Synthesis of novel spiro compounds using anthrone and pyrazole-5-thione moieties: a Michael addition approach

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Novel routes for the synthesis of spiro derivatives anthrone have been designed using a Michael addition reaction followed by a Dieckmann condensation and Thorpe–Ziegler cyclisation. Bis-Michael addition of pyrazole-5-thione with 1,5-diarylpenta-1,4-dien-3-one gave directly a spiro derivative of pyrazole-5-thione. An enol lactone was synthesised by using mono Michael addition on dimedone, followed by hydrolysis and condensation.

Keywords: Michael addition, spiro compounds, anthrone, pyrazole-5-thione, dimedone

Michael addition is one of the oldest well-known reactions, which involves the formation of a carbon–carbon bond and has found extensive applications in organic synthesis.[1] The reaction, usually carried out in basic conditions, deals with the addition of compounds containing active methylene group (donors) to activated π systems (acceptors). More recently, the use of organometallics[2] and ionic liquids[3] has gained considerable importance to carry out this reaction, since it leads to products with high enantioselectivity.

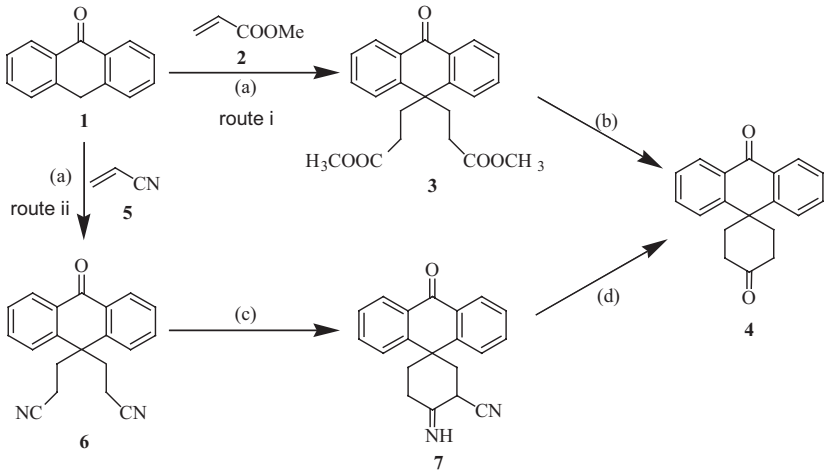
Over the past decade, we have reported some exciting synthetic strategies for the synthesis of this exclusive class of compounds.[4] Recently, we have been actively exploring the Michael addition reaction on heterocyclic and carbocyclic systems bearing active methine[5] and methylene[6] groups. We have successfully employed the Michael adducts as key intermediates for the synthesis of some interesting spiro compounds. Thus, continuing our work along this line, we report here the reaction of anthrone **1**, pyrazole-5-thiones **8** and dimedone **11** as Michael donors for the synthesis of novel spirocyclohexanone derivatives, which would further broaden the utility and scope of this reaction.

Results and discussions

Anthrone and anthracenol are typical examples of keto-enol isomerisation in solution.[7] Anthracenol ion generated from the deprotonation of anthrone by base leads to a consecutive double Michael addition.[8] In the presence of $ZnCl_2$ 1,4-conjugated addition of anthrone with α,β-unsaturated ketones/esters proceeds to give mono-Michael adducts.[9] In addition to the Michael addition of anthrone, Diels–Alder reactions of anthracenol have been investigated in conjunction with 9-substituted anthracenes.[8a,8b] Spiro compounds using anthrone are less reported in the literature[10] and using Michael addition reaction has not been observed. Hence we decided to utilise bis-Michael adducts for the synthesis of novel spiro derivatives of anthrone.

