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Michael additions: a regioselective approach to the synthesis of spirothiazolidinones

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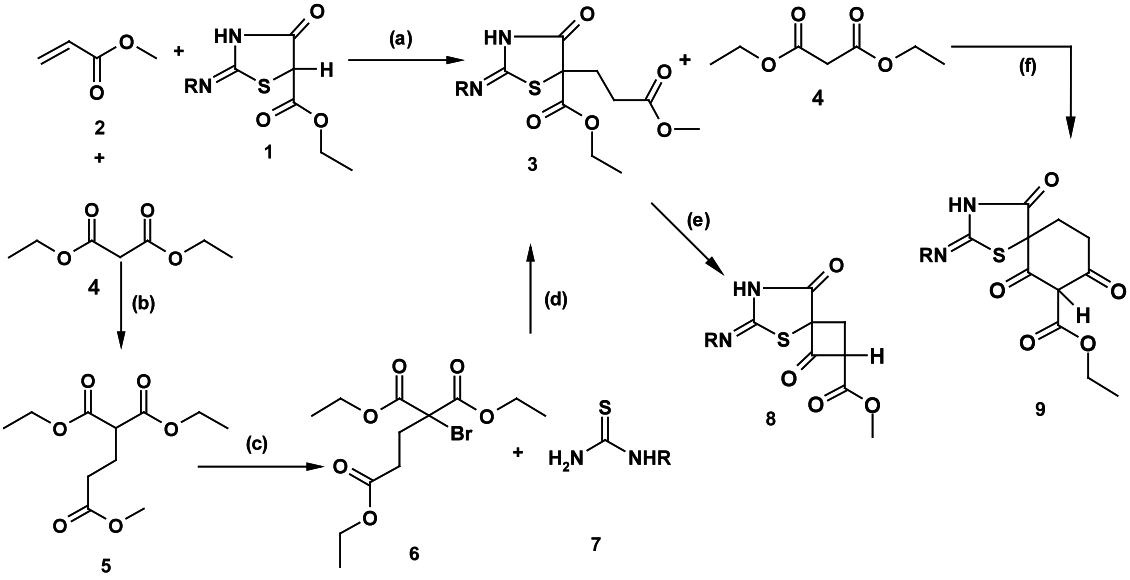
Abstract—Novel routes to the synthesis of spirothiazolidinones have been designed using a Michael addition reaction followed by a Dieckmann condensation and a Claisen type condensation reaction.

Michael additions involve carbon–carbon bond forming process with wide applications in organic synthesis. Of special interest are the additions of cyclic β-keto esters to vinyl compounds. The Michael adducts thus obtained have been utilized for the synthesis of various natural products and bridgehead compounds.[1] The inclusion of a sulfur functionality adjacent to the carbon atom having the ester linkage and the ability to carry out the Michael addition on the chiral centre would further broaden the utility and scope of such reactions. Also the key feature of our approach is to utilize the Michael adducts for constructing novel spiromolecules.

This paper focuses on the Michael additions of 2-alkyl/arylimino-5-carbethoxy-thiazolidin-4-one **1**.[2] Compounds possessing a thiazolidine as a basic structural unit have been utilized as active synthons mainly



Scheme 1. *Reaction conditions*: (a) $NaNH_2$/DMF, 28–30°C, 3 h. (b) NaOMe/MeOH, 10–15°C, 12 h. (c) Br_2/CCl_4, reflux, 30 min. (d) TEA or TBA/EtOH, reflux, 3 h. (e) Na powder/C_6H_6, reflux, 1 h. (f) NaOMe/MeOH, reflux, 3 h.

Keywords: thiazolidin-4-one; methyl acrylate; acrylonitrile; sodamide.

