SYNTHESIS OF HETEROCYCLES: PART I. N-IODOSUCCINIMIDE, A CONVENIENT OXIDATIVE CYCLISING AGENT IN THE SYNTHESIS OF OXAZOLE, ISOXAZOLE, BENZOFURAN, FUROXAN AND 1,2,3-TRIAZOLE-1-OXIDE DERIVATIVES

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Abstract — N-iodosuccinimide has been successfully employed as an oxidative cyclising agent for the synthesis of oxazole, isoxazole, benzofuran, furoxan and 1,2,3-triazole-1-oxide derivatives. Synthesis of compounds (II), (IV), (VI), (VIII) and (X) having these basic skeletons respectively are reported.

Earlier we employed N-iodosuccinimide as an oxidative cyclising agent in the terminal step of the total synthesis of machicendiol to build its benzofuran part. We then decided to look into the utility of this reagent in the synthesis of other heterocycles via suitable synthons capable of undergoing oxidative cyclisation in a free-radical pathway, and in this endeavour we were able to synthesise oxazole, isoxazole, 1,2,3-triazole-1-oxide and benzofuran derivatives in good to excellent yields and a furoxan derivative in a low yield. In each synthesis N-iodosuccinimide was used in the terminal step to build the respective heterocyclic moiety and this step always ended in a single product (the). Unlike N-bromosuccinimide, N-iodosuccinimide has not been explored earlier as a synthetic reagent; only a few isolated examples are available in the literature. The reagent was prepared according to the method of Benson et al. and stored in a coloured bottle wrapped with aluminium foil and kept in a frigidaire.

For oxazole derivatives suitable Schiff bases have been prepared by the usual method from an aromatic amine and an aromatic aldehyde as stated in the sequel; a solution of o-aminophenol in ethanol was added to a solution of the aromatic aldehyde in boiling ethanol. The boiling was continued for 15 min, cooled and the product obtained by filtration was crystallised from ethanol to give needles (yellow/orange) of the corresponding Schiff base (I). The latter was dissolved or suspended in carbon tetrachloride under nitrogen blanket. To it N-iodosuccinimide (2 equivalents) was added and the mixture was refluxed. After the completion of the reaction
(monitored by tlc), the solvent was removed under reduced pressure and the product was purified by column chromatography over silica gel followed by crystallisation from suitable solvents to yield the corresponding oxazole (II). Table 1 summarises the N-iodosuccinimide induced cyclisation of various Schiff bases to oxazoles.

Table 1. N-Iodosuccinimide induced cyclisation to oxazoles

<table>
<thead>
<tr>
<th>Schiff base (I)</th>
<th>Time of reflux</th>
<th>Oxazole derivative (II)</th>
<th>mp</th>
<th>lit. mp</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) R₁=R₂=R₃=H</td>
<td>3 hr</td>
<td>R₁=R₂=R₃=H</td>
<td>102°</td>
<td>101-103°</td>
<td>65</td>
</tr>
<tr>
<td>b) R₁=R₃=H, R₂=OCH₃</td>
<td>2.5 hr</td>
<td>R₁=R₂=H, R₂=OCH₃</td>
<td>99°</td>
<td>99°</td>
<td>75</td>
</tr>
<tr>
<td>c) R₁=R₃=H, R₂=N(CH₃)₂</td>
<td>1.5 hr</td>
<td>R₁=R₂=H, R₂=N(CH₃)₂</td>
<td>178°</td>
<td>182°</td>
<td>70</td>
</tr>
<tr>
<td>d) R₁,R₂=O(CH₂O)-, R₃=H</td>
<td>3 hr</td>
<td>R₁,R₂=O(CH₂O)-, R₃=H</td>
<td>151°</td>
<td>151°</td>
<td>80</td>
</tr>
<tr>
<td>e) R₁=R₂=H, R₂=O</td>
<td>0.5 hr</td>
<td>R₁=R₂=H, R₂=O</td>
<td>123°</td>
<td>122-123°</td>
<td>60</td>
</tr>
<tr>
<td>f) R₁=R₂=H, R₂=NO₂</td>
<td>4 hr</td>
<td>R₁=R₂=H, R₂=NO₂</td>
<td>264°</td>
<td>268°</td>
<td>60</td>
</tr>
</tbody>
</table>

