Hz, 2H), 6·7 (*br s*, 1H), 7·43 (*t*, *J* = 7·6 Hz, 2H), 7·54 (*t*, *J* = 7·36 Hz, 1H), 7·94 (*d*, *J* = 7·28 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) *d* 30·19, 34·06, 42·51, 61·92, 126·03, 128·12, 128·68, 133·40, 136·56, 173·37, 199·54 ppm.

3.7 *Reaction of N-1-(2-hydroxyethyl)-4-oxo-4-phenylbutanamide (**14**) with P_2O_5*

To N-1-(2-hydroxyethyl)-4-oxo-4-phenylbutanamide **14** (102 mg, 0·45 mmol) taken in 3 mL of benzene

phosphorous pentoxide (10 mg) was added and the resulting reaction mixture was heated at reflux. The progress of the reaction was monitored by TLC and showed no product formation even after 48 h. Similarly, there was no reaction even when toluene was used in place of benzene.

3.8 *Reaction of N-1-(2-hydroxyethyl)-4-oxo-4-phenylbutanamide (***14***) with* H_2SO_4

To N-1-(2-hydroxyethyl)-4-oxo-4-phenylbutanamide **14** (48 mg, 0·22 mmol) taken in 2 mL of dichloromethane, a catalytic amount of conc. H_2SO_4 was added and stirred at room temperature. There was no reaction (TLC) even after 24 h and there was only decomposition.

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