2-(Aminoaryl)alkanone *O*-phenyl oximes: versatile reagents for syntheses of quinazolines

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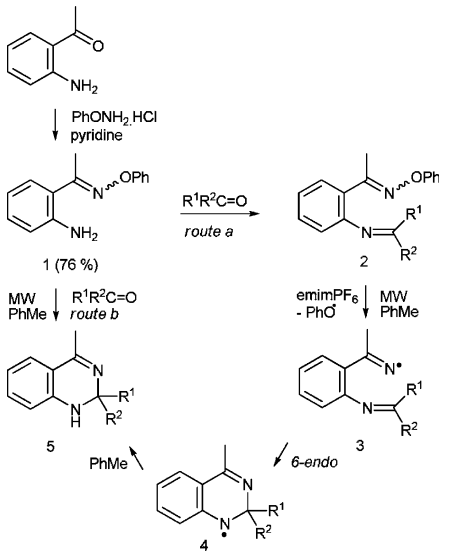
Microwave irradiations of 2-(aminoaryl)alkanone *O*-phenyl oximes and carbonyl compounds generate iminyl radicals in company with imines; iminyl on imine ring closure yields dihydroquinazolines or quinazolines when $ZnCl_2$ is included in the mixture.

The quinazoline ring is an important structural motif in many biologically active compounds. Interest in new ways of making derivatives is high because anticancer, antibacterial, anticonvulsant and diuretic activities have been reported for various quinazoline alkaloids.[1,2a–c] For example, 2-substituted-4-aminoquinazolines are known to be potent against several bacterial strains.[3] 1,2-Dihydro-4-aminoquinazoline derivatives are effective and selective inhibitors of inducible nitric oxide synthase and show anti-inflammatory activity *in vivo*.[4] With the exception of the $CuCl_2$ catalysed reaction of aldehydes with anthranilamide,[5] methods of forming the quinazoline ring either require multi-step preparations of special reagents/reactants or give moderate yields.[6]

Thermolyses of model *O*-phenyl oxime ethers were shown to release simple dialkyl- and diaryl-iminyl radicals together with phenoxyl radicals. In fact, the N–O bond dissociation enthalpies [BDE(R_2CN–OPh) $\sim$ 140 kJ mol^{-1} for R = Me or Ph] were found to be lower than the O–O BDEs of dialkyl peroxides [159–167 kJ mol^{-1}].[7] We recently discovered that for the special case of alkenone *O*-phenyl oximes, microwave irradiation was a suitable method for release of unsaturated iminyl radicals which ring closed to afford dihydropyrroles in good yields.[8,9]

We reasoned that other heterocycles could probably be made by using *O*-phenyl oximes containing different types of radical acceptors in their side chains. In particular, by use of imine functionality in the side chain, di-aza-heterocycles might be accessible under mild, neutral conditions with all the convenience and rapidity of a microwave-assisted process. The *O*-phenyl oxime of 2-aminoacetophenone **1** can be made in good yield by treatment of this ketone with commercially available *O*-phenylhydroxylamine hydrochloride.[7] Imines **2** *could* be made by condensation of **1** with aldehydes or ketones in the conventional way (*route a*, Scheme 1). On irradiation with microwaves the weak N–O bond of **2** should break releasing iminyl radical **3** together with the resonance-stabilised phenoxyl radical. The architecture of iminyl radical **3** favours ring closure onto the N=C bond in the 6-*endo*-trig mode because the resultant aminyl radical **4** will be strongly resonance stabilised. Hydrogen abstraction from the toluene solvent should then furnish dihydroquinazoline **5**.



Scheme 1 Projected annulations of 2-aminoacetophenone *O*-phenyl oxime with carbonyl compounds.

We conjectured, however, that the imine forming condensation would also be promoted by microwaves. There was a possibility therefore of assimilating imine formation with radical generation thus enabling the whole sequence to be combined in one pot (*route b*, Scheme 1).

To test this novel annulation sequence pent-4-enal (1 equiv.) and oxime ether **1** (1 equiv.) in toluene solution with 1-ethyl-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate ($emimPF_6$) as ionic liquid, were irradiated with microwaves (nominally 300 MHz) in a Biotage Initiator closed reactor. Dihydroquinazoline **5b** (R^1 = H, R^2 = but-3-enyl) was indeed formed with toluene as the H-atom donor solvent. After 30 min irradiation the ^{1}H NMR spectrum of the total product showed a very clean mixture with essentially quantitative production of **5b** together with an equal amount of phenol.[10] The latter is formed by H-abstraction from solvent by the co-produced phenoxyl radicals and is easily separated.

