Michael additions on isoxazole derivatives under solvent-free conditions

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Knoevenagel condensation of 3,5-dimethyl-4-nitroisoxazole 1 with aromatic aldehydes in solid state in the presence of piperidine gives 3-methyl-4-nitro-5-styrylisoxazoles 2 in excellent yields within few minutes. Michael addition of active methylene compounds 3 to 2 in piperidine affords β-diketones 4. Similarly 1 reacts with chalcones 5 in piperidine very efficiently to give Michael adducts 6 in excellent yields with substantial reduction in reaction time under solvent-free conditions.

Solid-state reactions have been attracting the synthetic organic chemists, as they provide enhanced reaction rates, less environmental pollution, greater selectivity, cleaner products and manipulative simplicity. Processes like Bayer-Villiger oxidation, NaBH₄ reduction of ketones, pinacol and benzyl acid rearrangements, Wittig reaction and aldol condensations, have recently been reported in solid-state by Toda. In view of the growing importance, and in continuation of our work in solid-state organic chemistry, we report herein for the first time the Michael additions on isoxazole derivatives in the absence of solvent at room temperature.

Knoevenagel condensation of 3,5-dimethyl-4-nitroisoxazole 1 with different benzaldehydes in the presence of piperidine without any solvent at room temperature results in the rapid formation of 5-styrylisoxazoles in excellent yields. The reaction is elegant and easy and is devoid of any side products. The product yields are excellent varying in the range of 80-90%, requiring 10 min time, compared to that of solution-state reactions which give products in less than 50% yield and take more time (2 hr) in all the cases (Table I).

Michael addition of active methylene compounds 3 to styryl isoxazoles 2 in the presence of piperidine without any solvent at room temperature results in the rapid formation of Michael adducts in excellent yields. In a typical reaction, a mixture of 2, acetyl acetone and piperidine was ground in mortar by pestle at room temperature for 15 min. The solid product obtained was taken in methanol and filtered off. Recrystallization resulted in β-diketones i.e., 3-[2-(3-methyl-4-nitro-5-isoxazolyl)-1-phenylethyl] pentane-2,4-diones 4 in 90% yield. When the same reaction was carried out in refluxing triethyl amine solvent according to reported procedure, the product yield was approximately 50% and the reaction required nearly 2 – 4 hr. In view of this, the solid reaction has greater advantage for reducing the reaction time period remarkably and product yield is greatly enhanced and it is environmentally benign. To our knowledge, the present work represents first report on the Michael additions in the solid state. The other active methylene compounds 3 utilised in the reaction are ethyl acetooacetate, diethyl malonate and ethyl cyanoacetate and benzoylelaceton. In all these cases, the Michael addition proceeds much faster and more efficiently in the absence of solvent as compared to solution state reactions.

Michael reaction of 3,5-dimethyl-4-nitroisoxazole 1 with chalcones 5 in the presence of piperidine and in the absence of solvent at room temperature resulted in very rapid formation of Michael adducts 6 in very good yields (Scheme I). In a typical reaction, compound 1, benzylidenecacetophenone and piperidine were grounded in mortar by pestle at ambient temperature for 15 min. The solid product thus obtained was taken in petroleum-ether and filtered off. Recrystallisation from ethanol gave 3-methyl-4-nitro-5-(1,3-diphenyl-1-oxo-4-n-butylisoxazole 6a in 80 - 85% yield. All the Michael reactions required only 15 min time for completion and the product yield was between 80-85%. When the same reaction was carried out in ethanol solution with traces of piperidine according to reported procedure, the product yield is approximately 40% and the reaction requires much longer time (2-3 days). In this context, the solid state reaction has greater advantage for enhancing the reaction rates by reducing the reaction time many folds (from days to minutes) and product yield is enormously increased besides being environmentally friendly. When all the above Michael reactions are carried out in solution state they resulted in gummy products, which are difficult to handle during the processing stage.

