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Microwave-Assisted Syntheses of *N*-Heterocycles Using Alkenone-, Alkynone- and Aryl-carbonyl *O*-Phenyl Oximes: Formal Synthesis of Neocryptolepine

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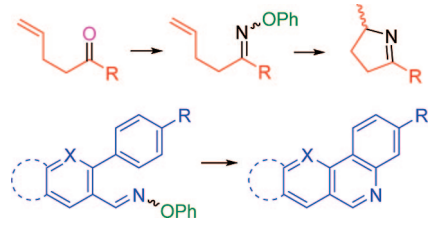
Received April 21, 2008



This research aimed to provide a new and "clean" synthetic method that would enable both known and novel *N*-heterocycles to be prepared efficiently. *O*-Phenyl oximes were found to be excellent precursors for iminyl radicals with a variety of acceptor side chains. Dihyropyrroles were made in good yields from *O*-phenyl oximes containing pent-4-ene acceptors. The analogous process with a hex-5-enyl acceptor did not yield a dihydropyridine, probably because the 6-*exo-trig* ring closure of the iminyl radical was too slow to compete with H-atom abstraction. The iminyl radical from a precursor with a pent-4-yne type side chain underwent ring closure followed by rearrangement to afford a pyrrole derivative. Suitably substituted iminyl radicals ring closed readily onto aromatic acceptors, thus enabling several polycyclic systems to be accessed. Quinolines were made from 3-phenylpropanones via their *O*-phenyl oximes. Syntheses of phenanthridines starting from 2-formylbiphenyls were particularly efficient, and this approach enabled the natural product trisphaeridine to be made. Starting from 2-phenylnicotinaldehyde derivatives, ring closures of the derived iminyl radicals onto the phenyl rings yielded benzo[*h*][1,6]naphthyridines. Similarly, ring closure onto a phenyl ring from a benzothiophene-based iminyl yielded a benzo[*b*-]thieno[2,3-*c*]quinoline. By way of contrast, iminyl radical ring closure onto pyridine rings was not observed. However, iminyl radicals did cyclize onto indoles, enabling indolopyridines to be prepared. The latter route was exploited in a short formal synthesis of neocryptolepine starting from 2-((1*H*-indol-3-yl)methyl)cyclohexanone.

Introduction

Radical-mediated methods of preparing heterocycles are steadily entering mainstream organic synthesis because their experimental conditions are usually mild and neutral and because novel derivatives can be accessed in this way.[1] Ring closures of iminyl radicals ($R_2C{=}N^{\bullet}$) appear particularly promising because the products are convenient for further functional group manipulations. The literature on iminyl radical cyclizations is not extensive, but the most studied process is the 5-*exo-trig* closure of pent-4-enyl-iminyl types yielding 3,4-dihydro-2*H*-pyrroles.[2] It can be inferred from available kinetic data that the rate constant for this iminyl cyclization is only about a factor of 20 less than that of the archetype hex-5-enyl radical[3] and therefore the reaction is fast enough for incorporation into a variety of preparative sequences.[1a,2] An important objective has been to find ways of generating iminyls that are "clean", flexible,

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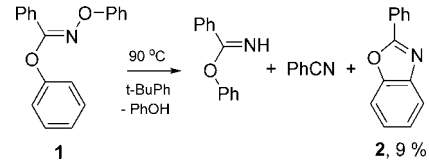
(3) Le Tadic-Biadatti, M.-H.; Callier-Dublanchlet, A.-C.; Horner, J. H.; Quiclet-Sire, B.; Zard, S. Z.; Newcomb, M. *J. Org. Chem.* **1997**, *62*, 559–563.

10.1021/jo800847h CCC: $40.75
Published on Web 06/13/2008

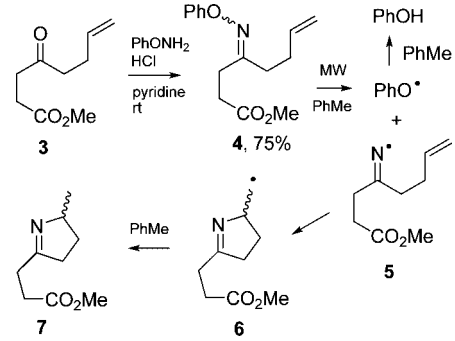
and simple. Iminyl radical precursors used with tin hydrides or transition metals, e.g., *N*-alkenyl-*S*-arylthiohydroxylamines,[4] *N*-benzotriazolylimines,[5] and oxime esters,[4,6] are not ideal because of the toxicity of the metals. Direct or sensitized photolyses of oxime esters of *N*-hydroxypyridine-2-thione,[7] of ketoxime xanthates,[8] of acyloximes,[9,10] and of *O*-(4-cyanophenyl)oximes[11] also yield iminyl radicals. However, for preparative work, thermal treatment of an appropriate precursor is usually a more desirable tactic because it is simpler and experimentally convenient and because it readily lends itself to scale-up. Scarcely any precursors suitable for thermal release of iminyls are known, except for special cases such as the formation of quinoline derivatives by heating suitably functionalized *O*-2,4-dinitrophenyloximes with sodium hydride[12] and preparations of several types of heterocycles in cascade processes involving iminyl formation from ring closure of imidoyl radicals onto cyanoalkyl groups.[13,14]