The Michael addition of **1** with Michael acceptors such as methyl acrylate **2** and acrylonitrile **5** proceeded smoothly leading to diadducts. Thus diadduct **3** were obtained by interaction of **1** with two equivalents of methyl acrylate **2** and catalytic amount of benzyltrimethylammonium hydroxide (triton B) in 1,4 dioxan at 60°C. The existence of a carbonyl peak at 184.6 ppm and tetrahedral carbon at 46.4 ppm in ^{13}C NMR spectrum of Michael diadduct **3** ruled out the possibility of the mono-Michael adducts, *O*-alkylated diadducts and Diels–Alder reaction products, and confirmed the regioselectivity of Michael addition. Dieckmann condensation of **3** in presence of sodium methoxide in methanol directly afforded the corresponding novel spirocyclohexanone derivative of anthrone **4**, which was confirmed on the basis of spectral analysis showing presence of two carbonyl peaks at 187.0 and 214.5 ppm, of two carbonyl groups (Scheme 1, route i).

The study of the Michael addition on **1** was further extended to acrylonitrile **5**. Under similar reaction experimental conditions Michael diadduct **6** was obtained in excellent yield. The IR spectrum displayed a sharp band at 2244 cm^{-1} due to nitrile group. Michael diadduct **6** on Thorpe–Ziegler cyclisation afforded desired spirocycloimino derivative **7**. The spirocyclohexanone derivative of anthrone **4** was obtained by hydrolysis and decarboxylation of the compound **7**.



Scheme 1 (a) Triton B/1,4- dioxan/60°C; (b) NaOMe/MeOH/reflux; (c) Na/toluene/reflux; and (d) HBr/acetic acid/reflux.

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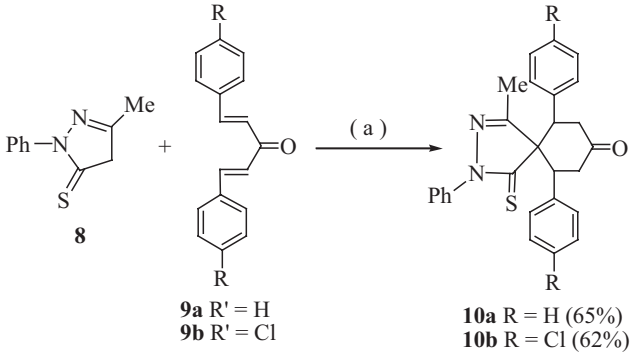
Therefore an alternative, unambiguous and independent method for the synthesis of compounds **4** has been established (Scheme 1, route ii).

In continuation to our work on the synthesis of novel spirocyclohexanone using 1,5-diarylpenta-1,4-dien-3-one as a Michael acceptor and their stereochemical studies,[6a, 6d] we now report the synthesis of novel spirocyclohexanone derivative of pyrazole-5-thiones **8** using 1,5-diarylpenta-1,4-dien-3-one **9** and their steriochemical study. Pyrazole-5-thiones **8** was prepared in good yield using microwave-assisted reaction of pyrazole-5-ones with Lawessons reagent, using methodology developed in our group.[6e] Spirocyclohexanone **10** was synthesised in a single step by Bis-Michael addition of pyrazole-5-thione **8** with 1,5-diarylpenta-1,4-dien-3-one **9** in presence of sodamide in dry DMF at 10–15°C in moderate yield (Scheme 2). Cyclohexanones and spirocyclohexanones have been extensively studied for their stereochemistry.[11] Spirocyclohexanone **10** can exhibit either symmetric **I** or antisymmetric **II** form (Fig. 1). In **10a**, H_A exhibited a doublet of doublets at 4.32 (dd, J = 4 Hz, 12 Hz), while H_M and H_X exhibited triplet and doublet of doublets at the region 3.87 (t, J = 13 Hz) and 3.50 (dd, J = 4 Hz, 12 Hz) respectively. The coupling constants of H_A are in agreement with those of axial–axial and axial–equatorial H–H couplings of a cyclohexane chair conformation. This confirmed the axial orientation for H_A and that the aryl substituents are in an equatorial orientation as shown in **I** (Fig. 1) and not in an axial–equatorial orientation as shown in **II** (Fig. 1). This was further confirmed by the ^{13}C NMR spectrum which highlighted the symmetry in the molecule, which could only occur when the aryl substituents are *dis*posed in equatorial orientations as shown in **I** (Fig. 1) Hence, only the *cis* 1,3–diequatorial isomer of **10 I** (Fig. 1) had been produced, selectively, and in moderate yield.



