

Note

Synthesis of 4-carbethoxy-4*H*-3-substituted-isoxazol-5-ones and their conversion into novel spiroheterocycles

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Interaction of diethyl α -acyl/aroylmalonates **1** with hydroxylamine hydrochloride **2** afford 4-carbethoxy-4*H*-3-substituted-isoxazol-5-ones **3** and 3-substituted-4*H*-5-oxo-isoxazol-4-carboxylic acids **4**. Bromination of **3** affords 4-bromo derivatives **5**, which with thiocarbamides, 4-substituted thiosemicarbazides give 2-alkyl/arylimino-4, 9-dioxo-3, 7-diaza-8-oxa-6-substituted-1-thia-(3*H*)-spiro[4.4]nonan-6-enes **7** and 2-alkyl/arylimino-5, 10-dioxo-9-oxa-7-substituted-1-thia-3, 4, 8-triaza-(3*H*, 4*H*)-spiro[5.4]dec-7-enes **8**. Characterisation of the products has been done on the basis of spectral (IR, ^1H NMR and ^{13}C NMR) data.

In continuation of our work on the synthesis of spiro compounds^{1,2}, we now report the synthesis of novel spiroheterocycles from 4-carbethoxy-4*H*-3-substituted-isoxazol-5-ones **3**, which were prepared from diethyl α -acyl/aroylmalonates **1**. Earlier Stugno¹ claimed to have synthesised 4-carbethoxy-4*H*-3-phenylisoxazol-5-one **3b** as a solid (mp 141°C) by the reaction of diethyl malonate with benzohydraxamoyl chloride in the presence of calculated quantity of alkali in ether. However, when we carried out the reaction of diethyl α -benzoylmalonate **1b** with hydroxylamine hydrochloride **2** in triethylamine, a bright yellow liquid was obtained (Scheme I). Its IR spectrum showed main bands at 2975 (v, -CH-), 1709 (shoulder, v, >C=O) and 1604 cm^{-1} (v, >C=O); ^1H NMR spectrum (CDCl_3): δ 1.399 (t, 3H, J = 7.2 Hz, -CH₃ of carbethoxy group), 4.394 (q, 2H, J = 7.2 Hz, -CH₂ of carbethoxy group), 4.850 (s, 1H, >CH at position-4 of isoxazolone ring) and 7.421-8.143 (m, 5H, Ar-H). On the basis of elemental analysis and spectral data the compound was identified as 4-carbethoxy-4*H*-3-phenylisoxazol-5-one **3b**. Continuation of the above reaction for longer duration gave 3-phenyl-4*H*-5-oxo-isoxazol-4-carboxylic acid **4b**, (mp 139°C); IR (KBr): 2925, 1755, 1645 cm^{-1} ; ^1H NMR (CDCl_3): δ 3.926 (s, 1H, >CH-proton at posi-

tion 4 of isoxazolone ring), 7.495-7.962 (m, 5H, Ar-H) and 12.9 (s, 1H, -COOH proton). Compound **4b** on esterification with absolute ethanol in the presence of conc. H_2SO_4 gave compound **3b**.

Stugno¹ has reported the isolation of **3b** as a solid, (mp 141°C). However, it could be seen by spectral and chemical data that what Stugno obtained was probably either compound **4b** formed by the hydrolysis of **3b** or further decarboxylation to afford 5-oxo-4*H*-isoxazole which melts at 142°C².