Oximes of certain α,β-unsaturated ketones were reported to cyclise to isoxazoles by iodine-potassium hydroxide in aqueous tetrahydrofuran containing sodium bicarbonate. Benzalacetone oxime (III), mp 116° (lit. 8 mp 116°) upon refluxing (1.5 hr, N₂) with N-iodosuccinimide (2 moles) in carbon tetrachloride afforded pale yellow needles of the hitherto unreported 3-methyl-5-phenyl-isoxazole (IV) (60%), mp 68° (chloroform-petrol), C₁₇H₁₂O₃ (M⁺ 240); δ 2.36 (3H, s, 3-CH₃), 6.36 (1H, d, 2-H), 7.41-7.55 (5H, m, H-3', H-4', H-5'), 7.71-7.85 (2H, d, H-2', H-6').

For synthesising 2-arylbenzofuran lignans we prepared a new model compound (VI): 2-hydroxy-(3', 4'-methylenedioxy)-trans-stilbene (V), mp 118°, C₁₅H₁₂O₃ (M⁺ 240) [ŋKBr max 960 cm⁻¹ (trans CH=CH); λ_max 338 nm (log e 4.34), 292 (4.12), 213 (4.51); δ 5.12 (1H, s, phenolic OH), 5.99 (2H, s, CH₂O₂)].
6.73-7.58 (g, m, aromatic H's and trans Q=O) \), prepared by Wittig reaction of salicylaldehyde with piperonyl triphenylphosphonium bromide in presence of phenyllithium, was refluxed (1.5 hr, N₂) with N-iodosuccinimide (2 moles) to afford colourless crystals of (VI) (95%), mp 105-104° (chloroform-petrol), C₁₅H₁₀O₃ (M⁺ 238); 6 6.0 (2H, g, aromatic H's).

\[ \text{(V) \rightarrow (VI)} \]

Diphenylfuroxan-2-oxide (VIII), mp 116° (lit, 9 mp 116-117°) and a new compound 2,4,5-triphenyl-1,2,3-triazole-1-oxide (X), mp 168° (chloroform-petrol), C₂₀H₁₅N₃O (M⁺ 313), were prepared by oxidative cyclisation of benzil dioxime (VII), mp 207° (chloroform) (lit. 10 mp 207°) and benzil monooxime monophenylhydrazone (IX), mp 125°, C₂₀H₁₇N₃O (M⁺ 315) respectively by refluxing (2 hr, N₂) with N-iodosuccinimide (2 moles) in carbon tetrachloride. In the former case the yield was poor (15%), perhaps due to low solubility of the dioxime in carbon tetrachloride, while the latter was obtained in high yield (78%) and no other side product could be isolated.

\[ \text{(VII)} \rightarrow \text{(VIII)} \rightarrow \text{(IX)} \rightarrow \text{(X)} \]

Compounds (VIII) and (X) were identified by their spectral (ir, nmr and mass) studies and comparison with their respective authentic samples prepared in our laboratory from the same synthons using nickel peroxide as the oxidative cyclising agent. In the latter case, unlike N-iodosuccinimide, a number of products were obtained.

In reviewing to date the other oxidative cyclising reactions of Schiff bases to oxazoles, N-iodosuccinimide induced cyclisation seems to be of special interest because unlike nickel peroxide and lead tetraacetate, N-iodosuccinimide can be stored even for a year; the yields are comparable and in some cases better (e.g., (Ie) 80%, reported yield 12 20%) and the reaction is a neat one. It is also worthy of mention that compound (I) was obtained by N-iodosuccinimide method in a remarkably high yield (78%) compared to the nickel peroxide method (15%).
ACKNOWLEDGEMENTS

We thank Professor N. Takahashi (Tokyo University), Professor N. Murofushi (Tokyo University) and Dr. D. F. Dance (University of Stirling, UK) for mass spectral measurements, Mr. A. Acharya of this Department for nmr measurements and the University Grants Commission, New Delhi for support by way of a Junior Research Fellowship (to P.C.).

REFERENCES


Received, 2nd June, 1980