Scheme 2 (a) $NaNH_2$/DMF/10–15°C.

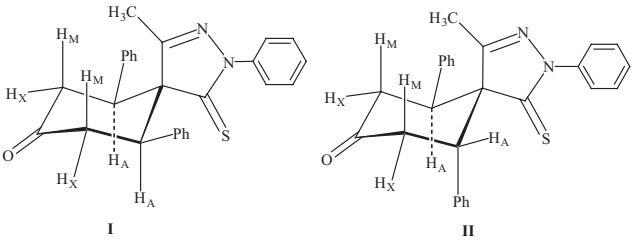
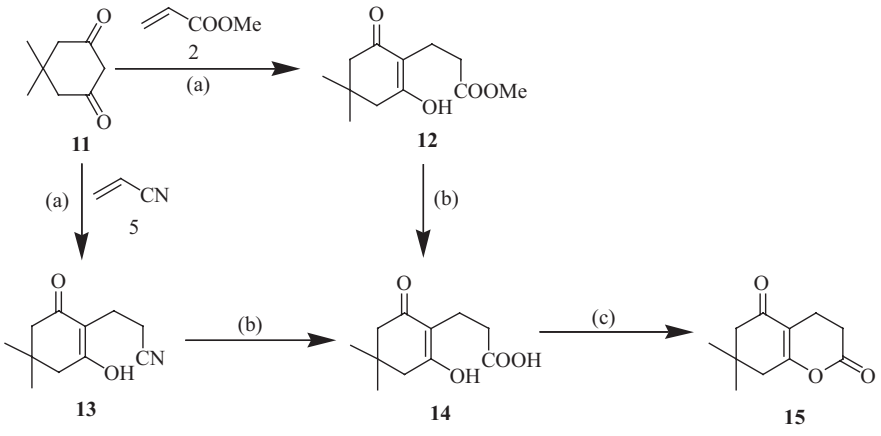


Fig. 1 **10a**

The reaction sequence shown in Scheme 3 illustrates the usefulness of mono Michael adduct of dimedone **12** and **13**, for the synthesis of enol lactone **15**. Enol lactone is an important functionalised substructure found in the skeletons of neoflavonoid and coumarin family which often shows a variety of interesting biological and pharmaceutical activities.[12] Although many synthetic routes have been developed for the construction of enol lactones, the effective synthetic reactions are quite limited.[13] Hence, we report here a very simple and efficient method for the synthesis of enol lactone. Dimedone is in toutomeric form with its enol form at equilibrium. Due to the presence of methylene group between two keto groups, it is well known nucleophile. When dimedone is treated with Michael acceptors, generally both mono and bis-Michael adducts were obtained.[16] We report here a very simple method for the regioselective synthesis of mono Michael adduct. Monoalkyl derivatives of dimedone **12** and **13** were prepared in high yields by Michael addition of **11** to methyl acrylate **2** and acrylonitrile **5** in presence of catalytic amount of sodamide in dry DMF at 10–15°C. Formation of the bis-Michael adduct was not observed even with 3 mol equivalence of the Michael acceptor, increment in amount of base or increase in reaction time and temperature.

Compound **12** was prepared by stirring dimedone **11**, methyl acrylate **2**, and $NaNH_2$, in dry DMF at 10–15°C. The presence of a triplet for the two methylene protons at δ 2.58 and two singlets for methoxy and hydroxyl protons at δ 3.75 and 9.35 respectively in the ^1H NMR, and presence of olefin carbon at 113.2 ppm in ^{13}C NMR, clearly indicated the formation of a mono-Michael adduct regioselectively over the other Michael adducts. Compound **12** was then hydrolysed using base hydrolysis to give the keto-acid derivative **14**. Cyclisation of **14** by refluxing it in acetic anhydride gave the expected enol lactone **15** in moderate yield (Scheme 3, route i).

