Microwave-assisted preparations of dihydropyrroles from alkenone *O*-phenyl oximes

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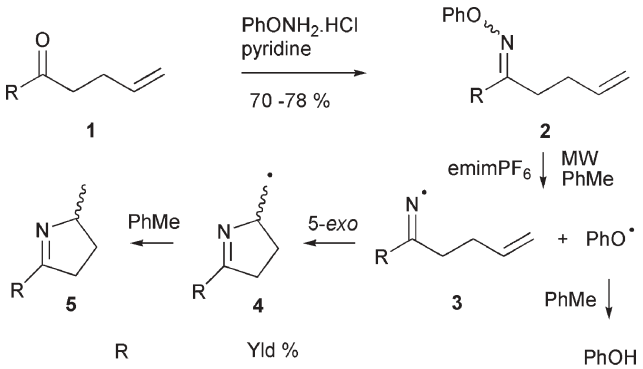
Microwave irradiation of alkenone *O*-phenyl oximes produces iminyl radicals that ring close to yield dihydropyrrole derivatives; pyrroles and pyridines can be obtained from related precursors.

Numerous bioactive alkaloids contain dihydropyrrole or related rings.[1a,b] Interest in preparing them from iminyl radicals has spiralled because radical ring closure conditions can be neutral and mild.[2] Iminyl radical precursors used with tin hydrides include *N*-alkenyl-*S*-arylthiohydroxylamines[3] and *N*-benzotriazolyl-imines.[4] Oxime esters release iminyl radicals on treatment with transition metals.[3,5] Direct or sensitised photolyses of *O*-carboxymethyl oxime esters of *N*-hydroxypyridine-2-thione,[6] of ketoxime xanthates,[7] of acyl oximes[8,9] and of *O*-(4-cyanophenyl) oximes[10] also yield iminyl radicals. Thermal methods are advantageous for synthetic work in terms of simplicity and ease of scale-up. Scarcely any clean precursors suitable for thermal release of iminyls are known. However, quinoline derivatives were obtained by heating suitably functionalised *O*-2,4-dinitrophenyl oximes with sodium hydride.[11] Several types of heterocycles were obtained in cascade processes involving iminyl formation from ring closure of imidoyl radicals onto cyanoalkyl groups.[12,13]

Thermolyses of *O*-phenyl oxime ethers were shown recently to release simple dialkyl- and diaryl-iminyl radicals.[14] Furthermore, the N–O bond dissociation enthalpies [BDE (R_2C=N–OPh) = 140 kJ mol^{-1} for R = Me or Ph] were found to actually be lower than the O–O BDEs of dialkyl peroxides (159–167 kJ mol^{-1}).[14] However, it proved difficult to develop conventional sealed tube type thermolyses of *O*-phenyl oxime ethers for preparative work; reaction times had to be long, the products were not cleanly formed and yields were disappointingly low. In view of this, we decided to investigate the reactions of *O*-phenyl oxime ethers promoted by microwaves. The starting *O*-phenyl oxime ethers can be prepared in good yields by condensation of ketones with the commercially available *O*-phenylhydroxylamine hydrochloride in the presence of pyridine.[14] 5-*exo*-Cyclisations of pent-4-en-1-iminyl radicals are comparatively fast and are thought be only about a factor of five slower than the archetype hex-5-enyl radical cyclisations.[2,15] We investigated iminyl radical generation and cyclisation using the set of functionalised *O*-phenyl oxime ethers **2a**–**2d** prepared from the corresponding pent-4-enyl ketones **1a**–**1d** (Scheme 1).[16] We anticipated that under microwave irradiation the main initial reaction would be scission of the N–O bond yielding butenyl-iminyl **3** together with the phenoxyl radical in equal proportions. Scission of the weak N–O bond is favoured because of the resonance stabilisation of the released phenoxyl radical. 5-*exo*-Ring closure of the iminyl radicals was expected to produce 3,4-dihydro[2*H*]pyrrolomethyl radicals **4** that would yield the corresponding substituted dihydropyrrole on hydrogen abstraction from solvent. The phenoxyl radicals were expected to abstract hydrogen from the solvent giving phenol as the main by-product.

