Synthesis of spirocyclohexanone ring containing thiazolidine nucleus: a regioselective approach

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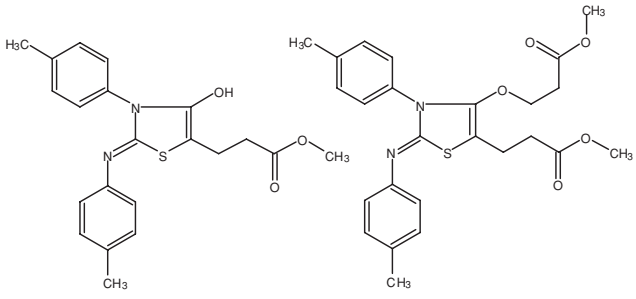
The paper highlights the Michael addition reactions of 2-arylimino-3-aryl-thiazolidin-4-one **1** with acceptors like methyl acrylate and acrylonitrile to furnish the diadducts **5** and **8**. Dieckmann condensation of **5** affords the spirocyclohexanone derivative. Also discussed is the interaction of **1** with 1,5-diarylpenta-1,4-dien-3-ones **9**.

Keywords: Michael additions, 2-arylimino-3-aryl-thiazolidin-4-one, methyl acrylate, acrylonitrile, 1,5-diaryl-1,4-pentadien-3-one

Michael additions of compounds containing an active methylene group to an α,β-unsaturated system in which the β-carbon atom is unsubstituted often leads to the formation of either a monoadduct or a mixture of mono and diadduct depending upon the reaction conditions.[1-4] When the β-carbon is loaded with an alkyl or aryl substituent it leads to the formation of a monoadduct only.[5,6]

We have been exploring the scope of Michael additions on active methylene/methine groups of various heterocyclic ring systems.[7,8] The present work is an account of the results that we have obtained based on our studies on Michael addition of 3-aryl-2-arylimino thiazolidin-4-one *viz.* 3-(*p*-tolyl)-2-[(*p*-tolyl) imino]– thiazolidin-4-one **1**.

The active methylene group of **1** at C-5 position adjacent to the carbonyl group makes the molecule an active Michael donor. On interaction with equimolar proportions of methyl acrylate **2**, it was expected to furnish a monoadduct **3**. Interestingly, bases like NaOMe, piperidine, triethylamine, KF/BTAB and hydroxides, however, failed to catalyse the addition. Sodamide in DMF was found to be the ideal condition in which the reaction proceeded smoothly at ambient temperature yielding a diadduct and unreacted **1**. When the reaction was repeated with two moles of methyl acrylate it was highly regioselective and afforded the diadduct **5** (Scheme 1). The reaction was clean without the formation of any kind of side products.



3 **4**

The possibility of the O-alkylated adduct **4** was ruled out on the basis of CMR spectrum, which displayed the carbonyl frequency due to the thiazolidone ring at δ 172.296ppm.

5 can be utilised as an active synthon for the construction of spiromolecules. Dieckmann condensation of the diadduct **5** in NaOMe/MeOH afforded the spiroderivative **6** (Scheme 1). Similar results were obtained when KOH/MeOH was used.

In order to establish the generality of Michael addition, the reaction was repeated with different Michael acceptor, *viz.* acrylonitrile **7**. Thus Michael addition of **1** with acrylonitrile **7** in presence of sodamide and DMF afforded the diadduct **8** (Scheme 1). Our attempts for Thorpe–Ziegler condensation on **8** was unsuccessful and furnished a highly impure product. Thus, sodamide and DMF is found to be an ideal condition which leads only to the formation of the diadduct.

The study of Michael additions on **1** was also extended to doubly unsaturated ketones, 1,5-diarylpenta-1,4-dien-3-one **9.**[9] This is mainly because both the double bonds in **9** tend to undergo Michael addition fairly independent to each other leading to the formation of six-membered carbocyclic ring.