Under similar experimental conditions, when Michael addition of **11** was extended to acrylonitrile **5**, the mono adduct **13** was obtained in excellent yield. The IR spectrum displayed a sharp band at 2250 cm^{-1} due to the nitrile group.



Scheme 3 (a) $NaNH_2$/DMF/10–15°C; (b) NaOH/H_2O/reflux; (c) Acetic anhydride/reflux.

Base hydrolysis of **13** gave expected acid derivative **14** in good yield, which on cyclisation furnished the desired enol lactone **15** (Scheme 3, route ii).

Conclusion

We have explored the scope and utility of Michael addition reaction for the synthesis of novel spiro/enol lactone derivatives of anthrone, pyrazol-5-thones, and dimedone using mono and bis-Michael adducts.

Experimental

Melting points were taken in open capillaries and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AMX 500 series (500 MHz) spectrometer at 25°C. IR spectra were recorded on Perkin-Elmer 257-FTIR 1600 series spectrometer using KBr discs. Mass spectra were recorded on Shimadzu QP 2010 GCMS instrument. Elemental analysis was recorded on Thermo-Quest 11112 series instrument.

Methyl-3-[9-(2-methoxycarbonyl ethyl)-10-oxo-9-10-dihydro-anthracene-9-yl]propionate (**3**)**:** Anthrone **1** (0.97 g, 5 mmol) and catalytic amount of Triton B were stirred in 15 ml. of 1–4 dioxane at room temperature. To this methyl acrylate **2** (0.86 g, 10 mmol) was added dropwise during 3 min. This reaction mixture was stirred at 60°C for 1.5 h and then allowed to stand for overnight at room temperature. The reaction mixture was poured onto crushed ice and acidified using aqueous 2N HCl to pH 2–3. Separated buff coloured solid was filtered off, washed with water, vacuum dried and recrystallised from benzene/pet ether to obtain white crystals of compound **3** (1.85 g, 90%). M.p. 117°C (lit.[8a] 116–118°C). (Found: C 72.10%, H 6.08%. $C_{22}H_{22}O_5$ requires C 72.12%, H 6.05%.). IR (cm^{-1}) 1736, 1668. δ_H 7.51–8.40 (m, 8 H, aromatic protons), 3.42 (s, 6H, 2 x –OCH_3), 2.61 (t, 4H, 2 x –CH_2), 1.57 (t, 4H, 2 x –CH_2). δ_C 184.6, 174.7 (2 x C=O), 146.4–127.5 (12 x aromatic carbons), 53.1 (2 x –OCH_3), 46.4 (tetrahedral carbon), 41.4, 30.7 (2 x –CH_2).

Spiro[anthracene-9,1'-cyclohexane]-4', 10-dione (**4**) *from* (**3**): To the stirred solution of methanol (25 ml.) containing sodium metal (0.12 g, 5 mmol) compound **3** (1.83 g, 5 mmol.) was added at room temperature. The reaction mixture was then refluxed for about 4 h. It was then poured onto the crushed ice and acidified using aqueous 2N HCl to pH 2–3. A yellow coloured product was obtained, it was then filtered, washed with water, vacuum dried and recrystallised from benzene/pet ether to afford pure compound **4** (1.11 g, 80%). M.p. 205°C. (Found: C 82.60%, H 5.88%. $C_{19}H_{16}O_2$ requires C 82.58%, H 5.84%.). IR (cm^{-1}) 1727, 1658. δ_H 7.21–8.42 (m, 8 H, aromatic protons), 2.03 (t, 4H, 2 x –CH_2), 1.47 (t, 4H, 2 x –CH_2). δ_C 214.5, 187.0 (2 x C=O), 134.1–127.0 (12 x aromatic carbons), 42.1 (spiro carbon), 38.6, 12.0 (4 x –CH_2).