Note
Table I—Formation of compounds 2, 4 and 6 in the absence of solvent and in the presence of solvent

<table>
<thead>
<tr>
<th>Compd</th>
<th>Ar</th>
<th>Ar&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Reaction Period (min)</th>
<th>m.p. Lit. m.p. (°C)</th>
<th>Yield (%)</th>
<th>In the absence of solvent</th>
<th>In the presence of solvent</th>
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<tr>
<td>2a</td>
<td>C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>10</td>
<td>155 (153)&lt;sup&gt;12&lt;/sup&gt;</td>
<td>90</td>
<td>50</td>
<td></td>
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<tr>
<td>2b</td>
<td>C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;-OCH&lt;sub&gt;3&lt;/sub&gt;(p)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>10</td>
<td>148 (150)&lt;sup&gt;12&lt;/sup&gt;</td>
<td>92</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>2c</td>
<td>C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;-CH&lt;sub&gt;3&lt;/sub&gt;(p)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>10</td>
<td>155 (156)&lt;sup&gt;12&lt;/sup&gt;</td>
<td>94</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>2d</td>
<td>C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;-Cl(r)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>10</td>
<td>162 (164)&lt;sup&gt;12&lt;/sup&gt;</td>
<td>95</td>
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<tr>
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<td>—</td>
<td>—</td>
<td>10</td>
<td>172 (174)&lt;sup&gt;12&lt;/sup&gt;</td>
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<td>55</td>
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<td>2f</td>
<td>C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;-NO&lt;sub&gt;2&lt;/sub&gt;(p)</td>
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<td>—</td>
<td>—</td>
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<td>170 (172)&lt;sup&gt;12&lt;/sup&gt;</td>
<td>92</td>
<td>52</td>
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</tr>
<tr>
<td>2g</td>
<td>C&lt;sub&gt;4&lt;/sub&gt;H&lt;sub&gt;6&lt;/sub&gt;-OH(o)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>10</td>
<td>230 (228)&lt;sup&gt;12&lt;/sup&gt;</td>
<td>93</td>
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<td>2h</td>
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<td>2i</td>
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<td>—</td>
<td>—</td>
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<td>—</td>
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<td>230 (228)&lt;sup&gt;12&lt;/sup&gt;</td>
<td>93</td>
<td>53</td>
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</tbody>
</table>

<sup>1</sup>Reaction was carried out by grinding a mixture of 1 and aromatic aldehydes, 2 and 3, 1 and 5 in piperidine separately by pestle in a mortar at room temperature.

<sup>2</sup>Reaction was carried out by mixing 1 and aromatic aldehyde in ethanol solvent, 2 and 3 in triethylamine solvent, 1 and 5 in ethanol solvent with traces of piperidine under boiling conditions.

All the compounds prepared by above three methods were characterised on the basis of their analytical and spectral data and on comparing with authentic samples. In all the cases the reaction proceeded much faster and more efficiently compared to solution state reactions, because the reactions in the absence of solvent had high concentration of reagents which resulted in faster reactions.

In conclusion, the present methodology affords efficient Michael addition reactions on isoxazole derivatives which proceeds under very mild conditions with many advantages i.e., substantial reduction in reaction times, greater product yields with purity and simplicity of performance.

**Experimental Section**

All the melting points were recorded on a Cintex melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellet on a Perkin-Elmer 337 spectrophotometer, 1H NMR spectra on a Varian Gemini 200MHz spectrometer using TMS as internal standard; and mass spectra on a VG micromass 7070H instrument operating at 70eV.

**General procedure for the preparation of 3-methyl-4-nitro-5-styrylisoxazoles 2.** Compound 1 (0.01 mole), benzaldehyde (0.01 mole) and piperidine (0.01 mole) were ground in mortar by pestle at ambient temperature for 10 min. The solid obtained was

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treated with methanol, filtered and recrystallized from hot alcohol to give 2 (Table I).

**General procedure for the preparation of 3-[2-(3-methyl-4-nitro-5-isoxazolyl)-1-phenylethyl]penta-2,4-diones 4.** Compound 2 (0.01 mole), acetyl acetone (0.01 mole) and piperidine (0.01 mole) were ground in mortar by pestle at room temperature for 15 min. The solid obtained was triturated with methanol and filtered. Recrystallization from benzene gave 4 as pure crystals (Table I).

**General procedure for the preparation of 3-methyl-4-nitro-5-(1,3-diphenyl-1-oxo-4-n-butylisoxazoles 6.** Compound 1 (0.01 mole), chalcone 5 (0.01 mole) and piperidine (0.01 mole) were ground in mortar by pestle at ambient temperature for 15 min. The resulting solid was processed with petroleum-ether and filtered. Recrystallisation from hot alcohol gave 6 (Table I).

**Acknowledgement**

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**References**