Quite recently it was discovered that *O*-phenyl oxime ethers (RR′C═N-OPh) are a new class of nonazo and nonperoxide free-radical initiators that release iminyl and phenoxyl radicals at relatively low temperatures.[15] From detailed studies of the thermal dissociation of a representative set of these compounds the N−O bond dissociation energies were determined to be only ca. 35 kcal mol^{-1} for R,R′ = Me and Ph. Thus the N−O bonds of these compounds are actually weaker than the O−O bonds of dialkyl peroxides.[15] *O*-Phenyl oxime ethers are easily prepared from aldehydes or ketones simply by condensing them with the commercially available *O*-phenylhydroxylamine hydrochloride in anhydrous pyridine at room temperature. We anticipated, therefore, that it would be possible to devise convenient thermal procedures for preparing dihydropyrroles and other heterocycles from conversion of unsaturated ketones to the corresponding *O*-phenyl oxime ethers. Thermal release of the unsaturated iminyl radicals would be followed by their ring closure. In practice, however, difficulties were encountered in preparative work. In conventional, sealed tube type thermolyses of *O*-phenyl oxime ethers derived from hexenone and related ketones, reaction times had to be long, products were not cleanly formed at higher temperatures, and yields were disappointingly low. Similarly, thermal decomposition of phenyl *N*-phenoxybenzimidate **1** in a sealed tube was still incomplete after 26 h at 90 °C and the ring-closed oxazole **2** (∼9%) was accompanied by significant amounts of phenyl benzimidate and benzonitrile (Scheme 1).[15]

SCHEME 1. Products from Thermal Reaction of Phenyl *N*-Phenoxybenzimidate 1



SCHEME 2. Microwave-Assisted Preparation of a Dihydropyrrole



It occurred to us that thermolyses of *O*-phenyl oxime ethers might give cleaner product mixtures and that the reaction times would be considerably shortened if microwave irradiation were to be employed. We therefore investigated iminyl radical generation and cyclization using microwave irradiation of a representative range of functionalized *O*-phenyl oxime ethers. We found that under appropriate microwave conditions good to excellent yields of heterocycles could indeed be obtained. In this paper we report that dihydropyrroles can be prepared from alkenone *O*-phenyl oximes and that phenanthridine, benzonaphthiridine, and indolopyridine derivatives can be made by iminyl ring closures onto aromatic radical acceptors. Part of this research has previously been published as a preliminary communication.[16]

Results and Discussion

Discovery and Optimization. The *O*-phenyl oxime ether **4** was prepared in 75% yield as a mixture of *E* and *Z* isomers by stirring methyl 4-oxooct-7-enoate **3** with *O*-phenylhydroxylamine hydrochloride in pyridine at room temperature. The fact that two isomers were present did not matter because both released the same iminyl radical **5** on scission of their N−O bonds (Scheme 2). Solutions of **4** in toluene were irradiated in a Biotage Initiator microwave reactor (nominally 300 MHz) at various temperatures and for various times. The loss factor of toluene is low (tan δ = 0.04), so the ionic liquid 1-ethyl-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate (emimPF_6, IL) was included to increase the microwave absorbance level of the medium. Encouragingly, this process cleanly gave the 3,4-dihydropyrrole **7** (1:1 mixture of enantiomers) and phenol as the only detectable products. The ionic liquid should be recoverable, but we made no attempt to recycle it.

The effect of different temperatures and reaction times on the yield of **7** was monitored by NMR spectroscopy, and the results are shown in Table 1. Entries 1−4 show that a temperature of 160 °C was necessary to achieve complete

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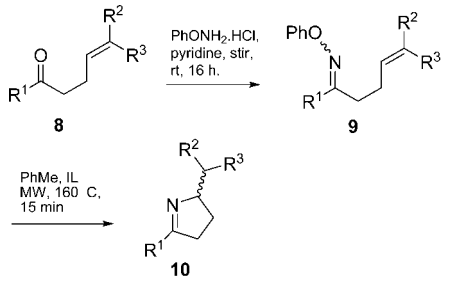
TABLE 1. Optimization of Dihydropyrrole Yield from Microwave Irradiations of 4[a]

entry	phenyl oxime **4** (mmol)	*T* (°C)	time (min)	yield of **7** (mol %)[b]
1	0.2	120	10	25
2	0.2	140	10	55
3	0.2	160	10	75
4	0.2	180	10	72[c]
5	0.2	160	5	66
6	0.2	160	15	99
7	0.2	160	20	96
8	0.3	160	15	78
9	0.4	160	15	67
10	0.5	160	15	59

[a] Reactions in PhMe (1.5 mL) containing $emimPF_6$ (0.05 g) with CH_2Br_2 as internal standard. [b] Yields in mol % determined by ^1H NMR. [c] Amount of $emimPF_6$ was 0.075 g.

TABLE 2. Preparation of 3,4-Dihydropyrroles from Alkenone *O*-Phenyl Oximes



	R^1	R^2	R^3
a	Me	Me	
b	$(CH_2)_2CO_2Me$	H	H
c	$(CH_2)_3CO_2Me$	H	H
d	4-$MeOC_6H_4$	H	H
e	2,4-di$MeOC_6H_3$	H	H

entry	ketone	yield of **9** (mol %)[a]	yield of **10** (mol %)[a]
1	**8a**	71	70
2	**8b**	75	78
3	**8c**	78	82
4	**8d**	73	68
5	**8e**	70	77

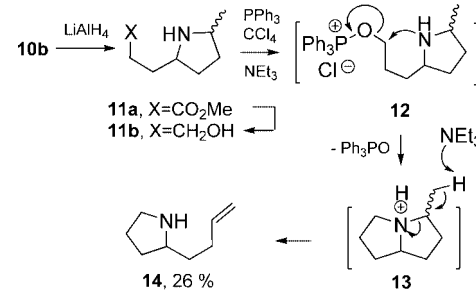
[a] Yields of isolated products.

conversion and high yields but that at higher temperatures side reactions/degradative process set in. Entries 3 and 5−7 show that at 160 °C best yields were obtained with an irradiation time of 15 min. However, for larger amounts of precursor **4** (entries 8−10), yields fell off in 15 min reactions.

The NMR spectrum of the total reaction mixture from entry 6 showed essentially quantitative formation of dihydropyrrole **7** together with an equal quantity of phenol. This supported the mechanism shown in Scheme 2 and indicated that microwave irradiation could be applied in an efficient method for use with *O*-phenyl oximes.

