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INTER- AND INTRA- MOLECULAR CYCLISATION REACTIONS OF AZOACETATES DERIVED FROM ARYL HYDRAZONES OF ETHYL ACETOACETATE AND ACETOACETANILIDES

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Abstract – The base induced cyclisations of azoacetates to azetidinones were investigated. In addition to the isolation of the desired products, it was found that 2-iminopyrrolidine-5-one derivatives as well as N-acyl hydrazides could be isolated when metal cyanides were employed as base. These entities were further modified to form pyrrolidine-2,5-diones and diazetidinones respectively.

INTRODUCTION

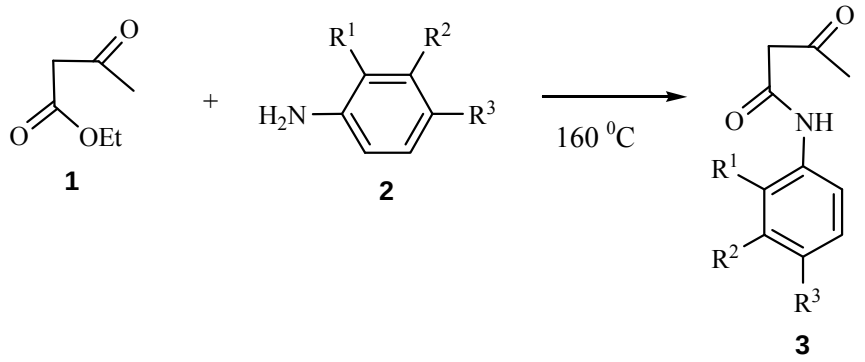
The search for new β-lactam species as antibacterial agents has been in decline in recent times due to problems encountered with the rapid development of resistant strains of bacteria. However due to the low levels of toxicity inherent to these compounds there has been a simultaneous surge in interest in any newly generated species in ancillary roles. Monocyclic β-lactams with non-classical features, bearing simple aryl and alkyl moieties have been of particular interest recently in a variety of roles ranging from anti-cancer agents,[1] and HIV-1 protease inhibitors,[2] to anti-fungal agents.[3] The synthesis of some azetidinones and diazetidinones through the reaction of the appropriate azoacetates with various bases has been previously reported by this group.[4] Herein we report in full the experimental details of these procedures and the related spectral data. In addition to these published intramolecular ring closures it has been discovered that products of intermolecular reactions between the azoacetate and the cyanide ion can be isolated in reasonable yields in some cases. The generation of the 2-iminopyrrolidine-5-ones derivatives is presumably due to a nucleophilic displacement of the acetate group by the cyanide ion to form the nitrile entity followed by spontaneous cyclisation. Relatively few examples of synthetic routes to these molecules can be found in the mainstream literature.[5] However it will be shown here that these compounds provide a valuable route to the synthetically and medicinally versatile pyrrolidine-2,5-dione

(succinimide) molecules.[6] The azoacetate derived from α,α-dimethyl ethyl acetoacetate was found to form an N-acyl hydrazide rearrangement product that could be isolated and subsequently, after hydrolysis of the ester moiety, cyclised to form a diazetidinone derivative. It was found that azo functionality in the azetidinones reported here could be easily oxidized to give the corresponding azoxy species. The scope of this reaction to furnish further compounds is currently under investigation. Also discussed is the unexpected cyclisation of the α,α-unsubstituted azoacetate derivatives to form pyrazole ring derivatives.

RESULTS AND DISCUSSION

The azoacetates in question were synthesized in several steps from simple inexpensive starting materials using facile procedures. Where possible commercially available acetoacetanilides were used as starting materials, the remainder were generated by simply heating the appropriately substituted aniline (**2a-e**) (1 molar equivalents) with ethyl acetoacetate (**1**) (5 molar equivalents) to 160 °C until the evolution of ethanol had ceased, after removing the bulk of the remaining ethyl acetoacetate by vacuum distillation the desired acetoacetanilides could be easily crystallized by scratching the reaction vessel.[7]

Table 1. Synthesis of acetoacetanilides from ethyl acetoacetate

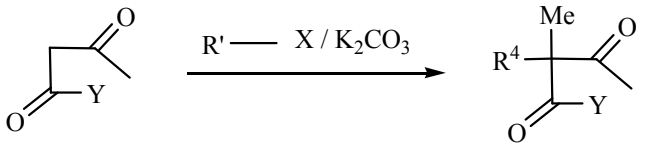


Entry	Substrate	R^1	R^2	R^3	Product	Yield (%)
1	**2a**	H	H	Br	**3a**	90
2	**2b**	H	H	OMe	**3b**	88
3	**2c**	Me	Me	H	**3c**	91
4	**2d**	H	H	Me	**3d**	85
5	**2e**	H	H	CO_2Et	**3e**	77

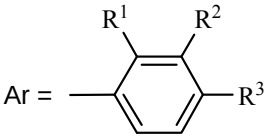
These were further purified by recrystallization from EtOAc/hexane before being used in the next stage. Dimethylation of the acetoacetanilides (**3a-j**) was achieved by refluxing overnight with an excess of methyl iodide (6 molar equivalents) and potassium carbonate (3 molar equivalents). In the case of the methyl, benzyl substituted example **7** the substrate acetoacetanilide was initially methylated using methyl iodide in a 1:1:1.5 ratio of substrate:base:methyl iodide. This resulted in the production of the mono-methylated species **6** as the major product but also resulted in the production of some of the

di-methylated product **5j**. It was found that the desired mono-methylated compound could be isolated in pure form after several recrystallizations from ethanol. The subsequent benzylation was carried out under similar reaction conditions using an excess of benzyl chloride as alkylating agent.

Table 2. Alkylation of ester and anilides



Substrate	Y	X	R'	Product
1	OEt	I	Me	**4**
3	NH-Ar	I	Me	**5**
3	NH-Ar	I	Me	**6**[a]
6	NH-Ar	Cl	Bn	**7**

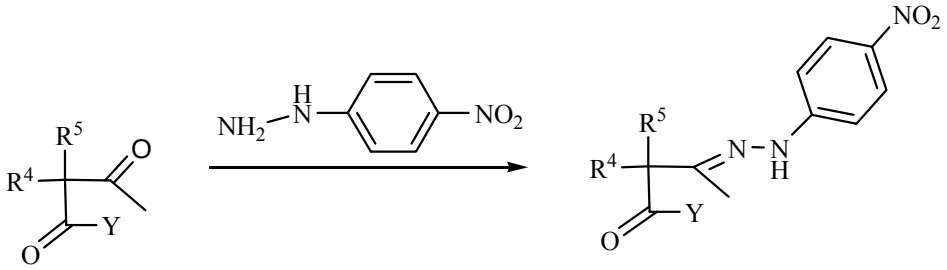


Entry	Substrate	Y = OEt or NH-Ar			Product	Yield (%)
		R^1	R^2	R^3		
1	**1**	-	-	-	**4**	80
2	**3a**	H	H	Br	**5a**	79
3	**3b**	H	H	OMe	**5b**	78
4	**3c**	Me	Me	H	**5c**	80
5	**3d**	H	H	Me	**5d**	83
6	**3e**	H	H	CO_2Et	**5e**	70
7	**3f**	H	H	H	**5f**	80
8[b]	**3g**	Me	H	Me	**5g**	67
9[b]	**3h**	Me	H	H	**5h**	75
10[b]	**3i**	OMe	H	H	**5i**	74
11[b]	**3j**	H	H	Cl	**5j**	69
12[b]	**3j**	H	H	Cl	**6**	74
13	**6**	H	H	Cl	**7**	90

[a] In all entries $R^4 = CH_3$, except in entry 12 (Product **6)** where, R^4 = H, and entry 13 (Product **7**) where, R^4 = Bn, [b]Starting materials were commercially available acetoacetanilides

4-nitrophenylhydrazone derivatives were prepared of the starting materials ethyl acetoacetate (**1**) and the acetoacetanilide (**3f**) along with α,α-disubstituted ethyl acetoacetate (**4**) and all of the α,α-disubstituted acetoacetanilides (**5a-j** and **7**) (Table 3) by stirring the substrates in a slight excess (1.1 molar equivalents) of 4-nitrophenylhydrazine in MeOH under mild acidic conditions (~5% acetic acid).[8] This procedure routinely furnished the desired hydrazones in reasonable yields (50-72%).