(10-Oxo-10H-anthracene-9,9-diyl)dipropionitrile (**6**): Anthrone **1** (0.97 g, 5 mmol) and catalytic amount of Triton B were stirred in 15 ml. of 1–4 dioxane at room temperature. To this, acrylonitrile **5** (0.53 g, 10 mmol) was added dropwise during 3 min. This reaction mixture was kept stirring at 60°C for 1.5 h and then allowed to stand for overnight at room temperature. The reaction mixture was poured onto crushed ice and acidified using aqueous 2N HCl to pH 2–3. The obtained pale yellow coloured solid was filtered off, washed with water and vacuum dried and recrystallised from benzene/pet ether to give white crystals of compound **6** (1.41 g, 94%). M.p. 215°C (lit.[8a] 213–215°C). (Found: C 79.78%, H 5.08%, N 9.17% $C_{20}H_{16}N_2O$ requires C 79.98%, H 5.37%, N 9.33%.). IR (cm^{-1}) 2244, 1662. δ_H 8.45–7.52 (m, 8 H, aromatic protons), 2.63 (t, 4H, 2 x –CH_2), 1.57 (t, 4H, 2 x –CH_2).

4'-imino-10-oxospiro[anthracene-9,1'-cyclohexane]-3-carbo-nitrile (**7**): Compound **6** (1.5 g, 5 mmol) was dissolved in 25 ml toluene. To this, pulverised sodium (0.12 g, 5 mmol) was then added. The reaction mixture was refluxed for 8 h. To this reaction mixture, a little methanol was added to react with the unreacted sodium metal. From the reaction mixture, solvent was removed by vacuum distillation and the remaining solid contents were poured onto crushed ice and acidified using aqueous 2N HCl to pH 2–3. The dark coloured solid obtained was then filtered, washed with water, vacuum dried, and recrystallised from benzene/pet ether to afford pure compound **7** (1.11 g, 74%). M.p. 246°C. (Found: C 79.80%, H 5.11%, N 9.18% $C_{20}H_{16}N_2O$ requires C 79.98%, H 5.37%, N 9.33%.). IR (cm^{-1}) 2252, 1668. δ_H 8.32–7.18 (m, 8 H, aromatic protons), 7.90 (br, 1H, –NH) (D_2O exchangeable), 2.53 (m, 1H, –CH), 2.33–1.96 (m, 6H, 3 x –CH_2). δ_C 187.0 (C=O), 164.5 (C=NH), 144.4–128.0 (12 x aromatic carbons), 118.1 (–CN), 38.4, 38.2, 26.0, (2 x –CH_2), 36.3 (spiro carbon), 24.9 (–CH).

Spiro[anthracene-9,1'-cyclohexane]-4', 10-dione (**4**) *from* (**7**): Compound **7** (1.5 g, 5 mmol) was placed in 25 ml glacial acetic acid. To this 10 ml of hydrobromic acid in acetic acid was added. The reaction mixture was refluxed for 4 h. From reaction mixture solvent was removed by distillation and remaining solid contents were poured onto crushed ice to yield the yellow coloured compound **4**. It was filtered, washed with water, vacuum dried and recrystallised from benzene/pet ether to afford pure compound **4** (1.04 g, 85%). M.p. 205°C.