Application to Dihydropyrrole Preparations. Numerous biologically active alkaloids contain dihydropyrrole or related rings.[17] Our thermal methodology appeared capable of converting ketones with but-3-enyl type substituents into dihydropyrroles in two steps. The scope of this pathway was probed by preparing the set of precursor oxime ethers shown in Table 2. Ketone **8a** was commercially available. The ester-containing ketones **8b,c** were prepared by treatment of the acid chlorides

SCHEME 3. Potential Route to a Pyrrolizidine Derivative



of 4-methoxy-4-oxobutanoic acid and 5-methoxy-5-oxopentanoic acid, respectively, with but-3-enylmagnesium bromide. The aryl-butenyl ketones **8d,e** were made by treatment of 4-methoxyacetophenone, and the 2,4-dimethoxy analogue, with KH and allyl bromide.

The conversions of the ketones to the corresponding oxime ethers **9a**−**e** by treatment with *O*-phenylhydroxylamine hydrochloride were straightforward, and yields of 70−75% were normally obtained (Table 2). The optimum conditions for microwave irradiations established before, i.e., 160 °C for 15 min, proved to be very effective. Entry 1 shows that the method was tolerant of a side chain containing an additional double bond. Entries 2 and 3 indicate good tolerance of ester groups. The final two entries (4 and 5) show that butenyl ketones with aromatic substituents also worked well, affording 5-aryldihydropyrroles in good yields.

We investigated methods for converting ester-containing dihydropyrrole **10b** into a pyrrolizidine derivative by means of an intramolecular nucleophilic substitution. Initially we hoped to achieve selective reduction of the imine bond in the dihydropyrrole ring to yield pyrrolidinyl ester **11a**. In practice, reactions with $NaBH_4$, $NaBH_3CN$, and $NaBH(OAc)_3$ all gave mixtures of **11a** and alcohol **11b** from reductions of both the ester and imine groups. Complete reduction of the imine and ester to cleanly give **11b** was therefore carried out with $LiAlH_4$.

Ring closure was first attempted via the mesylate. However, it was found that treatment of **11b** with $MeSO_2Cl$ led to a dimesylate from conversion of both the alcohol and amine groups. An alternative Appel type method, which has worked for other pyrrolizidine derivatives,[18] was therefore tried. Surprisingly, however, when amine **11b** was treated with PPh_3, CCl_4, and Et_3N in DCM, the main product (26%) was found to be 2-(but-3-enyl)pyrrolidine **14**. A mechanistic rationale of this result is shown in Scheme 3. The alcohol side chain is likely to react with the phosphonium chloride to yield alkoxy-triphenylphosphonium intermediate **12**.[19] Intramolecular nucleophilic displacement of the phosphonium group will generate pyrrolizidinyl-ammonium ion **13**. This intermediate will be susceptible to Hofmann type eliminations, promoted by the triethylamine base. In keeping with the Hofmann rule, one of the methyl H-atoms will be selectively removed by the base, rather than any of the secondary ring β-H atoms, to yield the least stable alkene **14**.

In principle, tetrahydropyridines might be obtained from *6-exo* ring closures of hexenyl-iminyls. The *O*-phenyl oxime of 1-phenylhex-5-en-1-one [i.e., PhO−N=C(Ph)$(CH_2)_3$CH=CH_2]

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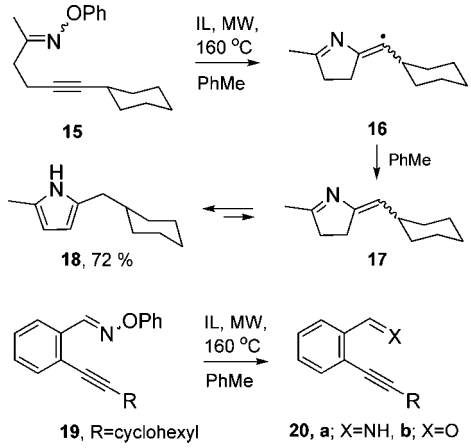
SCHEME 4. Pyrrole Formation from Iminyl Cyclization onto an Alkyne Acceptor



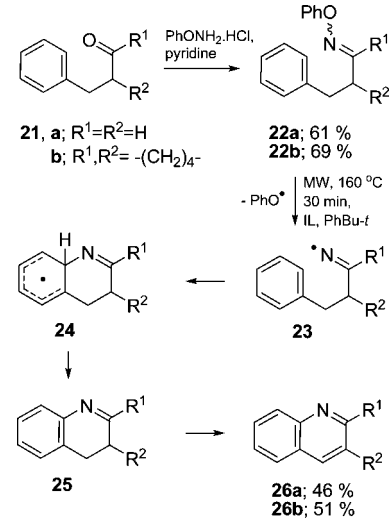
was examined as a model compound for this process. Microwave irradiation of this precursor in toluene, followed by the usual workup, gave phenol and 1-phenylhex-5-en-1-one, together with several minor components. The 1-phenylhex-5-en-1-one was almost certainly produced from in situ hydrolysis of the corresponding imine. The main reaction was therefore simply H-atom abstraction by the iminyl radical from the solvent and *6-exo*-cyclization was too slow to compete.

Cyclization onto an Alkyne Acceptor; Preparation of a Pyrrole Derivative. The *O*-phenyl oxime of cyclohexylhex-5-yn-2-one **15** was chosen as a precursor to probe the effectiveness of the alkyne group as an acceptor for iminyl radical cyclizations. Compound **15** was prepared by ruthenium catalyzed conjugate addition of ethynyl cyclohexane to methyl vinyl ketone using the method of Kim and co-workers,[20] followed by the standard *O*-phenyl oxime conversion. Microwave irradiation of **15** in toluene at 160 °C for 15 min gave pyrrole **18** in 72% yield (Scheme 4). Vinyl radical **16** was expected to rapidly abstract an H-atom from the solvent to produce **17**. However, under the microwave conditions, it appears that two 1,3-proton migrations converted **17** to pyrrole **18**, the aromaticity of this product ensuring this was a rapid and complete rearrangement.