Compound **2a** was chosen for detailed study to enable optimum reaction conditions to be established. Solutions of **2a** in toluene as the H-atom donor were irradiated in a Biotage Initiator microwave reactor (nominally 300 MHz). Experiments were carried out at different concentrations, temperatures and irradiation times with various proportions of the ionic liquid 1-ethyl-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate (emimPF_6). Reaction efficiency depended critically on temperature and time of irradiation. Optimum conditions were found to involve irradiation at 160 °C for 15 min with one equivalent of ionic liquid. ^{1}H NMR analysis of the total product mixture from **2a** under these conditions showed a very clean reaction with nearly quantitative production of both **5a** and phenol.[17] The isolated product yields, obtained from reactions of **2a**–**2d** under these optimised conditions, are shown in Scheme 1. As expected, in each case a 50 : 50 mixture of the two enantiomers was obtained. With toluene as the H-atom donor, premature reduction of iminyl radicals, yielding the corresponding uncyclised imines, was not observed for butenyl-iminyl radicals. These results indicated that the method is an



Scheme 1 Preparation and microwave-assisted reactions of alkenone *O*-phenyl oximes.

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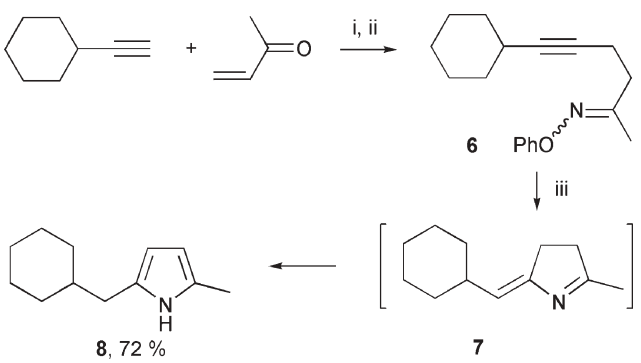
efficient way of preparing 3,4-dihydro[*2H*]pyrroles functionalised with alkyl or aryl groups adjacent to the C=N bond.

The *O*-phenyl oxime of 1-phenylhex-5-en-1-one (*i.e.* **2c** with the chain lengthened by one methylene unit) was next examined as a model compound for 6-*exo* ring closures, possibly giving access to tetrahydropyridines. Microwave irradiation of this compound in toluene, followed by the usual work-up, gave phenol and 1-phenylhex-5-en-1-one, together with several minor components. The 1-phenylhex-5-en-1-one is almost certainly produced from hydrolysis of the corresponding imine during work-up. It appears, therefore, that the main reaction is simply H-atom abstraction by the intermediate iminyl radical from the solvent and 6-*exo*-cyclisation is too slow to compete.

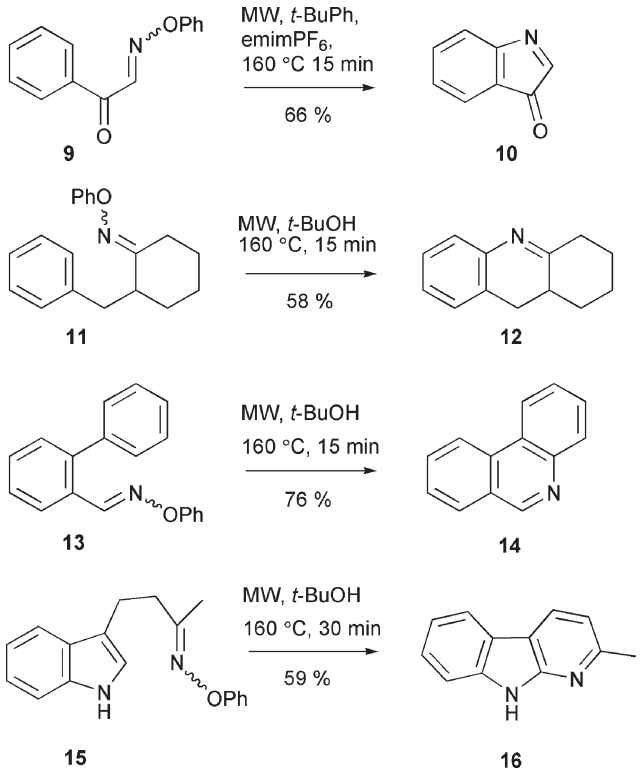
The *O*-phenyl oxime of cyclohexylhex-5-yn-2-one, *i.e.* **6**, was chosen as a model compound to probe the effectiveness of the alkyne group as an acceptor for iminyl radical cyclisations. Compound **6** was prepared by ruthenium catalysed conjugate addition of ethynylcyclohexane to methyl vinyl ketone using the method of Kim and co-workers.[18] Microwave irradiation of **6** in toluene at 160 °C for 30 min gave, not the expected methylene-dihydropyrrole **7**, but the corresponding pyrrole **8** (Scheme 2). The driving force for this rearrangement is evidently aromatisation of the ring.