Table 3. Synthesis of 4-nitrophenylhydrazone derivatives

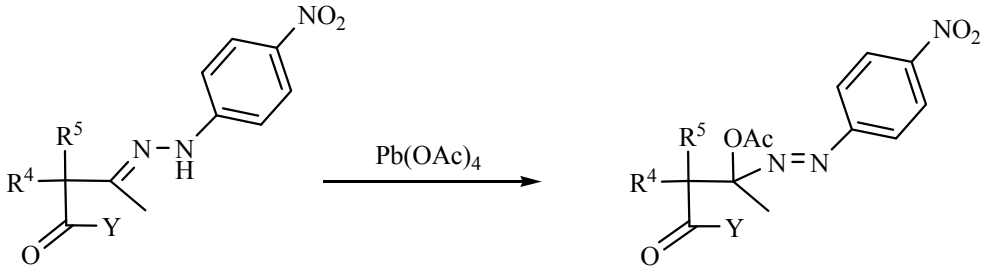


Substrate	Y	R^4	R^5	Product	Yield(%)
1	OEt	H	H	**8**	55
3f[a]	NH-Ar	H	H	**9f**	59
4	OEt	Me	Me	**10**	65
5a-j[a]	NH-Ar	Me	Me	**11a-j**	50-72
7[a]	NH-Ar	Me	Bn	**12**	39

[a] With reference to aromatic groups Ar, substitutions at R^1, R^2 and R^3 are as shown in Table 2

The synthesis of the azoacetates of these hydrazones was found to be equally facile (Table 4), once again it was found that merely stirring the substrate hydrazones overnight in a mildly acidic CH_2Cl_2 solution (10% acetic acid) containing a slight excess (1.1 molar equivalents) of $Pb(OAc)_4$ was sufficient to effect the desired transformation.[9] After a standard work-up, flash chromatography was used to separate the azoacetates from any persistent lead salt residues

Table 4. Synthesis of azoacetate derivatives

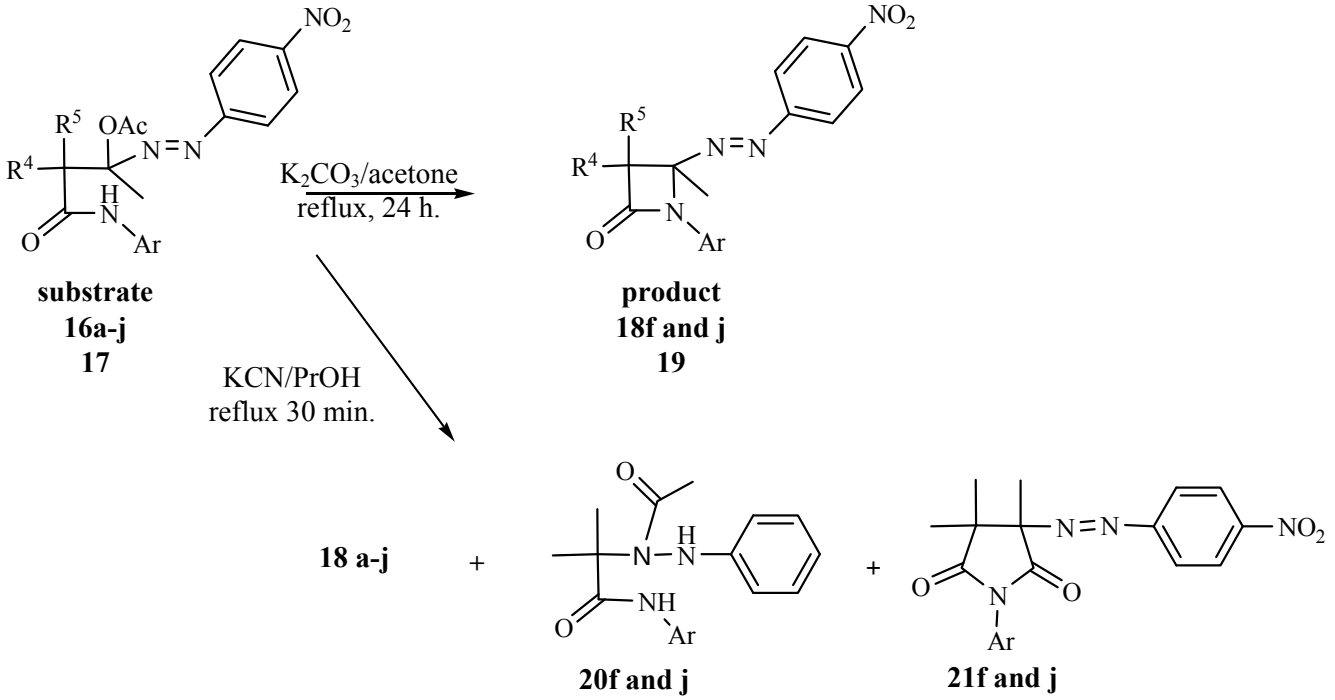


Substrate	Y	R^4	R^5	Product	Yield(%)
8	OEt	H	H	**13**	65
9f[a]	NH-Ar	H	H	**14f**	68
10	OEt	Me	Me	**15**	77
11a-j[a]	NH-Ar	Me	Me	**16a-j**	70-89
12[a]	NH-Ar	Me	Bn	**17**	56

[a] With reference to aromatic groups Ar, substitutions at R^1, R^2 and R^3 are as shown in Table 2

The reactions of the azoacetates with various bases produced the most interesting results (Scheme 1). It was found that the azoacetates derived from α,α-dimethylated acetoacetanilide or α-methyl-α-benzyl acetoacetanilide could be cyclised to azetidinones (**18f, 18j** and **19**) upon treatment with K_2CO_3 under

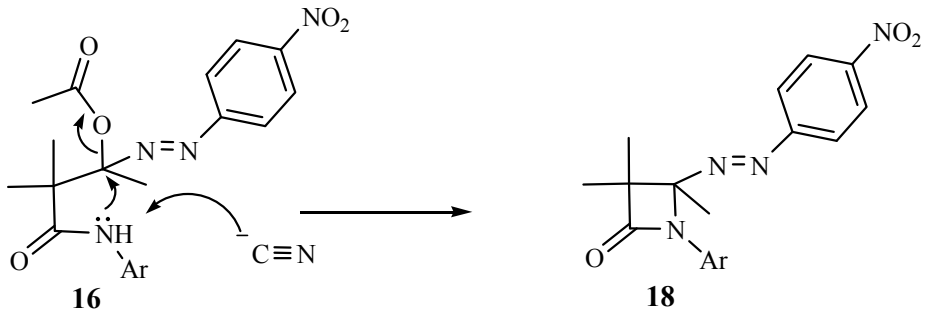
reflux in acetone. It was also found that the cyclisation could be carried out in other conditions; azetidinones (**18a-j**) were also isolated when the reaction was carried out in *n*-propanol using KCN as base. When the reactions of previously reported azoacetates (**16f** and **16j**) were more closely examined it was found that in addition to the reported rearrangement products **20f** and **20j**, an additional cyclised compound could be isolated in both cases. The isolation of these 2-iminopyrrolidine-5-one products (**21f** and **21j**) is a relatively rare example of the incorporation of cyanide moiety into a heterocyclic system in a one step process. It would seem that both the basic and nucleophilic properties of the cyanide species have an effect on the formation of reaction products in this case. The formation of these products has been confirmed by spectral analysis (NMR, IR, MS) and in the case of azetidinone (**18j**) and 2-iminopyrrolidine-5-one derivative (**21f**) by X-Ray crystal structure determination (Figures 1a and b).



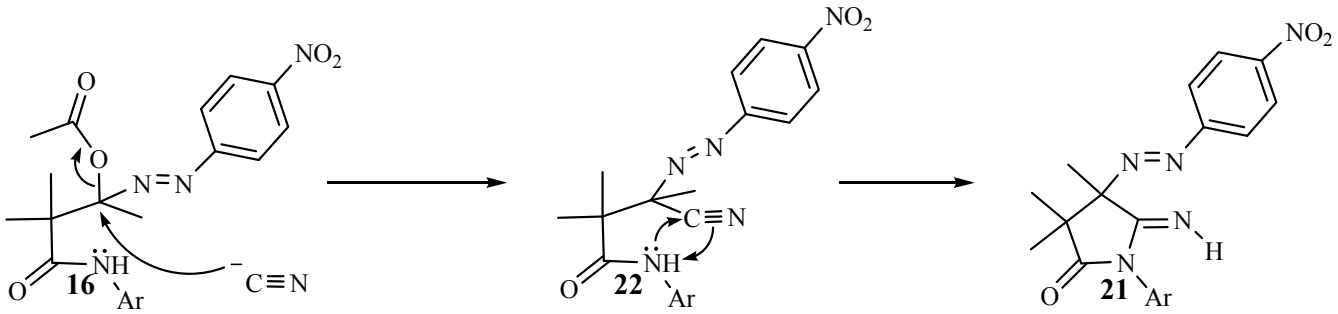
Scheme 1

The formation of these three products are clearly as a result of different reaction mechanisms, they do however all conform to previously postulated reaction pathways. Instances of the base induced abstraction of the relatively acidic amido-hydrogen, followed by cyclisation through loss of a leaving group (Scheme 2a) can be commonly found in the literature related to β-lactam formation.[10] However the acetate moiety acting as leaving group in this manner under such mild conditions has, to our knowledge, not been previously reported. Of note amongst the azetidinone products isolated was compound **18e**, it was found that the transesterification product of the azetidinone was isolated. The action of the base/propanol media in this case resulted in the isolation of the 4-propyl ester derivative as sole azetidinone product in this case. Also two diastereomeric forms of azetidinone derivative (**19**) were