O-Phenyl oxime ether **19**, with an alkynylaryl skeleton, was also prepared by Pd-catalyzed coupling of 2-bromobenzaldehyde with ethynylcyclohexane followed by condensation with *O*-phenylhydroxylamine hydrochloride. Microwave irradiation of **19** in toluene led to a complex mixture of products including the imine **20a**, its hydrolysis product **20b**, and trace amounts of the corresponding nitrile. In this case neither *5-exo* nor *6-endo* ring closure was fast enough to compete successfully with H-atom abstraction from solvent, and other side reactions.

Cyclization onto Phenyl Rings: Preparation of Quinoline, Phenanthridine, and Benzonaphthiridine Derivatives. With aromatic rings acting as iminyl radical acceptors, cyclohexadienyl-type radicals will be produced. In principle, cyclohexadienes, formed in a final H-atom transfer from solvent, could be expected, but in practice, removal of an H-atom and restoration of aromaticity to the ring has usually been observed.[1,10,16] Non-H-atom donor solvents were therefore required to facilitate this oxidative process. We originally tried some *5-exo*-type cyclizations, but apart from the microwave-assisted reaction of 2-oxo-2-phenylacetaldehyde oxime giving 3*H*-indol-3-one,[16] intractable mixtures were obtained. However, the methodology proved much more successful in preparations of six-membered ring azaaromatics from 6-*endo* ring closures of appropriate precursors. 3-Phenyl oxime ethers **22a,b** were easily prepared from the corresponding ketones (Scheme 5). When subjected to microwave irradiation in *tert*-butylbenzene as non-H-atom donor solvent and including emimPF_6, **22a** gave a 46% yield of quinoline (**26a**) and similarly **22b** afforded tetrahydroacridine (**26b**) in 51% yield. For these and subsequent cyclizations onto aromatic acceptors an irradiation time of 30 min was adopted to ensure complete reaction. 6-*Endo* cyclizations of the initial iminyl radicals **23a,b** will produce cyclohexadienyl radicals **24a,b**. Loss of an H-atom will restore aromaticity to the benzo rings with production of dihydroquinolines **25a,b**.[21] However, in both cases, a further in situ dehydrogenation took place such that only the fully aromatic quinolines **26a,b** could be isolated after the microwave irradiation.

SCHEME 5. Preparation of Quinolines



In another application we used an aromatic ring, rather than a chain, to support a second aromatic acceptor next to the oxime ether group, i.e., situated *ortho* to each other. In these systems the derived iminyl radicals are ideally placed for intramolecular addition to the ring of the adjacent acceptor. An iminyl radical mediated route to derivatives of phenanthridine is shown in Scheme 6. These azaaromatics are biologically active and have numerous other uses.[22] 2-Formylbiphenyls **27** were prepared by Pd-catalyzed coupling of 2-bromobenzaldehyde with various aromatic boronic acids[23] in yields ranging from 62% to 71% (Scheme 6). They were converted to the corresponding *O*-phenyl oximes **28a**−**d** by treatment with $PhONH_2 \cdot HCl$. Individual precursors in *t*-BuPh with emimPF_6 as ionic liquid were then irradiated with microwaves for 30 min. Using this methodology gave the parent phenanthridine **29a** which was isolated in 76% yield along with phenol. The reaction was equally successful

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(21) The cyclohexadienyl H-atoms could be abstracted by phenoxyl radicals or other radicals in the system, or possibly by electron transfer from **24** yielding the corresponding cyclohexadienyl cations which then lose a proton. The latter route seems unlikely in *t*-BuPh solvent and in the absence of a good electron-acceptor molecule. Air oxidation of **25a,b** during workup is another possibility.

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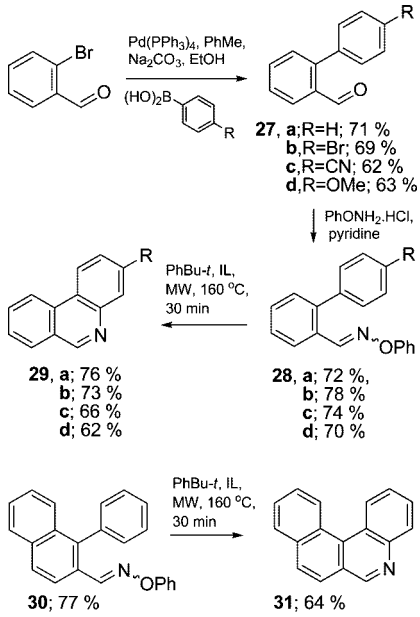
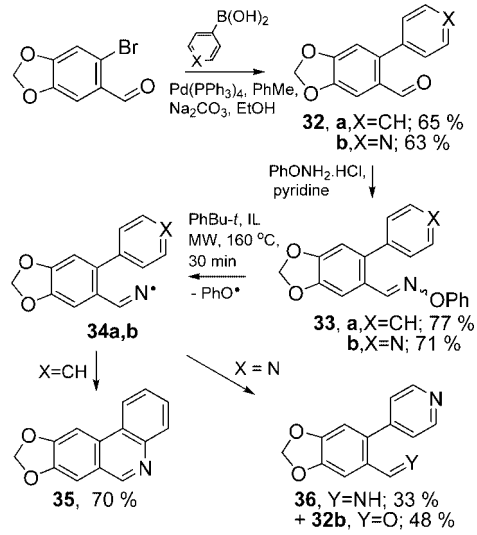
SCHEME 6. Preparations of Phenanthridines



SCHEME 7. Preparation of Trisphaeridine 35



for precursors containing electron-withdrawing substituents (Br, CN), which yielded **29b,c**, and for a precursor containing an electron-releasing substituent (OMe), which gave the 3-methoxy derivative **29d**. The 3-bromo and 3-cyano-phenanthridines are convenient for further functional group transformations.