1-methyl-3,6,10-triphenyl-4-thioxo-2,3-diazaspiro[5.4]dec-1-en-8-one (**10a**): Compound **8** (0.95 g, 5 mmol) and sodamide (0.39 g, 10 mmol) were stirred in DMF (20 ml.) at 10–15°C for 10 min. To this 1,5-diphenylpenta-1,4-dien-3-one **9a** (1.17 g, 5 mmol) was added. The reaction mixture was then stirred for 4 h at room temperature. This reaction mixture was then poured onto crushed ice and acidified using aqueous 2N HCl to pH 2–3. The obtained crude compound **10a** was filtered, washed with water and recrystallised from aqueous methanol (1.36 g, 65%). M.p. 92°C. (Found: C 76.30%, H 5.60%, N 6.49%, S 7.39% $C_{27}H_{24}N_2OS$ requires C 76.38%, H 5.70%, N 6.60, S 7.55%). IR (cm^{-1}) 1695, 1598. δ_H 7.72–7.07 (m, 5H, aromatic-H), 4.32 (dd, J = 4 Hz, 12 Hz, $2H_A$), 3.87 (t, J = 13, $2H_M$), 3.50 (dd, J = 4 Hz, 12 Hz, $2H_X$), 2.43 (s, 3H, –CH_3). δ_C 216.5 (C=O), 149.4 (C=S), 139.3 (C=N), 139.0, 128.8, 128.4, 127.9, 127.6, 127.2, 125.5, 125.0 (18 x aromatic C), 109.4 (spiro carbon), 55.1 (–CH), 48.3 (–CH_2), 13.5 (–CH_3). *m/z* (ESI) 424 (M^+).

1-methyl-6,10-bis(4-chlorophenyl)-3-phenyl-4-thioxo-2,3-diazaspiro[5.4]dec-1-en-8-one (**10b**): Compound **10b** was similarly prepared by reacting 8 with 1,5- di (4'-chlorophenyl)penta-1,4-dien-3-one **9b** (yield 62%, m.p. 170°C). (Found: C 65.63%, H 4.32%, N 5.52%, S 6.34%, Cl 14.20% $C_{27}H_{22}Cl_2N_2OS$ requires C 65.72%, H 4.49%, N 5.68, S 6.50%, Cl 14.37%). IR (cm^{-1}) 1704, 1597. δ_H 7.37–7.15 (m, 13H, aromatic H), 3.95 (dd, J = 4 Hz, 12 Hz, $2H_A$), 3.48 (t, J = 13, $2H_M$), 2.73 (dd, J = 4 Hz, 12 Hz, $2H_X$), 2.16 (s, 3H, –CH_3), δ_C 210.9 (C=O), 152.4 (C=S), 143.4 (C=N), 134.8, 130.4, 128.9, 128.8, 128.5, 128.4, 128.2, 125.4 (aromatic C), 106.7 (spiro carbon), 63.7 (–CH), 43.0 (–CH_2), 18.7 (–CH_3). *m/z* (ESI) 492 (M^+).

Methyl 3-[2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl] propionate (**12**): Dimedone **11** (0.7 g, 5 mmol) was added to the stirred solution of sodamide (catalytic amount) in DMF (15 ml) at 10–15°C. To this, methyl acrylate **2** (0.48 g, 5.5 mmol) was added dropwise for 3 min. This reaction mixture was then stirred for 2 h at room temperature. The reaction mixture was then poured onto the crushed ice and acidified using aqueous 2N HCl to pH 2–3. The separated compound **12** was filtered, washed with water and recrystallised from methanol/water to afford pure crystalline white compound **12**, which was air-dried (1.02 g, 90%). M.p. 119°C. (Found: C 63.55%, H 7.90% $C_{12}H_{18}O_4$ requires C 63.70%, H 8.02%). IR (cm^{-1}) 1735. δ_H 9.35 (s, 1H, –OH) (D_2O exchangeable), 3.75(s, 3H, –OCH_3), 2.58 (t, 4H, 2 x –CH_2), 2.38 (s, 2H, –CH_2), 2.21 (s, 2H, –CH_2), 1.05 (s, 6H, 2 x –CH_3). δ_C 198.3, 171.5 (2 x C=O), 171.3 (C=C–OH), 113.2 (C=C–OH), 50.7 (–OCH_3), 32.9 (tetrahedral carbon), 28.1 (2 x –CH_3), 42.8, 31.3, 16.3 (4 x –CH_2).