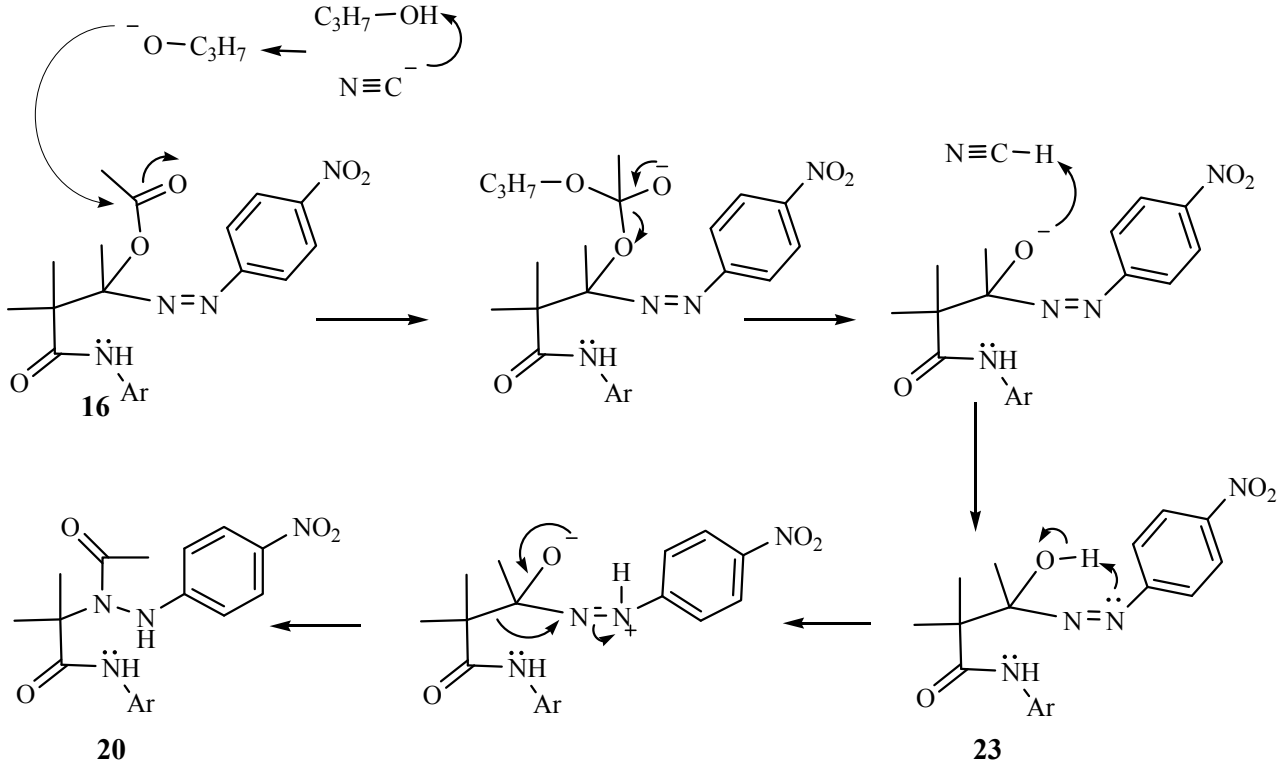
isolated and could be differentiated on the basis of differing chemical shift values for key NMR spectral values (e.g. benzyl CH_2 shift).



Scheme 2a. Proposed mechanism of formation of azetidinone **18**



Scheme 2b. Proposed mechanism of formation of **21**



Scheme 2c. Proposed mechanism of formation of **20**

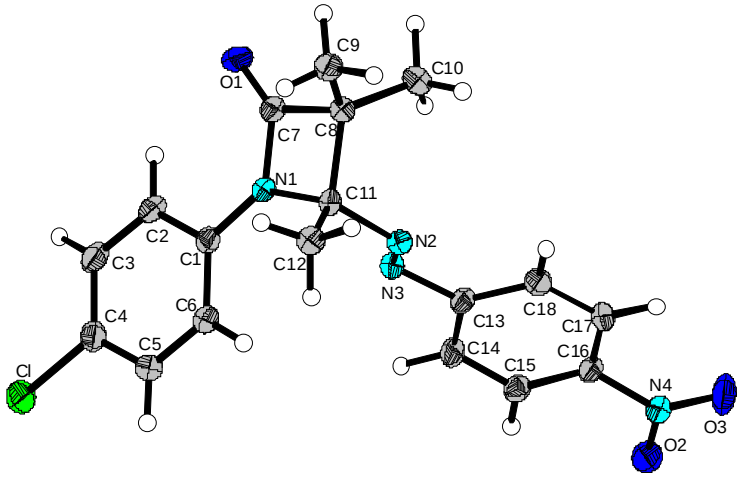


Figure 1a. X-Ray crystal structure of azetidinone **18j**

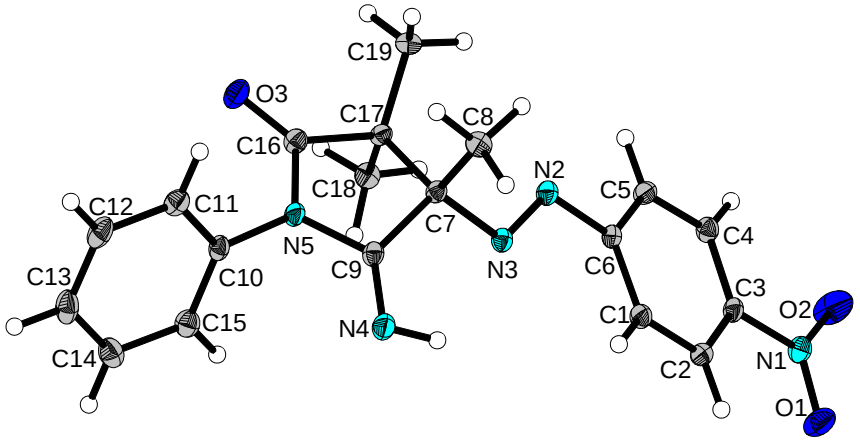


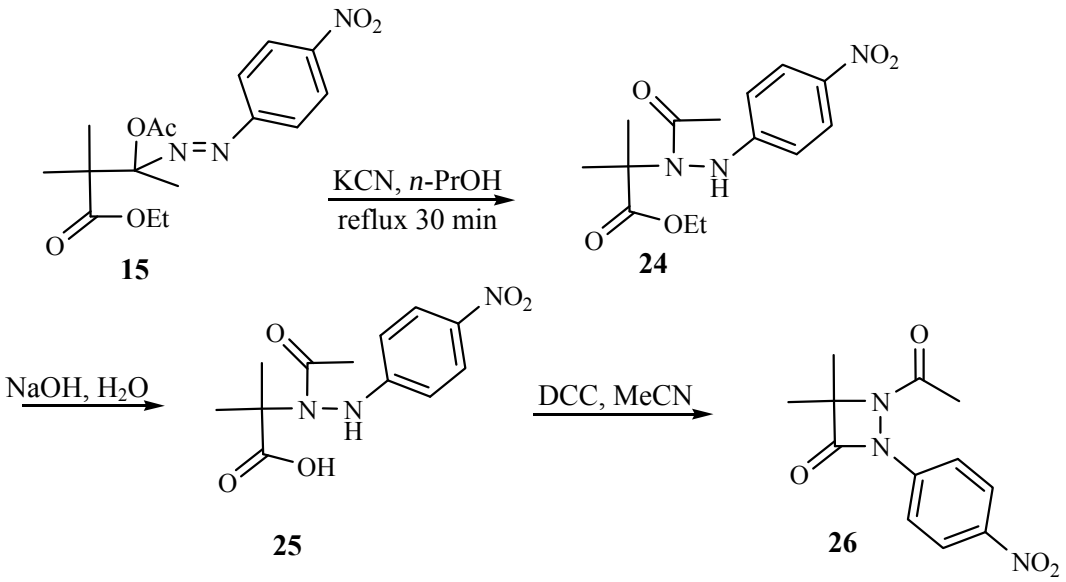
Figure 1b. X-Ray crystal structure of 2-iminopyrrolidine-5-one derivative **21f**

The α-azo-α-nitrile functionality is a known species and it has been demonstrated that in certain cases, the nitrile group can be introduced at a position α to an azo-group by reaction of a hydrazone with metal cyanides.[11] The intermolecular nucleophilic displacement of a leaving group by the cyanide species to form a nitrile followed by cyclisation, as in the case of the formation 2-iminopyrrolidine-5-ones (**21f** and **21j**) has also previously been studied by Nisole *et al.*[12] The isolation 2-iminopyrrolidine-5-ones directly upon treatment of carbamoylated chloroenamines with metal cyanides in alcohol have similarly been observed by Vilsmaier *et al.*[13] In that case, the cyclisation took place spontaneously under the action of the basic reaction media with a similar mechanism proposed; some parallels can be drawn to the observations made here, in so far as the isolation of the nitrile intermediate was not achieved. Since the formation of the cyclised product through incorporation of the cyanide ion is evident, it is reasonable to assume that the intermediate **22** in **Scheme 2b**, plays a role.

It is proposed that the rearrangement of azoacetates (**16f** and **16j**) to N-acyl hydrazides (**20f** and **20j**) takes place via an alcoholysis mechanism involving the formation of an azocarbinol species (a.k.a. α-hydroxy

phenylazo compounds) such as intermediate **23** in **Scheme 2c**. It seems most likely that it is this species that undergoes the rearrangement. The transformation of azoacetates to azocarbinols in this way has previously been shown to be possible.[14] Barton *et al*. utilized 2-*t*-butyl-1,1,3,3-tetramethyl guanidine base (Barton's base) to effect this type of transformation in ethanol, however efforts to isolate intermediate **23** in a similar manner failed. The azocarbinol species in general is notoriously unstable, and it would seem that the formation of the rearrangement product is the favored process in this case.

In order to further investigate the versatility of the compounds synthesized, some supplementary reactions were carried out on the products mentioned thus far and it was found that a further array of interesting compounds could be created. In the case of the N-acyl hydrazide derivative (**24**) isolated from the reaction of azoacetate (**15**) with potassium cyanide it was found that the ester moiety could be easily hydrolyzed to the carboxylic acid **25** and this could then be cyclised to give a diazetidinone product (**26**). The structure of the rearrangement product **24** was confirmed by X-Ray crystallography.