The interesting analog benzo[*k*]phenanthridine (**31**) appeared to be accessible via an analogous route. It had previously been made by cyclization of aryl formamides,[24] photocyclization of 4-phenyl-3-vinylquinolines,[25] and an anionic/aryne cyclization and in situ oxidation sequence starting from 2-bromonaphthyl-2-fluorophenylamine.[26] Our three-step preparative method is based on the naphthalene-containing precursor **30**, which was made by a Suzuki coupling route similar to that shown for **27** but starting from 2-bromonaphthaldehyde and phenylboronic acid. Microwave irradiation of **30** under the standard conditions in *t*-BuPh enabled **31** to be isolated in 64% yield.

In a similar vein, the natural product trisphaeridine **35** was prepared in three steps starting from commercial 6-bromopiperonal, via the corresponding formyl **32a** and oxime ether **33a** derivatives. A 70% yield of **35** was obtained from microwave irradiation of **33a** in *t*-BuPh. Previous syntheses have been accomplished via tributyltin hydride induced cyclization of *N*-(2-bromobenzyl)aniline,[27] via the internal Pd-catalyzed aryl-aryl coupling reaction of MOM protected halo amides, followed by reduction with $LiAlH_4$ and treatment with hydrochloric acid,[28] and by Pd[0]-mediated Ullmann cross-coupling of 1-bromo-2-nitrobenzene with 6-bromopiperonal.[29]

A simple extension of this method appeared to offer a route to benzo[*c*][1,7]naphthiridine derivatives. The sequence started with Pd-catalyzed coupling of 6-bromopiperonal with pyridin-4-ylboronic acid to give formyl derivative **32b**, which was then transformed to the *O*-phenyl oxime ether **33b** in good yield. However, when the latter was subjected to microwave irradiation, none of the desired benzonaphthiridine was formed. Instead, a mixture of imine **36** and its hydrolysis product **32b** was obtained. This result suggested that ring closure of intermediate iminyl radical **34b** onto the pyridine ring was slower than cyclization onto the phenyl ring and unable to compete with H-atom abstraction from other reaction components. Reports of ring closures of C-centered radicals onto pyridine rings are comparatively rare,[30] and the reaction is usually low-yielding in comparison with ring closure onto pyridinium salts.[31–33] Iminyl radicals are expected to be electrophilic in comparison with C-centered radicals, and therefore their even slower cyclization onto pyridine, due to an unfavorable polar effect with the ring N-atom, makes reasonable sense.

The methodology was, however, readily adapted for preparations of benzo[*h*][1,6]naphthyridines by using pyridine as the basal support for the aromatic acceptor and iminyl radical. 2-Bromonicotinaldehyde **37** underwent Pd-catalyzed couplings with phenylboronic acids to afford 2-aryl-3-formyl-pyridine derivatives **38a**−**c**, which were smoothly converted to the corresponding oxime ethers **39a**−**c** (Scheme 8). On irradiation of **39a** with microwaves in the usual way a very satisfactory yield of benzo[*h*][1,6]naphthyridine **40a** was obtained. The results from the precursors with CN and Br substituents showed that benzo[*h*][1,6]naphthyridines containing useful functionality at the 8-position **40b,c** could easily be accessed. A few benzo[*h*][1,6]naphthiridine derivatives have been reported in the literature,[34] but none appear to be commercially available. We also examined the use of benzothiophene as the support for the iminyl radical and acceptor. Thus, precursor **43** was prepared from 3-bromobenzothiophene-2-carbaldehyde **41** using an analogous sequence (Scheme 8). On irradiation with microwaves we were able to isolate benzo[*b*]thieno[2,3-*c*]quinoline **44** in a 53% yield.[35]

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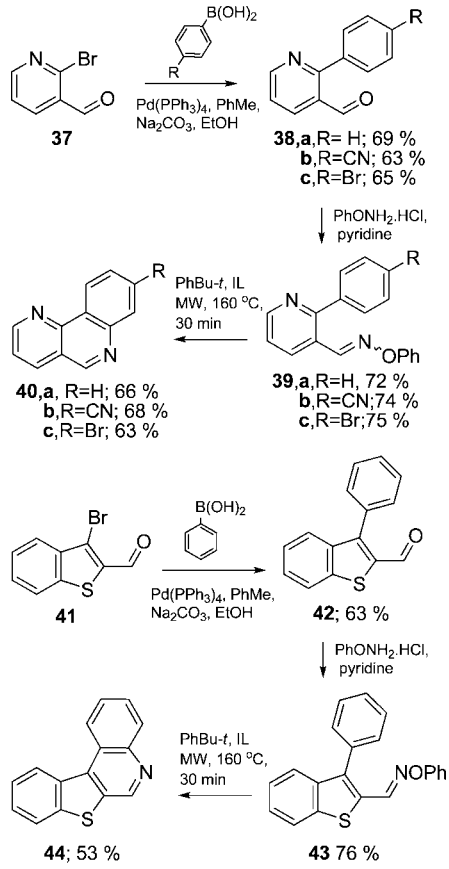
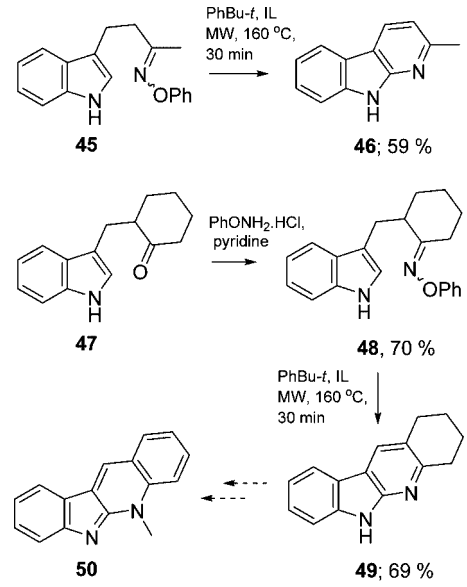
SCHEME 8. Preparation of Benzo[*h*][1,6]naphthyridines and Benzothiophenoquinolines



It is evident that iminyl ring closure onto the phenyl ring occurs readily, although the lower yield may indicate it is slightly more difficult with this architecture because of the larger bond angles of the adjacent iminyl and phenyl groups on the 5-membered ring as compared with a six-membered ring.