Thus, the interaction of equimolar proportion of **1** and **9** in the presence of NaOMe in methanol afforded the spirocyclohexanone derivative **10** in quantitative yields (Scheme 1). The presence of two different sets of peak for the two methine protons in **10** in the ^{1}H NMR spectrum suggested that both of them are in different magnetic environment. This is possible only when one methine proton occupies the axial position and other occupies the equatorial position. Thus, both the phenyl groups are having an axial-equatorial (ae) orientation. The ^{13}C NMR further confirms it as it displays different sets of signals for the methylene and methine carbon atoms.[10]

Thus, here we describe a very simple and efficient method, via Michael addition reaction, the synthesis of novel spirocyclohexanone derivatives containing the thiazolidine nucleus. All the compounds reported here are new compounds and their structures have been established on the basis of spectral and elemental analysis.

Experimental

Melting points reported were taken in open capillaries and are uncorrected. Elemental analyses were carried out in UDCT, Mumbai. IR spectra was recorded on Perkin-Elmer 257-FTIR 1600 series spectrometer using KBr discs. NMRs were scanned on Bruker AMX 500 series (500 MHz) spectrometer using deuterated chloroform as solvent.

Synthesis of 5,5-bis[2-(ethoxycarbonyl)ethyl]-3-(p-tolyl)-2-[(p-tolyl) imino]thiazolidin-4-one (5): 3-(*p*-Tolyl)-2-[(*p*-tolyl)imino] thiazolidin-4-one (**1**, 0.01mol) and sodamide (0.02mol, 0.8g) were stirred in DMF (20ml) at room temperature. To this methyl acrylate (**2**, 0.02mol) was added dropwise and the reaction was stirred for 2 h. It was then poured onto crushed ice, acidified to pH 2–3 and extracted with diethyl ether. The organic layer was dried over sodium sulphate , solvent removed under vacuum and the residual semi-solid was crystallised from 50% ethanol.

M.p. 100°; Yield: 92%; IR(cm^{-1}): 2948 (C–H str), 1739(C=O; ester), 1641 (C=O, amide); ^{1}H NMR ($CDCl_3$): δ 2.155–2.732 (m,14H, 2x-CH_3 and 4x-CH_2), 3.724 (s,6H, 2x-OCH_3), 6.793–7.351(m,8H, Ar-H); ^{13}C NMR: δ 20.789 and 21.153 (2x-CH_3), 29.546 (2x-CH_2), 34.332 (2x-CH_2CO), 51.826 (2x-OCH_3), 59.598 (tetrahedral carbon), 120.623, 127.488, 129.498, 129.927, 131.927, 134.128, 139.004 and 145.552 (12 aromatic carbons), 152.222 (C=N), 172.296 (C=O, amide), 175.232 (2xC=O, ester). Elemental analysis [Cal.(Obs.)]: C; 64.08% (64.07%), H; 6.02% (5.99%), N; 5.98% (5.95%), S; 6.84% (6.79%).

Synthesis of 3-(p-tolyl)-2-[(p-tolyl)imino]-1-thia-3-azaspiro[5.4] decane-4,8-dione (**6**): **5**(0.01 mol) was added to freshly prepared solution of sodium methoxide (0.01mol of sodium in 40ml methanol). The reaction mixture was refluxed for 2 h. The reaction mixture was then concentrated, poured onto crushed ice and acidified with dil HCl to pH 2–3. The product which separated was filtered, washed