Scheme 3

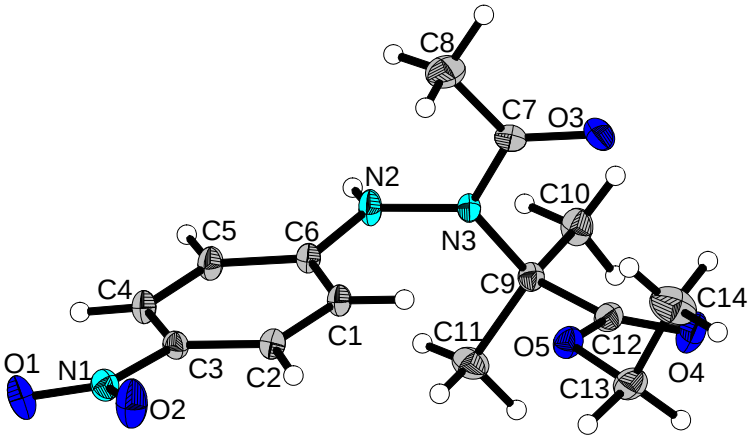
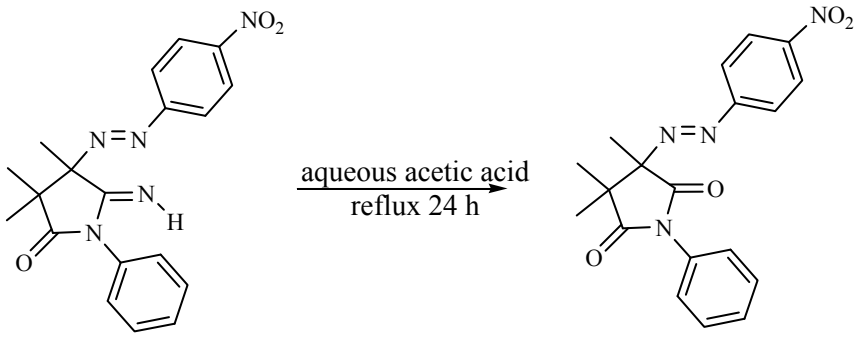


Figure 2. X-Ray crystal structure of rearrangement product **24**

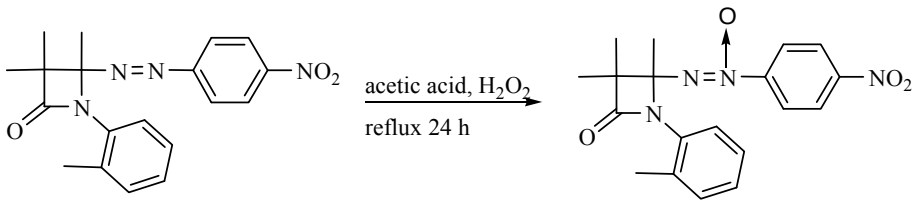
Among the many published synthetic routes to the versatile succinimide compounds perhaps the simplest is the acid catalyzed hydrolysis of 2-iminopyrrolidine-5-ones.[15] The appearances of several versions of the procedure in the literature show it to be a robust high-yielding technique that can be used when a variety of functional groups are present adjacent to the imino functionality. In the example presented here a smooth transition with high yield was achieved. 2-iminopyrrolidine-5-one (**21f**) was converted to the corresponding succinimide (**27f**). The substrate **21f** was introduced to a refluxing solution of aqueous acetic acid and allowed to reflux for a further 24 h after which the desired succinimide was easily extracted into organic solvent (CH_2Cl_2) and purified by flash chromatography.



21f **27f**

Scheme 4

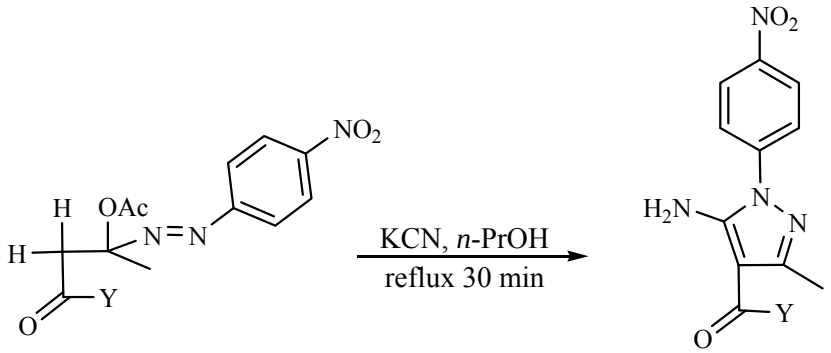
It was found that the azoxy derivative **28h** of azetidinone (**18h**) could be generated through reaction with hydrogen peroxide in the presence of acetic acid. Although all spectral data supports the formation of the azoxy functionality at a position adjacent to the phenyl group, since an X-Ray crystal structure of the product was not obtained in this case this characterization is somewhat tentatively assigned. The formation of the azoxy functionality is in little doubt; however guidelines to the assignment of the position of the azoxy oxygen found in the literature were at times contradictory and at best speculative. Some consensus seems to have been reached on the issue of the increase in the deshielding effect on groups adjacent to the newly formed azoxy group by comparison to the parent azo compound. The creation of the azoxy group presented here was indeed accompanied by a large downfield shift by the aromatic proton signals adjacent to the proposed site of the azoxy oxygen.



18h **28h**

Scheme 5

The production of the 2-iminopyrrolidine-5-one derivative (**21f**) raised the question of what might happen under similar conditions with an α,α-unsubstitued azoacetate. The investigations of this question led to an unexpected cyclisation. It was found that when these substrates **13** and **14f** were subjected to identical conditions to those used previously with the α,α-dimethylated azoacetate derivatives, that once again a cyano unit was incorporated into the cyclic product. However, in this case the absence of alkyl groups at positions α to the carbonyl allows for the formation of the pyrazole derivatives (**29** and **30f**) as the intermolecular reaction products.[16]



Substrate		**Product**
13	Y=OEt	**29**
[a]**14f**	Y=NH-Ar	**30f**

Scheme 6

Confirmation of the structure has been established by X-Ray crystal structure analysis in the case of compound **30f**. Although the isolation of these compounds has been previously reported, different methodologies were employed in the synthesis. Furthermore, the crystal structure of this species has not been published to date.

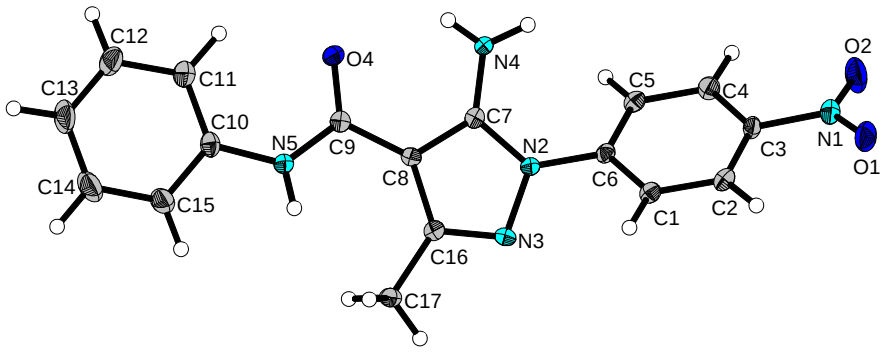
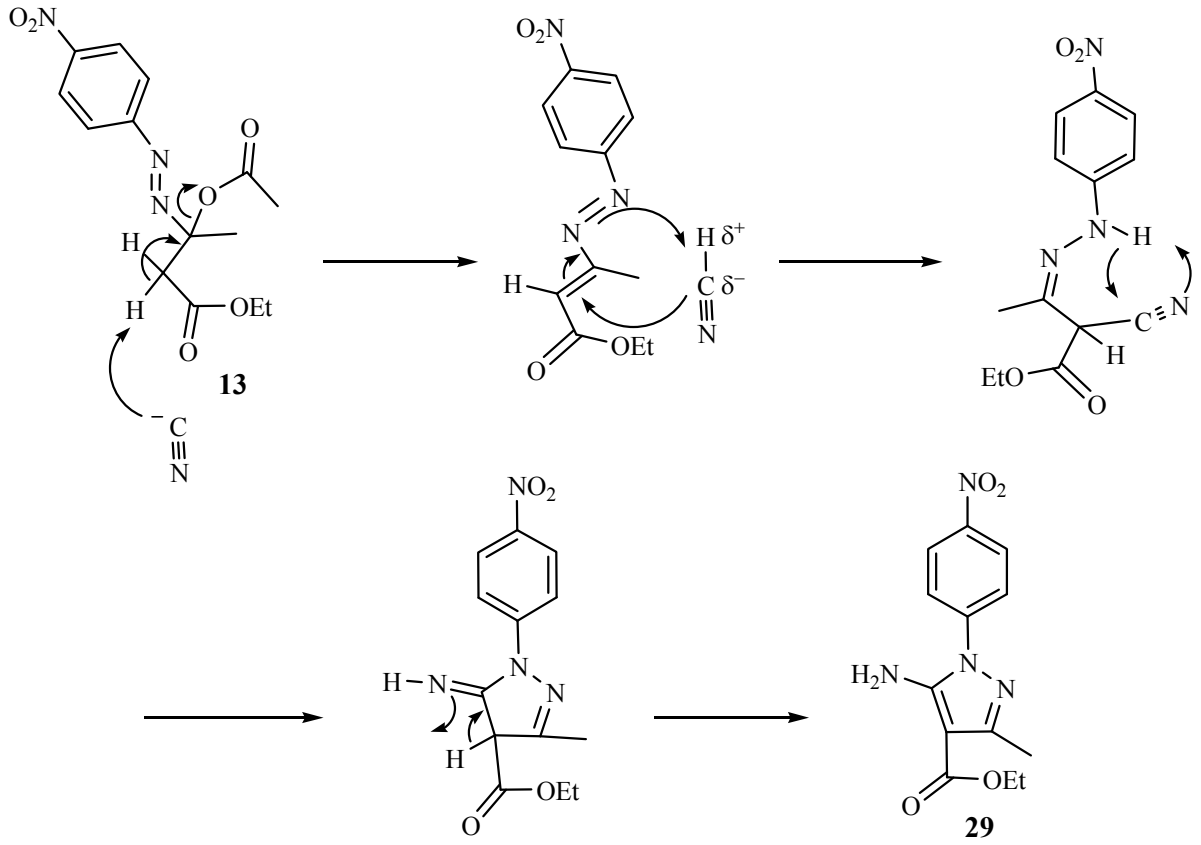