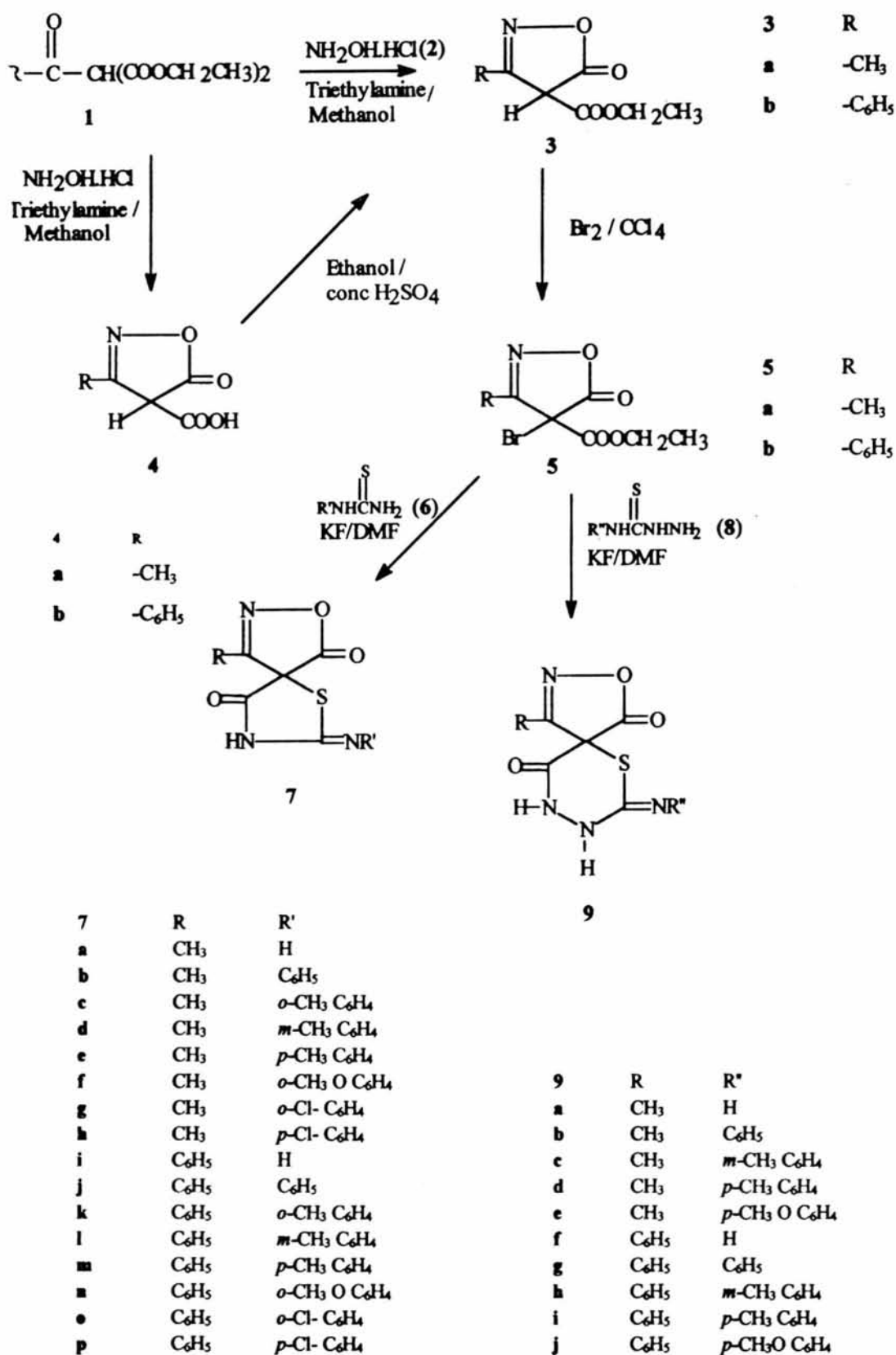
Compound **3b** on bromination gave the desired bromo compound, 4-bromo-4-carbethoxy-3-phenylisoxazol-5-one **5b** as a dark brown liquid, whose IR spectrum showed main bands at 2975 (v, -CH-), 1714 (broad, v, >C=O) and 1599 cm^{-1} (v, >C=N). Its ^1H NMR (CDCl_3) exhibited signals at δ 1.324 (t, 3H, J = 7.2 Hz, -CH₃ of carbethoxy group), 4.316 (q, 2H, J = 7.2 Hz, -CH₂ of carbethoxy group), 7.337-7.997 (m, 5H, Ar-H).

Compound **5b** on treatment with *p*-tolylthiocarbamide **6e** in DMF/KF afforded 3, 7-diaza-4, 9-dioxo-8-oxa-6-phenyl-1-thia-2-*p*-tolylimino-(3*H*)-spiro[4.4]nonan-6-ene **7m**; IR (KBr): 2945, 1710, 1610 cm^{-1} ; ^1H NMR ($\text{DMSO}-d_6$): δ 2.318 (s, 3H, Ar-CH₃), 7.248-7.621 (m, 9H, Ar-H) and 11.403 (s, 1H, -NHC=O, D₂O exchangeable).

Similarly, compound **5b** and *p*-anisyl thiosemicarbazides **8e** in DMF/KF afforded 5, 10-dioxo-9-oxa-2-*p*-anisylimino-7-phenyl-1-thia-3, 4, 8-triaza-(3*H*, 4*H*)-spiro[5.4]dec-7-ene **9j**. IR spectrum of the compound showed main peaks at 2950, 1695, 1625 cm^{-1} ; ^1H NMR in $\text{DMSO}-d_6$ revealed signals at δ 3.712 (s, 3H, Ar-OCH₃), 6.870-7.965 (m, 9H, Ar-H), 7.603 (s, 1H, NH at position 3), 8.364 (s, 1H, -NHC=S) and 12.917 (s, 1H, -NHC=O at position-4); ^{13}C NMR ($\text{DMSO}-d_6$): 55.150 (Ar-CH₃ carbon), 113.954 (spiro carbon), 119.926-132.816 (12 aromatic carbons), 152.957 and 154.341 (2 $\times$ >C=N carbons), 116.100 and 167.312 ppm (2 $\times$ >C=O)

Experimental Section

General. Melting points were determined in open glass capillaries and are uncorrected. IR were recorded on a Perkin-Elmer 1600 series FTIR and ^1H NMR and ^{13}C NMR on a 300 MHz VXR0 using



CDCl_3 or $\text{DMSO}-d_6$. TLC in various solvents showed the compounds to be homogeneous. C H N S data for all compounds were found to be within $\pm 0.2\%$ of calculated value.