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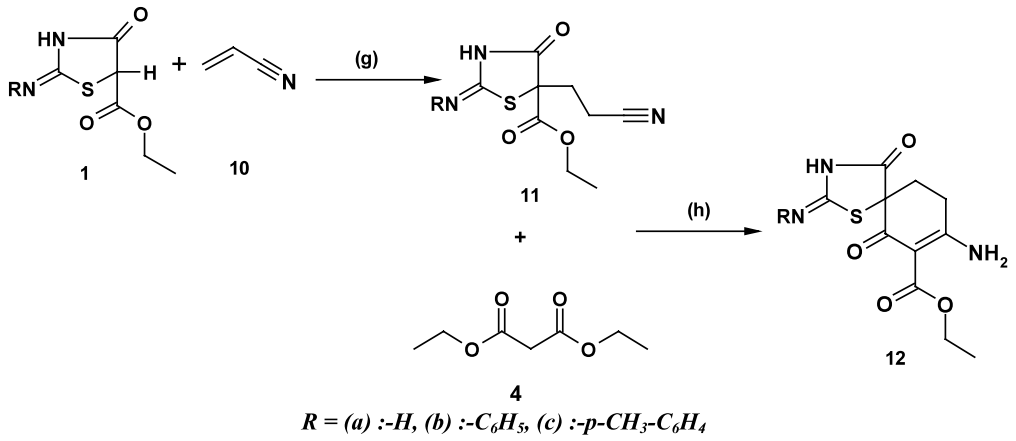

Scheme 2. *Reaction conditions*: (g) $NaNH_2$/DMF, 28–30°C, 2 h. (h) NaOMe/MeOH, reflux, 2 h.

because the derivatives of thiazolidin-4-ones are known to have biological activity.[3] The underlying synthetic strategy may obviously provide versatile routes for the synthesis of spirocompounds by Michael additions.

In the presence of a base, the Michael addition of methyl acrylate **2** with **1** could in principle lead to the following results, (1) addition at C-5, (2) *O*-alkylation or (3) additions to the imino or amido nitrogens.

Surprisingly, bases like pyridine, piperidine, triethylamine/tributylamine, hydroxides, alkoxides, fluoride ions in combination with PTCs failed to catalyze the addition and **1** was recovered in quantitative yield.

Sodamide in dry DMF was found to be ideal, the reaction proceeding smoothly at room temperature (Scheme 1). The addition was virtually free of side reactions and excellent yields of Michael adducts were obtained using stoichiometric amounts of reactants and base. An important feature is that the reaction exhibits striking regioselectivity yielding **3** as the only product.[4]

In an alternative synthesis of **3**, the Michael adduct **5**, obtained by the addition of diethyl malonate **4** to methyl acrylate **2**, was brominated to afford the α-bromo derivative **6**. The bromo derivative was found to be highly unstable and was utilized immediately for further reactions with thioureas **7** in the presence of triethylamine/tributylamine to yield **3**. The yields of the products thus obtained were low in comparison to the former route (Scheme 1).

Dieckmann condensation of **3** in the presence of metallic sodium in dry benzene gave extremely poor yields of cyclobutanone derivatives **8**[5] as semi-solids (Scheme 1). The carbonyl frequency, characteristic of the cyclobutanone ring, was observed at 1798 cm^{-1} in the IR spectrum. Compound **8** was found to be unstable and to undergo decomposition with time.

Claisen type condensation of **3** with diethyl malonate **4** using molar equivalents of sodium methoxide in methanol furnished the spiro derivative **9**[6] in 86–94% yield (Scheme 1).

Under similar experimental conditions, when Michael addition of **1** was extended to acrylonitrile **10**, the adduct **11**[7] was obtained in excellent yields. The IR spectrum displayed a sharp band at 2245 cm^{-1} due to CN. Claisen type condensation of **11** with diethyl malonate **4** afforded the spiro derivatives **12**[8] in quantitative yields (Scheme 2).

All the compounds reported in this paper are novel compounds. We have explored the scope and generality of this strategy successfully to other heterocyclic systems which will be communicated in due course.