The use of aromatic rings as iminyl radical acceptors was next examined. Ring closure onto an aromatic ring produces a cyclohexadienyl type radical that can regain aromaticity by transfer of a hydrogen atom. Non-H-atom donor solvents were therefore required to facilitate this oxidative process. Microwave irradiation of 2-oxo-2-phenylacetaldehyde oxime **9**, in *t*-butylbenzene as solvent, gave a 66% isolated yield of 3*H*-indol-3-one (**10**). 6-Membered ring heterocycles could also be prepared from appropriate precursors. Thus, with *t*-butanol as solvent, and in the absence of ionic liquid, useful yields of hexahydroacridine **12** and phenanthridine **14** were obtained from oxime ethers **11** and **13**, respectively (Scheme 3). The $ZrCl_4$ catalysed reaction[19] of indole with methyl vinyl ketone yielded 4-(1*H*-indol-3-yl)butan-2-one from which *O*-phenyl oxime ether **15** was obtained. Interestingly, microwave irradiation of **15** in *t*-butanol afforded pyridoindole derivative **16** in which both the acceptor ring and the pyridyl ring had become aromatic. 6-*endo*-Cyclisation was probably favoured in this example because this closure mode generates a resonance stabilised benzyl type radical.

Finally, intermolecular addition of 1-phenylethaniminyl radicals, derived from PhC(Me)=NOPh, to olefins and alkynes was



Scheme 2 i; $[RuCl_2(p\text{-cymene})]_2$, pyrrolidine, 60 °C, 12 h, 58%. ii; $PhONH_2{\cdot}HCl$, pyridine, 76%. iii; PhMe, $emimPF_6$, MW, 160 °C, 30 min.



Scheme 3 Iminyl radical ring closures onto aromatic rings.

investigated. Microwave irradiation of this oxime ether with ten equivalents of methyl acrylate in *t*-butanol at 160 °C gave mainly phenol and polymer. Similar reactions were carried out with excess phenylacetylene and with diphenylacetylene as acceptors but in both cases only intractable mixtures were produced.

In conclusion, we have found that the weak N–O bonds of *O*-phenyl oxime ethers readily cleave on irradiation by microwaves, releasing iminyl radicals together with resonance-stabilised phenoxyl radicals. Butenyl-iminyl radicals cyclise to dihydropyrroles, butynyl-iminyl radicals produce pyrroles and 3-arylalkyl-iminyls yield aromatic heterocycles. The phenol by-product is easily removed by chromatography. The process amounts to a convenient and rapid two step synthesis of heterocycles from unsaturated carbonyl compounds.

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16 In each case the *O*-phenyl oxime ether was obtained as a mixture of *E*- and *Z*-isomers.
17 Typical procedure: preparation of **5a**. 1-Ethyl-3-methylimidazolium hexafluorophosphate (0.5 g, 2.0 mmol) was added to a solution of **2a** (0.50 g, 1.91 mmol) in toluene (15 cm^3) and placed in a microwave vessel (5–20 cm^3). The vessel was sealed and subjected to microwave irradiation for 15 min at 160 °C. After cooling, the ionic liquid was filtered off and the toluene was evaporated under reduced pressure. The ^{1}H NMR spectrum of the crude mixture showed phenol and **5a** in equal proportions as essentially the only products. The residue was purified by flash column chromatography (10% EtOAc, hexane) to give methyl 3-(2-methyl-3,4-dihydro-2*H*-pyrrol-5-yl)propanoate **5a** as a red oil (0.25 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.15 (d, J = 6.67 Hz., 3H, CH_3), 1.33 (m, 1H, CH_2), 2.02 (m, 1H, CH_2), 2.39 (m, 1H, CH_2), 2.47 (m, 1H, CH_2), 2.53 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 3.61 (s, 3H, CH_3), 3.97 (sextet, J = 6.67 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$), δ 22.1, 28.5, 30.8, 38.0 (×2), 51.8, 67.9, 173.5, 174.9; IR ν_{max}/cm^{-1} 2958.8, 1735.2, 1644.7, 1435.6, 1169.1; *m/z* (CI) 170, [100%, $(M + H)^+$], [Found $(M + H)^+$, 170.1181, $C_9H_{16}NO_2$ requires 170.1186].
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