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

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Interaction of diethyl β-acyl/arylamalonates 1 with hydroxyylamine hydrochloride 2 afford 4-carbethoxy-4H-3-substituted-isoaxozol-5-ones 3 and 3-substituted-4H-5-oxo-isoaxozol-4-carboxylic acids 4. Bromanation of 3 affords 4-bromo derivatives 5, which with thiocarbamides, 4-substituted thiosemicarbazides give 2-alkyl/aryl/arylamalonates and 3H-isoaxazolones 6 in good yield. However, when we carried out the reaction of diethyl α-benzoylmalonate 1b with hydroxyylamine hydrochloride 2 in triethylamine, a bright yellow liquid was obtained (Scheme 1). IR spectrum showed weak bands at 2975 (ν, ν-H), 1709 (shoulder, ν, >C=O) and 1604 cm⁻¹ (v, ν-C=O). 1H NMR spectrum (CDCl₃): δ 1.399 (t, 3H, J = 7.2 Hz, CH₃ of carboxethoxy group), 4.394 (q, 2H, J = 7.2 Hz, CH₂ of carboxethoxy group), 4.850 (s, 1H, >CH at position-4 of isoaxazolone 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-4H-3-phenylisoaxozol-5-one 3b. Continuation of the above reaction for longer duration gave 3-phenyl-4H-5-oxo-isoaxozol-4-carboxylic acid 4b (mp 139°C); IR (KBr): 2925, 1755, 1645 cm⁻¹. 1H NMR (CDCl₃): δ 3.926 (s, 1H, >CH-proton at position 4 of isoaxazolone 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. H₂SO₄ gave compound 3b.

Stugno 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-4H-isoxazolone which melts at 142°C.

Compound 3b on bromination gave the desired bromo compound, 4-bromo-4-carbethoxy-3-phenylisoaxozol-5-one 5b as a dark brown liquid, whose IR spectrum showed main bands at 2975 (ν, ν-H), 1714 (broad, ν, >C=O) and 1599 cm⁻¹ (ν, ν-C≡N). Its 1H NMR (CDCl₃) exhibited signals at δ 1.324 (t, 3H, J = 7.2 Hz, CH₃ of carboxethoxy group), 4.316 (q, 2H, J = 7.2 Hz, CH₂ of carboxethoxy group), 7.337-7.997 (m, 5H, Ar-H).

Compound 5b on treatment with p-tolylthiocarbamid 6e in DMF/KF afforded 3, 7-diazao-4H-5-o xo-isoaxazol-3-one 7e as a brown solid, whose IR spectrum showed main bands at 2945 (ν, ν-H), 1710, 1610 cm⁻¹; 1H NMR (DMSO-d₆): δ 2.318 (s, 3H, Ar-CH₃), 7.234-7.621 (m, 9H, Ar-H) and 11.403 (s, 1H, >C=O). D₂O exchangeable.

Similarly, compound 5b and p-anisyl thiosemicarbazides 8e in DMF/KF afforded 3, 7-diazao-4H-5-oxo-isoaxazol-3-one 7e as a brown solid, whose IR spectrum showed main bands at 2945, 1650 cm⁻¹; 1H NMR in DMSO-d₆ 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, >NH=C=S) and 12.917 (s, 1H, >NH=C=O at position 4); 13C NMR (DMSO-d₆): 55.150 (Ar-CH₃ carbon), 112.954 (spiro carbon), 119.926-132.816 (12 aromatic carbons), 152.957 and 154.341 (2×>C≡N carbons), 116.100 and 167.312 ppm (2×>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 13C NMR on a 300 MHz VXR0 using

Note
Scheme I
CDCl₃ or DMSO-d₆. TLC in various solvents showed the compounds to be homogeneous. C H N S data for all compounds were found to be within ±0.2% of calculated value.

4-Carbethoxy-4H-3-substituted-isoxazol-5-ones 3: General procedure. Diethyl α-acylarylmalonate 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 dichyl 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°C/14 mm (66%); 3b: bp 201°C/14 mm (69%).

5 - Oxo-4H-3-substituted-isoxazol-4-carboxylic acids 4: General procedure. In the above reaction if the reflux 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 recrystallizing 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. H₂SO₄ (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 CCl₄ (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°C/14 mm (83%); 5b: bp 231°C/14 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) 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 (DMSO-d₆): δ 6.91-7.994 (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°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°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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References