Cyclization onto Indole: Syntheses of Functionalized Indolopyridines. Compounds related to indolopyridines and indoloquinolines are known to be cytotoxic and to have anticancer activity. For example, neocryptolepine derivatives (e.g., **50**) showed potent in vitro antimalarial activity.[36] Related heterocycles[37] including 5-aza-ellipticine analogues[38] are also biologically active. The $ZrCl_4$-catalyzed reaction of indole with methyl vinyl ketone yielded 4-(1*H*-indol-3-yl)butan-2-one from which *O*-phenyl oxime ether **45** was obtained. Interestingly, microwave irradiation of **45** in *tert*-butanol afforded indolopyridine derivative **46** in which both the acceptor ring and the pyridyl ring had become aromatic. 6-*Endo* cyclization was probably favored in this example because it generated a resonance stabilized benzyl type radical, unlike the alternative *5-exo* mode which would involve formation of a strained spiro-C-atom.

SCHEME 9. Preparation of Indolopyridine and Indoloquinoline Derivatives



An analogous sequence was designed for the preparation of the natural product neocryptolepine **50** (Scheme 9). The indoloketone **47** was obtained in 78% yield from reaction of gramine with 1-cyclohexenylpyrrolidine.[39] Conversion to the corresponding *O*-phenyl oxime ether **48** was accomplished in 70% yield. Microwave irradiation of **48** in *t*-BuPh afforded tetrahydroindolo[2,3-*b*]quinoline **49** in 69% yield. As with several previous products of these microwave-mediated reactions, a second in situ dehydrogenation step rendered the newly formed pyridine ring aromatic. Tetrahydroindolo[2,3-*b*]quinoline **49** is a known compound and has previously been converted to neocryptolepine **50** in two steps by dehydrogenation/aromatization with DDQ followed by methylation with methyl sulfate.[37a] Thus, overall, the sequence represents a formal synthesis of neocryptolepine **50** in five steps from gramine.

Conclusions

We have shown that *O*-phenyl oximes are excellent precursors for a variety of iminyl radicals. The oximes are easily made in one step from carbonyl compounds and can be stored indefinitely. Their microwave-assisted reactions have several advantages over existing methods for *N*-heterocycle preparations. Reactions are rapid (≤30 min), require no acids, bases, or toxic metals, and are comparatively mild and high-yielding. Unlike many other radical-mediated synthetic methods, no initiator is needed and hence no byproducts from initiator fragments contaminate the system. Comparatively few microwave-assisted synthetic methods, based around radical intermediates, are known.[40] The feature most such reactions have in common with

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our methodology is that the starting radicals are generated by direct homolysis of a weak bond in the relevant precursor, brought about by microwave heating, rather than by radical-induced dissociations brought about by peroxide- or azo-initiators.

Dihydropyrroles can be made in good yields from *O*-phenyl oximes containing pent-4-ene acceptors. However, the analogous process with a hex-5-enyl acceptor did not yield a dihydropyridine; probably because the 6-*exo-trig* iminyl radical ring closure was too slow to compete with H-atom abstraction. Reduction of dihydropyrrole **10b** gave 2-(5-methylpyrrolidin-2-yl)ethanol **11b**, which seemed suitable for conversion to a pyrrolizidine. In practice, treatment of **11b** under Appel type conditions yielded only 2-(but-3-enyl)pyrrolidine **14**. It is probable that this results from base attack on the 5-methyl group of a pyrrolizidinyl-ammonium ion intermediate in a Hofmann elimination. If this explanation is correct, similar eliminations can be expected for other 5-alkyl-substituted analogs.

Suitably substituted iminyl radicals ring closed readily onto aromatic acceptors, thus enabling several *N*-heterocyclic systems to be accessed. The favored mode of cyclization was 6-*endo* in this case because this generated resonance-stabilized cyclohexadienyl (or analogous) radicals. Quinoline was made from 3-phenylpropanone via the *O*-phenyl oxime; a process with obvious further scope. Syntheses of phenanthridines starting from 2-formylbiphenyls were particularly efficient and this approach enabled the natural product trisphaeridine to be made. Starting from 2-phenylnicotinaldehyde, and derivatives, ring closures of the derived iminyl radicals onto the phenyl rings yielded benzo[*h*][1,6]naphthyridines. Similarly, ring closure onto a phenyl ring from benzothiophene-based iminyl yielded benzo[*b*]thieno[2,3-*c*]quinoline. It was found that the analogous iminyl ring closure onto pyridine rings did not compete with other reactions of the iminyl radical. However, iminyl radical closure onto indole enabled indolopyridines to be prepared. This latter route was exploited in a short formal synthesis of neocryptolepine starting from 2-((1*H*-indol-3-yl)methyl)cyclohexanone. It is clear that microwave-assisted reactions of *O*-phenyl oximes are promising as "clean" and flexible routes to many biologically active compounds.

Experimental Section

General Procedure for Preparation of *O*-Phenyl Oximes. *O*-Phenylhydroxylamine hydrochloride (200 mg, 1.5 mmol) was dissolved in anhydrous pyridine (4.0 mL) under N_2 at room temperature, and the carbonyl compound (1.5 mmol) was added in one portion. The resulting solution was stirred at room temperature overnight, and the progress of the reaction was monitored by TLC (EtOAc/hexane, 1:2). Upon completion, the reaction mixture was poured into water (4.0 mL) and extracted with EtOAc (3 × 10 mL), and the combined organic phases were washed several times with saturated, aqueous $CuSO_4$ solution to remove any traces of pyridine. The solution was then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc/hexane).