Figure 3. X-Ray crystal structure of pyrazole derivative **30f**

Scheme 7 depicts a proposed mechanism for the formation of pyrazole derivative (**29**) from the corresponding azoacetate derivative (**13**). In light of the basic reaction conditions, the formation of the pyrazole is presumably due to initial elimination of a unit of acetic acid aided by stabilization of the product provided by the neighboring phenylazo group. Nucleophilic addition at this newly formed double bond provides a cyano substituted hydrazone substrate for cyclisation to the pyrazole ring, as has been previously proposed by Shawali *et al*.[17] In that case the proposed formation of the hydrazone species was as a result of the condensation of a hydrazidic halide and ethyl cyanoacetate.



Scheme 7

In conclusion the results presented here, demonstrate the synthetic versatility of these azoacetates derived from simple, inexpensive starting material. The examples shown here of both endo- and exocyclic incorporation of the azo functionality into heterocyclic systems demonstrate the value of a previously unexplored resource in the synthetic sphere. A range of products from established medicinally important families of compounds have been synthesized through simple modifications using facile procedures. It is deemed noteworthy to point out that the synthesis of products based solely on 4-nitrophenyl hydrazone derivatives was due to their inherent stability to the acidic conditions required for condensation. Some arylhydrazone of β-keto esters are prone to spontaneous cyclisation giving, pyrazoles and pyrazolones.[18]

Our research has not been based exclusively on arylhydrazones of this type, however these compounds were chosen for presentation at this time due to the reliability and reproducibility of the results obtained.

EXPERIMENTAL

Ethyl acetoacetate, iodomethane, benzyl chloride and substituted acetoacetanilides were purchased from the Sigma Aldrich chemical company and were used as received. All solvents were dried or distilled prior to use. Melting points were determined using a Griffin melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 2000FT-IR spectrometer. NMR spectra were recorded using a Bruker AC 400 NMR spectrometer operating at 400 MHz for ^{1}H NMR and at 100 MHz for ^{13}C NMR. The ^{1}H and ^{13}C NMR chemical shifts (ppm) are relative to TMS and all coupling constants (*J*) are in Hertz (Hz).

X-Ray crystallographic data

*"CCDC 272234 (**18j**), CCDC 686905 (**21f**), CCDC 686907 (**24**), and CCDC 686906 (**30f**), contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033."*

Preparation of acetoacetanilides (3a-e)

These compounds were prepared according to a general procedure a representative example is given.

Synthesis of 4-bromoacetoacetanilide **(3a)**

Ethyl acetoacetate (65.1 g, 0.5 mol) was heated to 160 ^{o}C in a round bottomed flask with reflux condenser fitted. To this was added 4-bromoaniline (17.0 g, 0.1 mol). When the evolution of EtOH began the reaction was allowed to reflux for 2-3 h until the reaction was complete (TLC) before the EtOH was distilled off. The bulk of the remaining ethyl acetoacetate was removed by vacuum distillation at 90^{o} C, 50mbar. The resulting oily residue was scratched with a glass rod to promote precipitation. The precipitate was filtered and washed with hexane before being recrystallised from an EtOAc:hexane 30:70 mixture. Yield (22.8 g, 90.1 %); mp 132-135 ºC; ^{1}H NMR (400MHz, DMSO-d_6): δ =, 2.21 (3H, s, CH_3), 3.56 (2H, s, CH_2), 7.48 (2H, ArH, *J* = 8.8), 7.55 (2H, d, ArH, *J* = 8.8) 10.21 (1H, s, NH); ^{13}C NMR (100MHz, DMSO-d_6) 30.2, 52.3, 114.9, 120.9, 131.5, 138.2, 165.2, 202.7; IR (KBr) 3292, 1718, 1661, 1607, 1554, 1491, 1396, 1162, 1075, 832, 505 cm^{-1}.

Preparation of α,α-dimethylethylacetoacetate (4) and α,α-dimethylacetoacetanilides (5a-j)

These compounds were prepared according to a general procedure a representative example is given.

***Synthesis of* α,α-*dimethyl-4-bromoacetoacetanilide* (5a)**

(6.62 g, 25.9 mmol) of 4-bromoacetoacetanilide was dissolved in 150 mL of acetone, to this was added K_2CO_3 (7.8 g, 56.4 mmol) and the reaction was set to reflux. Once the reaction had reached reflux temperature iodomethane (22.45 g, 158.2 mmol) was added and the reaction was allowed to reflux overnight. The solvent was reduced to 1/5 of the original volume by rotary evaporation and the entire contents of the reaction vessel were poured into a beaker containing 200 mL of ice-water. The product formed an oil and was extracted with CH_2Cl_2 (5 x 50 mL). The organic extracts were combined, dried over magnesium sulfate and evaporated to an oil under reduced pressure. A small portion of the oil was removed and precipitation was induced by scratching, this was then returned to the bulk in order to seed the crystallization of the remaining oil. The solid was filtered and washed with hexane, this was further recrystallized from an EtOAc:hexane 70:30 mixture. Yield (5.84 g, 79.4%); mp 85-87 ºC; ^{1}H NMR (400MHz, DMSO-d_6): δ =, 1.37 (6H, s, 2 x CH_3), 2.15 (3H, s, CH_3), 7.48 (2H, ArH, J = 9.2), 7.61 (2H, d, ArH, J = 8.8), 9.57 (1H, s, NH); ^{13}C NMR (100MHz, DMSO-d_6) 21.8, 25.7, 56.5, 115.3, 122.2, 131.3, 138.2, 171.8, 207.2; IR (KBr) 3361, 1684, 1531, 1490, 1394, 1310, 1239, 1240, 1117, 1071, 818 cm^{-1}.

Preparation of α-methyl-4-chloroacetoacetanilide (6) and α-methyl-α-benzyl-4-chloroacetoacetanilide (7)

***Synthesis of α-methyl-4-chloroacetoacetanilide* (6)**

(10.8 g, 51.2 mmol) of 4-chloroacetoacetanilide **(3j)** was dissolved in acetone (75 mL) and) K_2CO_3 (7.2 g, 52.0 mmol) was added and the reaction brought to reflux. Iodomethane (10.66 g, 75.1 mmol) was added dropwise with stirring to the reaction vessel over 1 h and the reaction was allowed to reflux for a further 2 h. The reaction mixture was cooled and poured into ice-water (150 mL) and allowed to stir for 30 min, a white precipitate **(6)** was collected and recrystallized several times from aqueous EtOH to remove any dimethylated product **(5j)**. Yield (8.59 g, 74.4%); mp 125-129 ºC; ^{1}H NMR (400MHz, DMSO-d_6): δ =, 1.23 (3H, d, CH_3, J = 6.8), 2.17 (3H, s, CH_3), 3.65 (1H, q, CH, J = 6.8), 7.37 (2H, d, ArH, J = 8.8), 7.50 (2H, d, ArH, J = 8.8), 10.34 (1H, s, NH); ^{13}C NMR (100MHz, DMSO-d_6) 13.0, 28.2, 54.5, 120.8, 127.1, 128.6, 137.8, 168.9, 204.3. IR (KBr) 3241, 1720, 1654, 1604, 1543, 1494, 1403, 1081, 826 cm^{-1}.

***Synthesis of α-methyl-α-benzyl-4-chloroacetoacetanilide* (7)**

(6.8 g, 30.2 mmol) of α-methyl-4-chloroacetoacetanilide (**6**) was dissolved in acetone 50 mL and (7.2 g, 52.0 mmol) of K_2CO_3 was added and the reaction brought to reflux. Benzyl chloride (6.58 g, 52.0 mmol) was added dropwise with stirring to the reaction vessel over 1 h and the reaction was allowed to reflux overnight. The reaction mixture was cooled and poured into ice-water (150 mL) and allowed to stir for 30 min, a white precipitate (**7)** was collected and recrystallized from an EtOAc:hexane 70:30 mixture. Yield: (8.53 g, 89.5%); mp 124-127 ºC; ^{1}H NMR (400MHz, DMSO-d_6): δ =, 1.27 (3H, s, CH_3), 2.20 (3H, s,

CH_3), 3.07 (1H, d, CH_2, J = 13.6), 3.36 (1H, d, CH_2, J = 13.6), 7.11-7.23 (5H, m, ArH), 7.77 (2H, d, ArH, J = 8.8), 7.43 (2H, d, ArH, J = 8.8), 9.68 (1H, s, NH); ^{13}C NMR (100MHz, DMSO-d_6) 18.7, 26.3, 39.7, 61.3, 122.3, 126.5, 127.6, 128.0, 128.1, 130.1, 136.7, 137.5, 170.2, 206.3; IR (KBr) 3328, 1720, 1654, 1604, 1543, 1494, 1403, 1081, 826 cm^{-1}.