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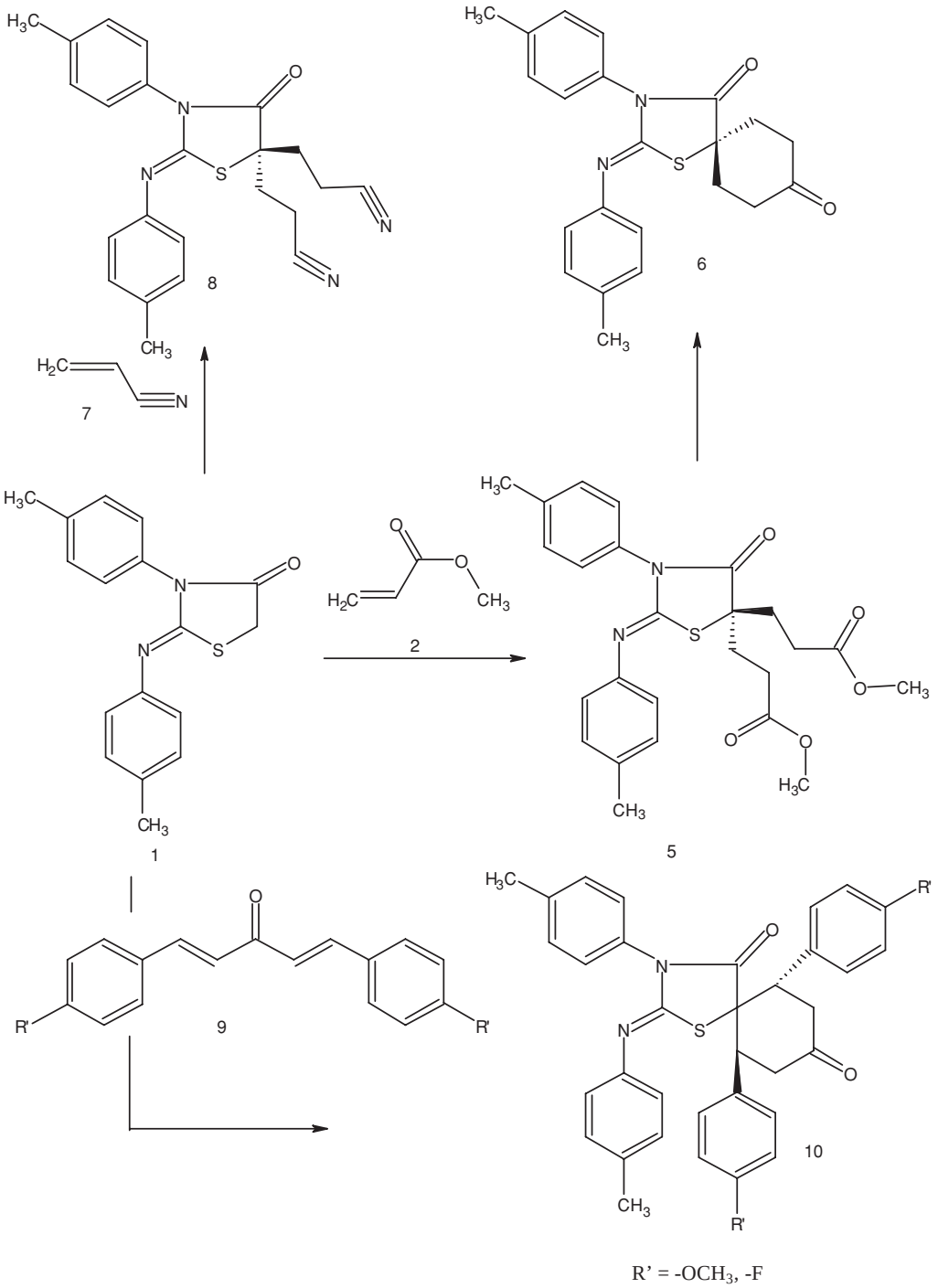

R' = -OCH_3, -F

Scheme 1

well with water and crystallised from ethanol. M.p. 120°, Yield; 84%, IR (cm^{-1}); 3015 (C–H str.), 1712 (C=O str, cyclohexanone), 1638 (C=O, amide), 1602 (C=N str.); ^{1}H NMR($CDCl_3$): δ 2.163–3.261 (m,14H, 4x-CH_2, 2x-CH_3), 6.805–7.394 (m, 8H, Ar-H); ^{13}C NMR: δ 20.751 and 21.243 (2x-CH_3), 29.558 (2x-CH_2), 34.170 (2x-$\underline{C}H_2CO$), 59.587 (tetrahedral carbon), 120.857, 127.670, 129.526, 129.706, 130.706, 131.934 135.794 and 139.200 (12 aromatic carbons), 175.847 (C=O, amide), 219.946(C=O, cyclohexanone ring); Elemental Analysis [Cal.(Obs)]: C; 69.81% (69.77%), H; 5.86% (5.84%), N; 7.41% (7.37%), S; 8.47% (8.39%).