4-Carbethoxy-4H-3-substituted-isoxazol-5-ones

3: General procedure. Diethyl α -acyl/aroylmalonate **1** (0.05 mole), hydroxylamine hydrochloride **2** (0.05 mole) and triethylamine (0.05 mole) were refluxed together in methanol (25 mL) for 15 min. The contents were poured into ice-cold water, and extracted with diethyl ether. The ethereal layer was removed, washed successively with cold water, 5% aq. sodium bicarbonate and cold water, dried and evaporated to get compound **3**. The compounds **3a, b** were prepared similarly. **3a**: bp $168^\circ\text{C}/14\text{ mm}$ (66%); **3b**: bp $201^\circ\text{C}/14\text{ mm}$ (69%).

5 - Oxo-4H-3-substituted-isoxazol-4-carboxylic acids 4: General procedure. In the above reaction if the refluxion was continued for 30 min, compound **3** got hydrolysed to an acid 5-oxo-4H-3-substituted-isoxazol-4-carboxylic acid **4**. Compound **4** was purified by dissolving in aq. sodium bicarbonate and reprecipitating with cold dilute HCl, filtered, washed with water, dried and recrystallised from aq. ethanol. By adopting similar procedure, compounds **4a, b** were prepared. **4a**: mp 111°C (80%); **4b**: mp 139°C (84%).

Esterification of 5-oxo-4H-3-substituted-isoxazol-4-carboxylic acids 4: Formation of 4-carbethoxy-4H-3-substituted-isoxazol-5-ones 3: An alternate synthesis. 5-Oxo-3-substituted-isoxazol-4H-4-carboxylic acid **4** (0.05 mole) and conc. H_2SO_4 (2 mL) were refluxed in absolute ethanol (25 mL) for 4-5 hr. The solvent was removed and the reaction mixture poured into ice-cold water, extracted with ether, washed, dried and distilled to give compound **3**.

4-Bromo-4-carbethoxy-3-substituted-isoxazol-5-ones 5: General procedure. 4-Carbethoxy-4H-3-substituted-isoxazol-5-one **3** (0.05 mole) was taken in CCl_4 (25 mL) and stirred. Bromine (0.05 mole, 2.6 mL) was added dropwise with magnetic stirring in the presence of UV light. The contents were poured into ice-cold water and the organic layer separated, washed with 5% aq. sodium carbonate followed by water. On evaporation of the solvent, the desired bromo compound was obtained. Compounds **5a, b** were prepared similarly. **5a**: bp $177^\circ\text{C}/14\text{ mm}$ (83%); **5b**: bp $231^\circ\text{C}/14\text{ mm}$ (85%).

2-Alkyl/arylimino-4, 9-dioxo-3, 7-diaza-8-oxa-6-substituted-1-thia-(3H)-spiro[4.4]nonan-6-enes 7:

General procedure. Substituted thiocarbamide **6** (0.01 mole), 4-bromo-4-carbethoxy-3-substituted-isoxazol-5-one **5** (0.01 mole), KF (0.01 mole) and dry DMF (10 mL) were refluxed together for 1.5 hr. The reaction mixture was cooled and poured onto ice, filtered and washed with water and finally with hot ethanol to afford **7**. Compounds **7a-p** were prepared similarly. **7a**: (61%); **7b**: (73%); **7c**: (74%); **7d**: (73%); **7e**: (72%); **7f**: (75%); **7g**: (77%); **7h**: (78%); **7i**: (71%); **7j**: (73%); ^1H NMR ($\text{DMSO}-d_6$): δ 6.913-7.994 (m, 10 H, Ar-H) and 9.853 (s, 1H, -NH-); **7k**: (70%); **7l**: (71%); **7m**: (73%); **7n**: (74%); **7o**: (76%); **7p**: (79%). Compounds **7a-p** have melting points $>270^\circ\text{C}$.

2-Alkyl/arylimino-5, 10-dioxo-9-oxa-7-substituted-1-thia-3, 4, 8-triaza-(3H, 4H)-spiro[5.4]dec-7-enes 9:

General procedure. Thiosemicarbazide **8** (0.01 mole) and 4-bromo-4-carbethoxy-3-substituted-isoxazol-5-one **5** (0.01 mole) were dissolved in DMF (10 mL) and KF (0.01 mole) added to it. The contents were refluxed for 1.5 hr. The reaction mixture was then cooled and poured onto crushed ice, filtered, washed with water and finally with hot ethanol to afford **9**. By adopting similar procedure, compounds **9a-j** all having melting points $>270^\circ\text{C}$ were prepared. **9a**: (59%); **9b**: (66%); **9c**: (69%); **9d**: (69%); **9e**: (68%); **9f**: (63%); **9g**: (67%); **9h**: (65%); **9i**: (70%); **9j**: (73%).

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