Preparation of hydrazone derivatives (8, 9a and **f, 10, 11a-j, 12)**

These compounds were prepared according to a general procedure a representative example is given.

Synthesis of 4-nitrophenyl hydrazone derivative of α,α-dimethyl-4-bromoacetoacetanilide **(11a)**

(4.0 g, 14.0 mmol) of 2,2-dimethyl-4-bromoacetoacetanilide (**5a**) was dissolved in MeOH 75 mL, (2.6 g, 16.8 mmol) of 4-nitrophenylhydrazine was dissolved in warm acetic acid (3.25 mL) and added to the stirring reaction vessel. After 1-2 min a yellow precipitate began to fall from solution, the reaction was allowed to stir overnight and the precipitate collected and dried. Yield (4.01 g, 68%); mp 197-200 ºC; ^{1}H NMR (400MHz, DMSO-d_6): δ = 1.48 (6H, s, 2 x CH_3), 1.96 (3H, s, CH_3), 7.27 (2H, d, ArH, J = 8.8), 7.50 (2H, d, ArH, J = 9.2), 7.65 (2H, d, ArH, J = 8.8), 8.12 (2H, d, ArH, J = 8.8), 9.43 (1H, s, NH), 9.97 (1H, s, NH); ^{13}C NMR (100MHz, DMSO-d_6) 13.7, 23.5, 51.3, 111.6, 115.1, 122.5, 125.8, 131.2, 138.1, 138.5, 151.8, 151.9, 173.5; IR (KBr) 3322, 1671, 1596, 1492, 1324, 1260, 1113, 1089, 841, 821 cm^{-1}.

Preparation of azoacetate derivatives (13, 14a and **f, 15, 16a-j, 17)**

These compounds were prepared according to a general procedure a representative example is given.

Synthesis of azoacetate derivative of α,α-dimethyl-4-bromoacetoacetanilide **(16a)**

(3.0 g, 7.15 mmol) of the hydrazone substrate (**11a**) was dissolved in CH_2Cl_2 (100 mL). To this was added (3.8 g, 8.6 mmol) of lead tetraacetate with stirring. 5 mL of glacial acetic acid was added to aid the dissolution of the lead tetraacetate and the solution was allowed to stir overnight. When the reaction was judged complete (TLC) the solvent volume was reduced by 75% and the remaining CH_2Cl_2 solution was washed alternately with 5 x 50 mL portions of water and 5% aqueous sodium bicarbonate solution. The organic portion was dried over magnesium sulfate and evaporated to dryness and any persistent lead residues were removed by flash chromatography using a 25:75 EtOAc:hexane mixture as eluent. Yield (2.80 g, 82%); mp 202-205 ºC; ^{1}H NMR (400MHz, DMSO-d_6): δ =, 1.28 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.86 (3H, s, CH_3), 2.18 (3H, s, CH_3), 7.48 (2H, d, ArH, J = 8.8), 7.57 (2H, d, ArH, J = 9.2), 7.75 (2H, d, ArH, J = 8.8), 8.37 (2H, d, ArH, J = 8.8). 9.19 (1H, s, NH); ^{13}C NMR (100MHz, DMSO-d_6) 17.2, 20.5, 20.6, 21.5, 51.0, 103.6, 115.5, 123.0, 123.2, 125.0, 131.2, 138.0, 148.5, 153.9, 168.8, 171.1; IR (KBr) 3324, 1731, 1687, 1605, 1539, 1344, 1240, 1175, 868 cm^{-1}.

Preparation of azetidinones derivatives (18f and **19) procedure 1**

Synthesis of azetidinone derivative **(18f)** ***using procedure 1***

Anhydrous potassium carbonate (0.5 g, 3.6 mmol) was added to azoacetate **16f** (1.2 g, 3 mmol) in 50 mL of refluxing acetone. The solution was allowed to reflux for 22 h after which time (TLC) showed the reaction to be complete. The insoluble material was filtered from the solution and the filtrate evaporated to dryness. The azetidinone product (**18f**) was isolated after silica gel column chromatography using $CHCl_3$ as eluent. Yield (0.223 g, 22%); mp 87-89 ºC; ^{1}H NMR (400MHz, $CDCl_3$): δ = 1.08 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.92 (3H, s, CH_3), 7.15-7.11 (1H, m, ArH), 7.35-7.03 (2H, m, ArH), 7.43 (2H, d, ArH, *J* = 8.8), 7.88 (2H, d, ArH, *J* = 8.8), 8.37 (2H, d, ArH, *J* = 9.2); ^{13}C NMR (100MHz, $CDCl_3$) 17.3, 19.1, 19.2, 60.5, 90.2, 118.3, 123.4, 124.4, 124.9, 129.1, 137.2, 149.2, 154.1, 170.5; IR (KBr) 1759, 1599, 1527, 1495, 1368, 1346, 862, 756, 690 cm^{-1}.

Synthesis of azetidinone derivative* (19) *using procedure 1

(19a) Yield (8.3%); mp 139-141 ºC; ^{1}H NMR (400MHz, $CDCl_3$): δ = 0.85 (3H, s, CH_3), 1.94 (3H, s, CH_3), 3.01 (1H, d, CH, *J* = 14.4), 3.32 (1H, d, CH, *J* = 14.4), 7.27-7.07 (9H, m, ArH,), 7.78 (2H, d, ArH, *J* = 8.8), 8.29 (2H, d, ArH, *J* = 8.8); ^{13}C NMR (100MHz, $CDCl_3$) 16.8, 17.8, 30.6, 64.6, 91.1, 120.0, 125.3, 124.9, 127.2, 128.5, 128.5, 129.1, 129.9 136.1, 136.6, 149.7, 154.2 170.0; IR (KBr) 1745, 1527, 1494, 1383, 1342, 1091, 827, 692 cm^{-1}. Anal. Calcd for $C_{24}H_{21}ClN_4O_3$: C, 64.21; H, 4.72; N, 12.48. Found: C; 64.01, H; 4.84, N; 12.18.

(19b) Yield (11.6%); mp 137-139 ºC; ^{1}H NMR (400MHz, $CDCl_3$): δ = 1.43 (3H, s, CH_3), 1.99 (3H, s, CH_3), 2.67 (1H, d, CH, *J* = 14.4), 2.90 (1H, d, CH, *J* = 14.8), 7.27-7.10 (9H, m, ArH,), 7.87 (2H, d, ArH, *J* = 8.8), 8.36 (2H, d, ArH, *J* = 9.2); ^{13}C NMR (100MHz, $CDCl_3$) 15.1, 15.9, 36.3, 62.7, 89.2, 118.0, 122.0, 123.3, 125.2, 126.7, 127.5, 127.9, 128.4, 134.2, 134.7,147.8, 152.3, 168.0; IR (KBr) 1757, 1528, 1494, 1367, 1345,1180, 1092, 820, 745 cm^{-1}.

Preparation of azetidinones derivatives (18a-j) procedure 2

Synthesis of azetidinone derivative* (18a) *using procedure 2

(1g, 2.1 mmol) of the azoacetate derivative (**16a**) was dissolved in hot propanol (40 mL) to which (0.15 g, 2.3 mmol) of potassium cyanide was added. The solution was allowed to reflux for 30 min, after which TLC showed development of product spots and total consumption of the starting material, this was evaporated to dryness. Water (100 mL) was added to the reaction vessel and this was extracted with EtOAc (2 x 25 mL) followed by CH_2Cl_2 (2 x 25 mL). The combined extracts were dried over magnesium sulfate and upon evaporation to dryness an orange oil was collected. The product was isolated after column chromatography. Yield (0.14 g, 16%); mp 155-158 ºC; ^{1}H NMR (400MHz, $CDCl_3$): δ = 1.19 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.62 (3H, s, CH_3), 7.18 (2H, d, ArH, *J* =8.8), 7.55 (2H, d, ArH, *J* =8.8), 7.76 (2H, d, ArH, *J* = 9.2), 8.28 (2H, d, ArH, *J* = 8.8); ^{13}C NMR (100MHz, $CDCl_3$) 13.3, 17.8, 24.4, 49.3, 83.0, 122.5, 123.4, 124.9, 127.7, 130.8, 132.4, 153.8, 174.0, 180.1; IR (KBr) 1755, 1520, 1489, 1362, 1347,

827, 753 cm^{-1}. Anal. Calcd for $C_{18}H_{17}BrN_4O_3$: C, 51.81; H, 4.11; N, 13.43. Found: C; 52.10, H; 4.28, N; 13.21.

Synthesis of azetidinone derivative* (18b) *using procedure 2

Yield (0.15 g, 20%); mp 95-98 ºC; ^{1}H NMR (400MHz, $CDCl_3$): δ = 0.98 (3H, s, CH_3), 1.40 (3H, s, CH_3), 1.77 (3H, s, CH_3), 3.71 (3H, s, OCH_3), 6.77 (2H, d, ArH, *J* = 9.2), 7.28 (2H, d, ArH, *J* = 9.2), 7.79 (2H, d, ArH, *J* = 9.2), 8.28 (2H, d, ArH, *J* = 8.8); ^{13}C NMR (100MHz, $CDCl_3$) 17.2, 19.1, 19.2, 55.5, 60.4, 90.3, 114.3, 120.3 123.3, 124.8, 130.2, 149.2, 154.1, 156.5, 170.2; IR (KBr) 1759, 1513, 1392, 1346, 1247, 1184, 1164, 1031, 860, 828, 751, 688 cm^{-1}.