Synthesis of 5,5-di(2-cyanoethyl)-2-(p-tolyl)imino-3(p-tolyl) thiazolidin-4-one (**8**): To a stirring solution of sodamide (0.02mol) in DMF (20ml) was added **1** (0.01mol) at room temperature. This was followed by the addition of acrylonitrile (**7**, 0.02mol). The reaction mixture was then stirred for 3 h, quenched with water and acidified to pH 2–3 with dil HCl. The product was filtered and crystallised from 50% ethanol. M.p. 110°C, Yield; 94%, IR (cm^{-1}): 3009 (C–H str.), 2245 (C=Nstr.), 1642 (C=O st.), 1604 (C=Nstr.) ^{1}H NMR($CDCl_3$): δ 2.126–2.751 (m,14H, 4x-CH_2, 2x-CH_3), 6.839–7.341 (m,8H, Ar–H) ppm, ^{13}C NMR: δ 13.285 (2x-$\underline{C}H_2CN$), 20.901 and 21.246 (2x-CH_3), 34.726(2x-$\underline{C}H_2CH_2CN$), 58.464 (tetrahedral carbon), 117.693 and 119.795 (2x-C≡N), 120.543, 127.393, 129.322, 129.823, 131.601, 134.821, 139.549 and 145.092 (aromatic carbons), 149.952 (C=N) and 173.634 (C=O). Elemental analysis [Cal.(Obs)]: C; 68.63 %(68.58%), H; 5.51% (5.43%), N; 13.92% (13.86%), S; 7.97% (7.93%)

Synthesis of trans-6,10-diaryl-3-(p-tolyl)-2-[(p-tolyl)imino]-1-thia-3-azaspiro[5.4] decane-4,8-dione (**10**): **1** (0.01mol) was added to a freshly solution of sodium methoxide (0.02mol) in methanol (50ml). This was followed by the addition of 1,5-diarylpenta-1,4-dien-3-one (**9**, 0.02mol). The reaction mixture was refluxed for 3 h. The excess of alcohol was removed under vacuum and the residue was diluted with water and acidified with 5% HCl. The product which separated was filtered, washed well with water and crystallised from ethanol.

10a (R'=-OCH_3): m.p. 214° C, Yield; 92%; IR 2926 (C-H str.), 1712 (C=Ostr, cyclohexanone), 1641 (C=O, amide carbonyl), 1605 (C=Nstr.); ^{1}H NMR($CDCl_3$): δ 2.362 (s, 3H, -CH_3), 2.371 (s, 3H, -CH_3), 3.851 (s, 3H, -OCH_3), 3.858 (s, 3H, -OCH_3), 2.775–2.832 (dd,2H, equatorial –CH_2), 3.421–3.475 (dd, 2H, axial –CH_2), 3.610–3.642 (dd, 1H, equatorial –CH), 4.10–4.132(dd,1H, axial –CH), 6.78–7.58 (m,16H, Ar–H), ^{13}C NMR: δ 20.894 and 21.218 (2x-CH_3), 43.247 and 43.448 (2x-CH_2), 46.794 and 48.059 (2x-CH), 55.291 and 55.374 (2x-OCH_3), 65.840 (tetrahedral carbon), 113.612–151.97 (24 aromatic carbons), 161.558 (C=N), 174.593 (C=O, thiazolidine ring), 209.465 (C=O, cyclohexanone ring), Elemental Analysis [Cal.(Obs)]: C; 73.20% (73.18%), H; 5.80% (5.77%), N 4.74% (4.71%), S 5.43% (5.35%).

10b (R'= –F): m.p. 178°C, Yield; 88%, IR (cm^{-1}); 2928 (C–H), 1715 (C=O, cyclohexanone), 1644 (C=O; amide), 1610 (C=N); ^{1}H NMR(CDCl3): δ 2.254 (s, 3H, –CH_3), 2.327 (s, 3H, –CH_3), 2.816–2.876 (dd, 2H, equatorial-CH_2), 3.312–3.354 (dd,2H, axial –CH_2), 3.616–3.640 (dd,1H, equatorial –CH), 4.194–4.209(dd, 1H, axial –CH), 6.091–7.171 (m, 16H, Ar–H); Elemental analysis [Cal.(Obs)]: C; 72.07% (72.05%), H; 4.98% (4.96%), N; 4.94% (4.88%), S 5.66% (5.56%)

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