3-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)propionic acid (**14**) *from* (**12**): Compound **12** (1.13 g, 5 mmol) was refluxed in water (25 ml) containing NaOH (0.5 g) for 2 h. The reaction mixture was poured onto crushed ice and acidified using aqueous 2N HCl to pH 2–3. Separated product was filtered, washed with water, vacuum dried and recrystallised from methanol/water to afford crystalline colourless compound **14** (0.90 g, 85%). M.p. 140°C. (Found: C 62.21%, H 7.49% $C_{11}H_{16}O_4$ requires C 62.25%, H 7.60%). IR (cm^{-1}) 1706. δ_H 10.90–10.10 (br. 2H, –COOH and –OH) (D_2O exchangeable), 2.42 (s, 2H, –CH_2), 2.38 (t, 2H, –CH_2), 2.29 (s, 2H, –CH_2), 2.14 (t, 2H, –CH_2), 0.97 (s, 6H, 2 x –CH_3). δ_C 198.3 (C=O; ketone), 174.6 (C=O; acid), 153.1 (C=C–OH), 111.9 (C=C–OH), 50.7 (–OCH_3), 32.6 (tetrahedral carbon), 37.0, 31.6,17.5 (4 x –CH_2), 28.0 (2 x –CH_3). *m/z* (ESI) 212 (M^+).

3-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)propionitrile (**13**): Dimedone **11** (0.7 g, 5 mmol) was added to the stirred solution of sodamide (catalytic amount) in DMF (15 ml) at 10–15°C. To this acrylonitrile **5** (0.30 g, 5.5 mmol.) was added dropwise for 3 min. A reaction mixture was then stirred for 2 h at room temperature. The reaction mixture was then poured onto the crushed ice and acidified using aqueous 2N HCl to pH 2–3. Separated solid was filtered, washed with water, vacuum dried and recrystallised from methanol/water to afford crystalline white compound **13** (0.87 g, 90%). M.p. 150°C (lit.[14a] 150–151°C). (Found: C 68.20%, H 7.75%, N 7.12% $C_{11}H_{15}NO_2$ requires C 68.37%, H 7.82%, N 7.25%).

IR (cm^{-1}) 3418, 2959, 2250, 1707. δ_H 9.40 (br, 1H, –OH), 2.72 (m, 4H, 2 x $–CH_2$), 2.39 (s, 2H, $–CH_2$), 2.22 (s, 2H, $–CH_2$), 1.10 (s, 6H, 2 x $–CH_3$).

3-(2-Hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)propionic acid (**14**) from (**13**): Compound **13** (0.97 g, 5 mmol) was refluxed in water (25 ml.) containing NaOH (0.5 g) for 2 h. The reaction mixture was then poured onto the crushed ice and acidified using aqueous 2N HCl to pH 2–3. Separated solid was filtered, washed with water, vacuum dried and recrystallised from methanol/water to afford crystalline white compound **14** (0.88 g, 85%). M.p. 140°C.

7,7-Dimethyl-3,4,7,8-tetrahydro-2H-chromene-2,5(6H)-dione(**15**): The keto-acid **14** (1.06 g, 5 mmol) was refluxed in freshly distilled acetic anhydride (25 ml.) under nitrogen atmosphere at 150°C. After 2 h, anhydrous sodium acetate (catalytic amount) was added. Boiling was continued for another 2 h. The acetic anhydride was removed by distillation and to remaining material, diethyl ether was added. It was washed with dilute sodium carbonate solution twice followed by water. The ether layer was then dried by using sodium sulfate, and on evaporation gave a white product (0.63 g, 65%). M.p. 56°C (lit.[15] 56–58°C). (Found: C 62.87%, H 7.14% $C_{11}H_{14}O_3$ requires C 68.02%, H 7.26%). IR (cm^{-1}) 1782, 1655. δH 2.72 (m, 2H, $–CH_2$), 2.62 (s, 2H, $–CH_2$), 2.28 (s, 2H, $–CH_2$), 2.20 (m, 2H, $–CH_2$), 1.11 (s, 6H, 2 x $–CH_3$).

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