Synthesis of azetidinone derivative* (18c) *using procedure 2

Yield (0.21 g, 25%); mp 112-116 ºC; ^{1}H NMR (400MHz, $CDCl_3$): δ = 1.08 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.62 (3H, s, CH_3), 2.24 (3H, s, CH_3), 2.25 (3H, s, CH_3), 7.06-6.96 (3H, m, ArH), 7.76 (2H, d, ArH, *J* = 9.2), 8.29 (2H, d, ArH, *J* = 9.2); ^{13}C NMR (100MHz, $CDCl_3$) 15.2, 17.4, 19.3, 19.9, 20.7, 59.6, 91.8, 123.2, 124.3, 124.9, 125.8, 129.8, 132.9, 135.1, 138.5, 149.1, 154.2, 171.6; IR (KBr) 1757, 1526, 1471, 1366, 1345, 1134, 1093, 869,792, 752, 688 cm^{-1}. Anal. Calcd for $C_{20}H_{22}N_4O_3$: C, 65.56; H, 6.05; N, 15.29. Found: C; 65.61, H; 6.02, N; 15.20.

Synthesis of azetidinone derivative* (18d) *using procedure 2

Yield (0.13 g, 15%); mp 103-107 ºC; ^{1}H NMR (400MHz, $CDCl_3$): δ = 1.07 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.89 (3H, s, CH_3), 2.33 (3H, s, CH_3), 7.13 (2H, d, ArH, *J* =8.0), 7.32 (2H, d, ArH, *J* =8.4), 7.88 (2H, d, ArH, *J* = 9.2), 8.37 (2H, d, ArH, *J* = 8.8); ^{13}C NMR (100MHz, $CDCl_3$)17.3, 19.1, 19.2, 21.0, 60.4, 90.1, 118.3, 123.4, 124.9, 129.6, 134.1, 134.6, 149.2, 154.1, 170.3; IR (KBr) 1751, 1523, 1513, 1347, 1164, 1131, 861, 817, 752, 688 cm^{-1}. Anal. Calcd for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90. Found: C; 64.81, H; 5.73, N; 15.85.

Synthesis of azetidinone derivative* (18e) *using procedure 2

In the case of azetidinone derivative (**18e**) *it was the propanol transesterification product that was isolated*

Yield (0.10 g, 11%); mp 97-100 ºC; ^{1}H NMR (400MHz, $CDCl_3$): δ = 0.94 (2H, t *J* =7.6), 1.00 (3H, s, CH_3), 1.29 (2H,m), 1.31 (3H, s, CH_3), 1.72-1.67 (1H, m), 1.88 (3H, s, CH_3), 4.18 (1H, t, *J* =6.4), 4.27 (1H, q, *J* =5.2), 7.38 (2H, d, ArH, *J* =8.8), 7.78 (2H, d, ArH, *J* =8.8), 7.91 (2H, d, ArH, *J* = 9.2), 8.27 (2H, d, ArH, *J* = 8.8); ^{13}C NMR (100MHz, $CDCl_3$) 9.5, 13.3, 16.5, 17.9, 18.1, 59.8, 65.5, 89.2, 116.3, 122.4, 123.9, 124.9, 129.7, 140.0, 148.3, 152.9, 165.0, 169.6; IR (KBr) 1749, 1709, 1509, 1352, 1270, 849, 769 cm^{-1}.

Synthesis of azetidinone derivative* (18f) *using procedure 2

Azetidinone derivative (**18f**) was prepared using procedure 2 as outlined above; two additional compounds were isolated during the chromatographic separation (**20f** and **21f**).

(18f) Yield (0.10 g, 12%). Spectra identical to those reported using *procedure 1*

(20f) Yield (0.14 g, 16%); mp 195-197 ºC ^{1}H NMR (400MHz, DMSO-d_6): δ = 1.49 (3H, s, CH_3), 1.53 (3H, s, CH_3), 1.92 (3H, s, CH_3), 6.96 (1H, s br, ArH),7.07 (1H, t, ArH, *J* = 7.2), 7.33-7.26 (3H, m, ArH), 7.61 (2H, d, ArH, *J* = 7.6), 8.15 (2H, s br, ArH), 9.06 (1H, s br, NH), 9.48 (1H, s br, NH); ^{13}C NMR (100MHz, DMSO-d_6) 21.7, 22.9, 24.3, 65.6, 110.5 (d, *J* = 222), 120.8, 123.5, 126.2 (d, *J* = 69), 128.3, 138.7, 138.9, 154.2, 171.8, 172.8. IR (KBr) 3338, 3288, 1647, 1592, 1522, 1329, 1272, 1108, 750, 695 cm^{-1}.

(21f) Yield (0.17 g, 18%); mp 142-145 ºC ^{1}H NMR (400MHz, DMSO-d_6): δ = 1.19 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.61 (3H, s, CH_3), 7.34-7.28 (2H, m, ArH), 7.41-7.39 (1H, m, ArH), 7.52-7.47 (2H, m, ArH,), 7.76 (2H, d, ArH, *J* = 8.8), 8.26 (2H, d, ArH, *J* = 9.2); 9.00 (1H, s NH); ^{13}C NMR (100MHz, DMSO-d_6) 13.3, 17.9, 24.4, 49.3, 83.1, 123.4, 124.8, 126.3, 128.7, 129.2, 131.9, 149.3, 153.9, 174.3, 180.5; IR (KBr) 1661, 1528, 1377, 1346, 1161, 1107, 862 cm^{-1}

Synthesis of azetidinone derivative* (18g) *using procedure 2

Yield (0.21 g, 25%); orange oil; ^{1}H NMR (400MHz, $CDCl_3$): δ = 1.06 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.63 (3H, s, CH_3), 2.23 (3H, s, CH_3), 2.32 (3H, s, CH_3), 6.88 (1H, d, ArH, *J* =8.0), 7.02 (2H, d, ArH, *J* =8.0), 7.75 (2H, d, ArH, *J* = 9.2), 8.28 (2H, d, ArH, *J* = 8.8); ^{13}C NMR (100MHz, $CDCl_3$) 17.5, 18.9, 19.3, 19.8, 21.1, 59.5, 91.7, 123.1, 124.9, 126.3, 127.1, 130.5, 131.9, 136.2, 138.1, 149.1, 154.2, 171.5. IR (liquid film) 1762, 1527, 1504 1370, 1347, 1139, 862, 753, 739 cm^{-1}.

Synthesis of azetidinone derivative* (18h) *using procedure 2

Yield (0.18 g, 22%); mp 108-110 ºC; ^{1}H NMR (400MHz, $CDCl_3$): δ = 1.06 (3H, s, CH_3), 1.45 (3H, s, CH_3), 1.65 (3H, s, CH_3), 2.37 (3H, s, CH_3), 7.22-7.06 (4H, m, ArH,), 7.76 (2H, d, ArH, *J* = 8.8), 8.29 (2H, d, ArH, *J* = 8.8); ^{13}C NMR (100MHz, $CDCl_3$) 17.6, 19.1, 19.3, 19.9, 59.6, 91.8, 128.2, 124.9, 126.2, 126.4, 128.2, 131.3, 133.3, 136.4, 149.1, 154.1, 171.3; IR (KBr) 1761, 1530, 1493, 1346, 1133, 874, 769 cm^{-1}. Anal. Calcd for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90. Found: C; 64.66, H; 5.69, N; 15.83.

Synthesis of azetidinone derivative* (18i) *using procedure 2

Yield (0.14 g, 16%); mp 98-100 ºC; ^{1}H NMR (400MHz, $CDCl_3$): δ = 1.04 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.60 (3H, s, CH_3), 3.67 (3H, s, OCH_3), 6.89-6.85 (2H, m, ArH,), 7.19-7.15 (1H, m, ArH,), 7.60-7.58 (1H, m, ArH,), 7.79 (2H, d, ArH, *J* = 9.2), 8.29 (2H, d, ArH, *J* = 8.8); ^{13}C NMR (100MHz, $CDCl_3$) 16.9, 18.9,

19.9, 55.6, 59.8, 91.5, 112.0, 120.8, 123.1, 123.9, 124.9, 127.6, 128.4, 149.0, 153.9, 154.4, 172.4; IR (KBr) 1761, 1524, 1497, 1390, 1345, 1242, 1106, 1025, 858, 770, 752.

Synthesis of azetidinone derivative* (18j) *using procedure 2

(18j) Yield (0.17 g, 20%); mp 132-134 ºC; ^{1}H NMR (400MHz, $CDCl_3$): δ = 0.98 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.82 (3H, s, CH_3), 7.18 (2H, d, ArH, *J* =8.8), 7.29 (2H, d, ArH, *J* =9.2), 7.78 (2H, d, ArH, *J* = 8.8), 8.28 (2H, d, ArH, *J* = 9.2); ^{13}C NMR (100MHz, $CDCl_3$) 17.3, 19.0, 19.1, 60.7, 90.3, 119.5, 123.4, 124.9, 129.1, 129.5, 135.8, 149.3, 154.0, 170.3; IR (KBr) 1753, 1534, 1346, 1144, 869, 851, 705 cm^{-1}. Anal. Calcd for $C_{18}H_{17}ClN_4O_3$: C, 57.99; H, 4.60; N, 15.03. Found: C; 57.99, H; 4.73, N; 14.81.