(5*E*)-6,10-Dimethylundeca-5,9-dien-2-one *O*-Phenyl Oxime (9a). Red oil, 71%; two isomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50−1.78 (12H, m, CH_3), 2.08 (4H, m, CH_2), 2.32 (4H, m, CH_2), 5.12 (1H, m, CH), 5.19 (1H, m, CH), 6.98 (1H, J = 7.3 Hz, CH), 7.21 (2H, m, CH), 7.31 (2H, m, CH); ^{13}C NMR δ 11.3/14.1, 20.4, 23.1 (CH_3), 24.2/24.3 (CH_2), 25.3 (CH_3), 26.7, 30.0/30.2, 40.0 (CH_2), 115.0 (CH × 2), 122.0, 123.1, 124.3, 129.8 (CH × 2), 131.3, 136.5, 159.8, 161.5/161.8 (C); IR 2965, 1590, 1488 cm^{-1}; HRMS (CI^+) calcd for $C_{19}H_{28}NO$ 286.2171; found 286.2177.

General Procedure for Suzuki Coupling.[41] The bromo-compound (3 mmol) and the boronic acid (3 mmol) were dissolved in toluene (40 mL), and sodium carbonate (6 mmol, 2M) was added. To this reaction mixture was added ethanol (2 mL) followed by tetrakis(triphenylphosphine)-palladium (2%). The reaction mixture was refluxed overnight under N_2 and then diluted with water, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with water (3 × 30 mL) and brine (1 × 30 mL) dried over $MgSO_4$ and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/EtOAc).

4-(3-Formylpyridin-2-yl)benzonitrile (38b). White solid, 63%; 138−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (1H, t, J = 8.0, CH), 7.65 (2H, d, J = 8.5 Hz, CH), 7.76 (2H, d, J = 8.5 Hz, CH), 8.27 (1H, dd, J = 7.9, 1.8 Hz, CH), 8.84 (1H, dd, J = 4.7, 1.7 Hz, CH), 9.97 (1H, s, CH); ^{13}C NMR δ 113.5, 118.3 (C), 123.6 (CH), 129.8 (C), 131.0 (CH × 2), 132.4 (CH × 2), 136.4 (CH), 141.5 (C), 153.8 (CH), 160.0 (C), 190.8 (CH); IR 3020, 2233, 1699, 1581 cm^{-1}; HRMS (CI^+) calcd for $C_{13}H_9N_2O$ 209.0715; found 209.0712.

General Procedure for Microwave-Induced Reactions of *O*-Phenyl Oximes. The *O*-phenyl oxime (∼100 mg) and emimPF_4 (1 equiv) were dissolved in toluene (sufficient to make the solution 0.15 M) in a microwave vessel (2−5 mL). For ring closures onto aromatic acceptors, *tert*-butylbenzene was used as solvent. The vessel was sealed and subjected to microwave irradiation for 15 min at 160 °C (30 min for aromatic acceptors) in a Biotage Initiator system. The temperature was measured by an infrared temperature probe that determined the temperature on the surface of the vial. After cooling the ionic liquid was filtered off and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (25% EtOAc/hexane).

5-Methyl-2-(6-methylhept-5-en-2-yl)-3,4-dihydro-2*H*-pyrrole (10a). Yellow oil, 70%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71/0.89 (3H, d, J = 6.8 Hz, CH_3), 1.09 (1H, m, CH_2), 1.32−1.54 (2H, m, CH_2), 1.53 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.78−1.92 (2H, m, CH_2), 1.95 (3H, s, CH_3), 2.05 (2H, m, CH_2), 2.36 (2H, m, CH_2), 3.80 (1H, m, CH), 5.04 (1H, m, CH); ^{13}C NMR δ 14.6/16.3, 17.7, 19.7 (CH_3), 24.5 (CH_2), 25.7 (CH_3), 25.8/26.2, 32.9/34.3 (CH_2), 37.1/37.8 (CH), 39.1/39.2 (CH_2), 77.3/77.9, 124.8/124.9 (CH), 131.4, 174.0 (C); IR 2964, 1652 cm^{-1}; HRMS (CI^+) calcd for $C_{13}H_{24}N$ 194.1909; found 194.1909.

2-(Cyclohexylmethyl)-5-methyl-1*H*-pyrrole (18). Orange oil, 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75−1.71 (11H, m, CH_2, CH), 2.16 (3H, s, CH_3), 2.33 (2H, d, J = 7.1 Hz, CH_2), 5.70 (2H, m, CH), 7.45 (1H, s, NH); ^{13}C NMR δ 12.0 (CH_3), 25.3 (CH_2 × 2), 25.4, (CH_2), 32.2 (CH_2 × 2), 34.9 (CH_2), 37.8, 104.6, 104.8 (CH), 124.6, 129.0 (C); IR 3370, 2921, 1595, 1448 cm^{-1}. HRMS (CI^+) calcd for $C_{12}H_{20}N$ 178.1596; found 178.1601.

Phenanthridine-3-carbonitrile (29c). Yellow solid, 66%; mp 117−119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75−7.83 (2H, m, CH), 7.90 (1H, t, J = 7.8 Hz, CH), 8.06 (1H, d, J = 7.7 Hz, CH), 8.46 (1H, d, J = 1.6 Hz, 1H), 8.58 (2H, d, J = 8.9 Hz, 2H), 9.31 (1H, s, CH); ^{13}C NMR δ 112.0, 118.6 (C), 122.5, 123.7 (CH), 127.0, 127.4 (C), 128.7, 129.2, 129.4 (CH), 131.5 (C), 132.0, 135.1 (CH), 143.7 (C), 155.5 (CH); IR 3020, 2232, 1593, 1480 cm^{-1}. HRMS (ES^+) calcd for $C_{14}H_9N_2$ 205.0766; found 205.0764.