Acknowledgements

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References

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4. Spectral data of **3c**: ^1H NMR (in ppm): 1.25–1.30 (t, 3H, $J=7.0$ Hz, CH_3 of carbethoxy), 2.33–2.60 (m, 7H, 2×CH_2 and CH_3 on aromatic ring), 3.65 (s, 3H, OCH_3), 4.20–4.28 (q, 2H, $J=7.0$ Hz, CH_2 of carbethoxy), 7.21–7.29 (m, 4H, Ar-H), 7.55 (br, 1H, NHCO; D_2O exchangeable). ^{13}C NMR (in ppm): 13.75 (CH_3 of carbethoxy group), 20.93 (aromatic -CH_3), 29.40 and 29.50 (2×CH_2), 51.71 (OCH_3), 62.85 (OCH_2 of carbethoxy ester), 66.74 (chiral carbon), 123.31, 130.03, 135.48, 137.41 (six aromatic carbons), 167.55 (C=N), 172.35, 174.69, 180.86 (3×C=O carbons). Mass: M^+ 364, *m*/*z* 232, 207, 168, 159, 132, 103, 73, 44, 32. Mol. formula $C_{17}H_{20}N_2O_5S$. Elemental analysis [calcd/found %]: C, 56.03/56.01; H, 5.53/5.48; N, 7.69/7.56; S, 8.80/8.74.
5. Spectral data of **8c**: ^1H NMR (in ppm): 2.47 (s, 3H, CH_3), 2.50–2.63 (m, 2H, CH_2), 3.50 (s, 3H, OCH_3 of carbmethoxy group), 4.10–4.20 (dd, 1H, CH), 7.26–7.40 (m,

4H, Ar-H), 7.70 (br, 1H, NHCO; D_2O exchangeable). ^{13}C NMR: 14.12 (CH_3), 28.44 (CH_2), 51.18 (OCH_3), 60.78 (tetrahedral carbon), 110.11 (CH of cyclobutanone ring), 122.77, 126.68, 128.30, 130.03 (aromatic carbons), 169.61 (C=N), 172.16, 181.18 and 208.58 (3×C=O).

Mol. formula: $C_{15}H_{14}N_2O_4S$. Elemental analysis [calcd/found %]: C, 56.59/56.51; H, 4.43/4.38; N, 8.80/8.72; S, 10.07/10.04.

6. Spectral data of **9b**: ^1H NMR (in ppm): 1.28–1.40 (t, 3H, $J=7.5$ Hz, CH_3 of carbethoxy group), 2.15–2.89 (m, 4H, 2×CH_2), 3.81–3.83 (m, 1H, CH), 4.15–4.29 (q, 2H, $J=7.5$ Hz, CH_2 of carbethoxy group), 6.97–7.41 (m, 5H, Ar-H), 7.85 (br, 1H, NHCO; D_2O exchangeable). A proper resolution could not be observed in the CMR spectrum even after scanning it for a longer duration of time.

   Mol. formula $C_{17}H_{16}N_2O_5S$. Elemental analysis [calcd/found %]: C, 56.66/56.58; H, 4.48/4.44; N, 7.77/7.69; S, 8.90/8.81.

7. Spectral data of **11b**: ^1H NMR (in ppm): 1.26–1.31 (t, 3H, $J=7.2$ Hz CH_3 of ester), 2.47–2.69 (m, 4H, 2×CH_2), 4.24–4.30 (q, 2H, $J=7.2$ Hz, CH_2 of ester), 7.33–7.49 (m, 5H, Ar-H) and 7.70 (br, 1H, NHCO; D_2O exchangeable). ^{13}C NMR: 13.23 ($\underline{C}H_2CN$), 13.73 (CH_3 of carbethoxy group), 30.21 ($\underline{C}H_2CH_2CN$), 63.31 (OCH_2 of carbethoxy group), 65.68 (tetrahedral carbon), 118.02 (C≡N), 123.33, 125.67, 129.64, 137.92 (six aromatic carbons), 166.86 (C=N), 174.04 and 180.07 (2×C=O carbons). Mass: M^+ 317, m/z 277, 244, 205, 145, 118, 98, 58, 44.

   Mol. formula: $C_{15}H_{15}N_3O_3S$. Elemental analysis [calcd/found %]: C, 56.77/56.74; H, 4.76/4.72; N, 13.24/13.19; S, 10.10/10.06.

8. Spectral data of **12b**: ^1H NMR (in ppm): 1.22–1.39 (t, 3H, $J=7.5$ Hz, CH_3) 2.37–2.80 (m, 4H, 2×CH_2), 4.20–4.38 (q, 2H, $J=7.5$ Hz, CH_2 of ester), 6.05–6.42 (br, 2H, NH_2; D_2O exchangeable), 7.30–7.62 (m, 5H, Ar-H), 7.75 (br, 1H, NHCO; D_2O exchangeable).

   Mol. formula $C_{17}H_{17}N_3O_4S$. Elemental analysis [calcd/found %]: C, 56.81/56.80; H, 4.77/4.72; N, 11.69/11.66; S, 8.92/8.88.