(21j) Yield (0.21 g, 23%); mp 201-203 ºC; ^{1}H NMR (400MHz, DMSO-d_6): δ = 1.07 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.60 (3H, s, CH_3), 7.32 (2H, d, ArH, *J* =8.4), 7.38 (2H, d, ArH, *J* =8.4), 7.89 (2H, d, ArH, *J* = 9.2), 8.40 (2H, d, ArH, *J* = 9.2), 9.08 (1H, s, NH); ^{13}C NMR (100MHz, DMSO-d_6) 13.8, 17.9, 22.9, 48.5, 81.6, 123.2, 125.1, 128.8, 129.3, 132.3, 132.8, 148.7, 154.0, 165.3, 179.1. IR (KBr) 3300, 1742, 1661, 1532, 1492, 1344, 1102, 1085, 713.7, 687.2 cm^{-1}.

Synthesis of N-acyl hydrazide derivative as rearrangement product (24)

(1g, 2.8 mmol) of the azoacetate derivative (**15**) was dissolved in hot EtOH (40 mL) to which (0.24 g, 3.7 mmol) of potassium cyanide was added. The solution was allowed to reflux overnight, before being evaporated to dryness. Water (100 mL) was added to the reaction vessel and this was extracted with EtOAc:EtO_2 (15:85). The combined extracts were dried over magnesium sulfate and upon evaporation to a reduced volume a pale brown solid precipitated. The precipitate was filtered off and washed with petroleum ether and dried. Yield (0.31 g, 35%); mp 172-174 ºC; ^{1}H NMR (400MHz, DMSO-d_6): δ = 1.23 (3H, t, CH_3, *J* = 6.8), 1.27 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.88 (3H, s, CH_3), 4.16-4.06 (2H, m, CH_2), 6.90 (1H, d, ArH , *J* = 7.6), 7.15 (1H, d, ArH, *J* = 7.6), 8.11 (1H, d, ArH, *J* = 8.0), 8.17 (1H, d, ArH, *J* = 7.6), 9.58 (1H, s, NH). Anal. Calcd for $C_{13}H_{19}N_3O_5$: C, 54.36; H, 6.14; N, 13.58. Found C, 54.53; H, 6.29; N, 13.51.

Synthesis of N-acyl hydrazide derivative (25) by decarboxylation

(0.5 g, 1.6 mmol) of N-acyl hydrazide derivative (**24**) was added to a 2.5 molar solution of sodium hydroxide (3.99 g dissolved in 40 mL of water) the solution was allowed to reflux for 4 h. The pH was adjusted to 7-8 with conc. HCl to give a yellow precipitate which was extracted into EtOAc (3 x 20 mL) dried over magnesium sulfate and evaporated to dryness Yield (0.41 g, 90%); mp 215-216 ºC; ^{1}H NMR (400MHz, DMSO-d_6): δ = 1.21 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.94 (3H, s, CH_3), 6.90-6.85 (1H, m, ArH), 7.15-7.10 (1H, m, ArH), 8.27-8.23 (2H, m, ArH) 9.50 (1H, s, NH); IR (KBr) 3347, 1710, 1619, 1599 cm^{-1}. Anal. Calcd for $C_{12}H_{15}N_3O_5$: C, 51.24; H, 5.38; N, 14.94. Found C, 51.12; H, 5.50; N, 14.71.

Synthesis of diazetidinone derivative (26)

A 0.05 M solution of N-acyl hydrazide derivative (**25**) was made up in MeCN (0.85 g/60 mL). (3.7g, 18 mmol) of dicyclohexylcarbodiimide was added and the reaction refluxed overnight under a nitrogen atmosphere. After removal of the bulk of the excess dicyclohexylcarbodiimide and dicyclohexylurea by filtration, the remaining organic elements were evaporated to dryness and subjected to flash column chromatography to separate any persistent dicyclohexylurea. The desired diazetidinone derivative (**26**) was isolated and further purified by recrystallization from pet. ether EtOAc 20:80. Yield (0.35g, 45%); mp 112-114 ºC; ^{1}H NMR (400MHz, $CDCl_3$): δ = 1.70 (6H, s, 2 x CH_3), 2.20 (3H, s, CH_3), 7.33-7.28 (2H, m, ArH), 8.30-8.22 (2H, m, ArH); IR (KBr) 1796, 1696, 1627 cm^{-1}. Anal. Calcd for $C_{12}H_{13}N_3O_5$: C, 54.75; H, 4.98; N, 15.96. Found C, 54.38; H, 4.93; N, 15.84.

Synthesis of succinimide derivative (27f)

(200 mg, 0.54 mmol) of the 2-iminopyrrolidine-5-one derivative **21f** was dissolved in 10 mL of aqueous acetic acid. The solution was heated to 50 ^{o}C for 24 h, 100 ^{o}C for a further 24 h and finally refluxed for 4 h after which TLC showed total consumption of the starting material. The solution was allowed to cool and added to ice-water (100 mL) which induced precipitation of a pale yellow solid that was filtered from solution. Yield (153 mg, 78%); product decomposed in air over 24 h; ^{1}H NMR (400MHz, $CDCl_3$): δ = 1.19 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.61 (3H, s, CH_3), 7.30-7.25 (2H, m, ArH), 7.35-7.32 (1H, m, ArH), 7.43-7.37 (2H, m, ArH), 7.76 (2H, d, ArH, *J* = 8.8), 8.26 (2H, d, ArH, *J* = 9.2); ^{13}C NMR (100MHz, $CDCl_3$) 13.3, 17.9, 24.4, 49.3, 83.1, 123.4, 124.8, 126.3, 128.7, 129.2, 131.9, 149.3, 153.9, 174.3, 180.5; IR (KBr) 1719, 1529, 1396, 1374, 1346, 1146, 1126 cm^{-1}.

Synthesis of azetidinone derivative (28h)

(100 mg, 0.28 mmol) of the azetidinone derivative (**18h**) was dissolved in glacial acetic acid (25 mL) and heated to 80 ^{o}C, to this was added 0.5 mL of hydrogen peroxide solution (35% by weight) at 15 min intervals over 3 h. After 5 h the reaction mixture was treated with 2 mL of the hydrogen peroxide solution and allowed to stir at 80 ^{o}C overnight. A further 2 mL of hydrogen peroxide solution was added to the reaction mixture and the reaction allowed to stir for a further 3 h after which no starting material could be detected by TLC The reaction was cooled to room temperature and poured into 150 mL of ice-water which induced precipitation of a pale yellow solid that was filtered from solution. Yield (66 mg, 63.9%); mp 132-134 ºC; ^{1}H NMR (400MHz, $CDCl_3$): δ = 1.29 (3H, s, CH_3), 1.51(3H, s, CH_3), 1.69 (3H, s, CH_3), 2.37 (3H, s, CH_3), 7.24-7.17 (3H, m, ArH,), 7.38 (1H, d, ArH, *J* = 8.8), 8.26 (2H, d, ArH, *J* = 9.6), 8.29 (2H, d, ArH, *J* = 10.0); ^{13}C NMR (100MHz, $CDCl_3$) 14.5, 17.7, 18.7, 19.0, 60.3, 86.3, 123.4, 124.6, 126.6, 127.2, 128.6, 131.3, 132.5, 136.7, 149.9, 150.4, 171.0; IR (KBr) 1752, 1535, 1485, 1465, 1385, 1346, 1310, 868, 850, 760, 703 cm^{-1}.

Synthesis of pyrazole derivatives (29 and **30f)**

***Synthesis of pyrazole derivative* (29)**

(1 g, 3.1 mmol) of the azoacetate derivative (**13**) was dissolved in hot *n*-PrOH (40 mL) to which (0.3 g, 4.6 mmol) of potassium cyanide was added. The solution was allowed to reflux for 4 h, before being evaporated to dryness. Water (100 mL) was added to the reaction vessel and this was extracted with CH_2Cl_2 (15:85). The combined extracts were dried over magnesium sulfate and upon evaporation to a reduced volume a pale brown solid precipitated. The precipitate was filtered off and washed with petroleum ether and the product isolated after flash chromatography. Yield (0.13 g, 15%) mp 210-212 ºC; ^{1}H NMR (400MHz, DMSO-d_6): δ = 1.27 (3H, t, CH_3, J = 7.2), 2.26 (3H, s, CH_3), 4.20 (2H, q, CH_2, J = 7.2), 6.64 (2H, s br, CH_2), 7.81 (2H, d, ArH , J = 7.2), 8.32 (2H, d, ArH, J = 7.2); ^{13}C NMR (100MHz, DMSO-d_6) 14.3, 14.4, 59.1, 93.9, 123.0, 124.9, 143.1, 144.9, 150.6, 151.2, 164.0. IR (KBr) 3349, 1676, 1548, 1344, 1286, 1131, 1112, 857, 789 cm^{-1}.

***Synthesis of pyrazole derivative* (30f)**

Yield (0.12 g, 15%); mp 181-183 ºC; ^{1}H NMR (400MHz, DMSO-d_6): δ = 2.94 (3H, s, CH_3), 6.60 (2H, s br, CH_2), 7.06 (1H, t, ArH , J = 7.6), 7.32 (2H, t, ArH, J = 7.6), 7.63 (2H, d, ArH , J = 7.6), 7.88 (2H, d, ArH , J = 9.2), 8.35 (2H, d, ArH, J = 9.2), 8.85 (1H, s, NH,); ^{13}C NMR (100MHz, DMSO-d_6) 14.2, 98.4, 120.4, 122.6, 123.3, 124.9, 128.5, 138.8, 143.3, 144.7, 148.2, 150.7, 163.3; IR (KBr) 3455, 3429, 3313, 1650, 1599, 1543, 1495, 1343, 864, 745, 684 cm^{-1}.

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