Benzo[*k*]phenanthridine (31).[42] Brown solid, 64%; mp 108−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.77 (4H, m, CH), 7.89 (1H, d, J = 8.4 Hz, CH), 7.96 (1H, d, J = 8.4 Hz, CH), 8.02 (1H, d, J = 7.0 Hz, CH), 8.26 (1H, d, J = 8.1, 1.6 Hz, CH), 9.05 (1H, d, J = 8.5 Hz, CH), 9.15 (1H, d, J = 8.0 Hz, CH), 9.29 (1H, s, CH); ^{13}C NMR δ 119.0, 124.1 (CH), 124.2 (C), 125.8, 125.9, 126.0

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(CH), 126.5 (C), 127.1, 127.2 (CH), 127.4 (C), 127.8, 128.0, (CH), 128.0, (C), 129.2 (CH), 134.2, 145.7 (C), 151.6 (CH); IR 2923, 1579, 1451, 1381 cm^{-1}.

[1,3]Dioxolo[4,5-*j*]phenanthridine (Trisphaeridine, 35).[43] Brown solid, 70%; mp 144−146 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.00 (2H, s, CH_2), 7.33 (1H, s, CH), 7.62 (1H, td, J = 7.5, 1.5, CH), 7.62 (1H, td, J = 7.5, 1.2 Hz, CH), 7.91 (1H, s, CH), 8.13 (1H, dd, J = 7.4, 1.2 Hz, CH), 8.37 (1H, dd, J = 8.4, 1.2 Hz, CH), 9.08 (1H, s, CH); ^{13}C NMR δ 99.9 (CH), 101.9 (CH_2), 105.5, 122.0 (CH), 123.0, 124.3 (C), 126.7, 128.0, 130.0 (CH), 130.3, 144.0, 148.2, 151.5 (C), 151.7 (CH); IR 2904, 1620, 1580, 1498, 1464 cm^{-1}; HRMS (CI^+) calcd for $C_{14}H_{10}NO_2$ 224.0712; found, 224.0712.

Benzo[*h*][1,6]naphthyridine (40a).[44] Brown solid, 66%; mp 95−97 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (1H, dd, J = 8.0, 4.4 Hz, CH), 7.72 (1H, t, J = 7.6 Hz, 7.81 (1H, t, J = 7.6 Hz, CH), 8.20 (1H, d, J = 8.3 Hz, CH), 8.31 (1H, dd, J = 8.0, 1.8 Hz, CH), 9.10 (1H, d, J = 8.0 Hz, CH), 9.14 (1H, dd, J = 4.4, 1.8 Hz, CH), 9.27 (1H, s, CH); ^{13}C NMR δ 120.3 (C), 120.7 (CH), 125.1 (C), 127.6, 127.8, 129.2, 129.4, 140.8 (CH), 146.2, 147.4 (C), 151.6, 152.4 (CH); IR 1589, 1440 cm^{-1}. HRMS (CI^+) calcd for $C_{12}H_9N_2$ 181.0766; found 181.0761.

[1]Benzothieno[2,3-*c*]quinoline (44). Brown solid, 53%; mp 129−131 °C, ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (2H, m, CH), 7.71 (2H, m, CH), 8.01 (1H, m, CH), 8.26 (1H, m, CH), 8.84 (2H, m, CH), 9.30 (1H, s, CH); ^{13}C NMR δ 121.9, 122.8, 124.4 (CH), 124.5 (C), 125.1 (CH), 126.6 (CH × 2), 126.9, 129.7 (CH), 131.6, 132.3, 134.2, 140.5, 141.5 (C), 145.2 (CH); IR 3018, 1502 cm^{-1}. HRMS (CI^+) calcd for $C_{15}H_{10}NS$ 236.0534; found 236.0538.

2-Methyl-9*H*-pyrido[2,3-*b*]indole (46).[45] Brown solid, 59%; mp 219−220 °C**;** ^1H NMR (400 MHz, $CDCl_3$) δ 2.67 (3H, s, CH_3), 7.00 (1H, d, J = 7.8 Hz, CH), 7.18 (1H, m, CH), 7.43 (2H, m, CH), 7.95 (1H, d, J = 7.7 Hz, CH), 8.17 (1H, d, J = 7.8 Hz, CH), 9.42 (1H, s, NH); ^{13}C NMR δ 24.2 (CH_3), 111.3, 115.3 (CH), 115.5 (C), 120.4, 120.7 (CH), 120.8 (C), 126.6, 129.4 (CH), 139.5, 143.8, 146.3 (C); IR 1602, 1456, 1417 cm^{-1}. HRMS (CI^+) calcd for $C_{12}H_{11}N_2$ 183.0922; found 183.0928.

6*H*-1,2,3,4-Tetrahydroindolo[2,3-*b*]quinoline (49).[37a] Brown solid, 69%; mp 220−221 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.79−1.98 (4H, m, CH_2), 2.90 (2H, t, J = 6.11 Hz, CH_2), 3.10 (2H, t, J = 6.5 Hz, CH_2), 7.16 (1H, t, J = 7.4 Hz, CH), 7.36 (1H, t, J = 7.5 Hz, CH), 7.43 (1H, d, J = 8.1 Hz, CH), 7.91 (1H, d, J = 7.7 Hz, CH), 7.96 (1H, s, CH), 10.20 (1H, s, NH); ^{13}C NMR δ 22.2, 22.2, 28.0, 31.7 (CH_2), 110.2 (CH), 113.9 (C), 118.8, 119.6 (CH), 120.1, 122.8 (C), 125.4, 128.5 (CH), 137.9. 149.4, 152.5 (C); IR 3128, 2931, 1609, 1458 cm^{-1}. HRMS (CI^+) calcd for $C_{15}H_{15}N_2$ 223.1235; found 223.1231.

Acknowledgment. We thank GSK and EaStChem for financial support and Dr. M. C. Clarke and Prof. R. Morris for the loan of microwave reactors.

Supporting Information Available: Preparation and characterization of *O*-phenyl oxime ethers, aromatic carbonyl compounds and *N*-heterocycles. NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800847H

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