Table 1 shows that reactions with aliphatic aldehydes delivered the corresponding dihydroquinazolines in high yields (entries 1–3). Reaction of **1** with benzaldehyde gave a 72% yield of the corresponding dihydroquinazoline (entry 4). For other aromatic aldehydes, and for ketones, the reactions tended to be incomplete and lower yields were obtained. However, cyclohexanone afforded an interesting

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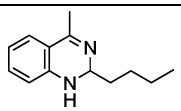
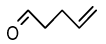
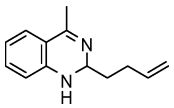
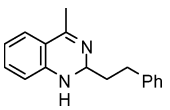
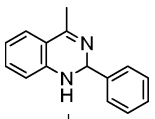
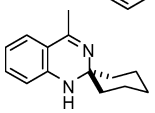
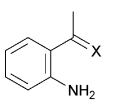
Table 1 Yields of dihydroquinazolines from reactions of **1**

Entry	Carbonyl compound	Dihydroquinazoline	Yield (mol%)[a]
1			91
2			94[b]
3			92[b]
4	PhCHO		72
5			78

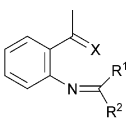
[a] *Reaction conditions*: emimPF_6 (1 equiv.), solvent: PhMe, MW for 30 min at 160 °C. All yields are isolated yields. [b] Solvent: *t*-BuOH.

spirodihydroquinazoline (entry 5) in a very acceptable yield of 78%. The 1,2-dihydroquinazolines with only one substituent at the 2-position (entries 1–4) slowly oxidised to the corresponding quinazolines over a period of weeks when stored in air at rt.

If H-atom abstraction from solvent by the iminyl radical generated from **1** before imine formation had been important, then **6a** or its hydrolysis product **6b** should have been formed.



6a; X=NH
b; X=O



7a; X=NH
b; X=O

Similarly, if H-atom abstraction from solvent by radical **3** had been faster than ring closure then **7a**, or its hydrolysis product **7b**, should have been detected. In practise, neither **6a**,**b** nor **7a**,**b** were observed. Imine production from **1** and an aldehyde takes place *via* a series of equilibria involving hemiaminal formation, water loss and several protonation/deprotonation steps. The dehydration step is acid catalysed and the rates of individual steps depend on pH and on solvent.[11] The absence of **6a**,**b** shows that the equilibria must be fast in comparison with radical generation. The step **3** → **4** is a novel 6-*endo*-trig cyclisation of an iminyl radical onto a C=N bond. Kinetic data for this particular type of ring closure are not available. However, the known rate constants for 6-*endo*-trig cyclisations of C-centred radicals onto C=N bonds,[12] and for iminyl radicals onto C=C bonds,[13,14] suggest **3** → **4** would be a fast process at 160 °C with a rate constant at least equal to that of a C-centred radical onto a C=C bond, and probably greater because of the resonance stabilisation in **4**. This is consistent with the absence of compounds **7a**,**b** in the product mixture. Evidently imine is rapidly trapped by the cyclisation step but the fast imine formation equilibria ensure a constant supply until reactant depletion sets in.

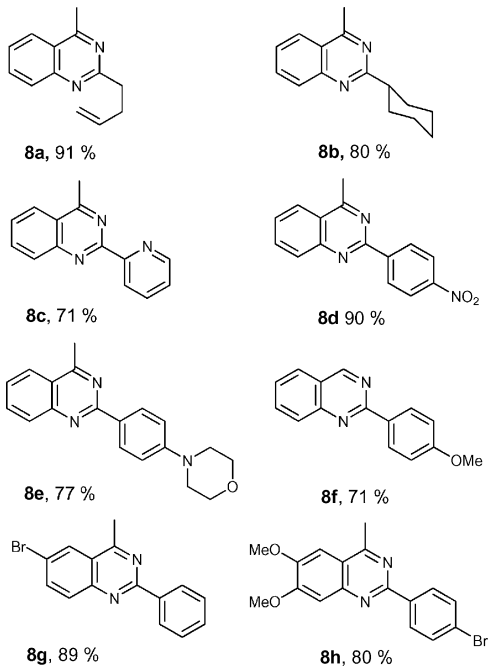


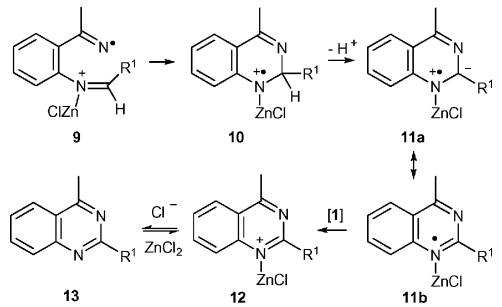
Fig. 1 Quinazolines prepared in $ZnCl_2$ promoted reactions of **1** with aldehydes.

It is known that imine formation is promoted by inclusion of zinc chloride.[15] We surmised, therefore, that addition of $ZnCl_2$ as a promoter would improve the product yields when less reactive carbonyl compounds were employed. When pent-4-enal was reacted with **1** in the presence of 0.3 equivalents of $ZnCl_2$, a high yield was obtained, but the interesting outcome was that the quinazoline, rather than the dihydroquinazoline, was formed under these circumstances.

Products and yields of quinazolines obtained from annulations with a variety of aldehydes are shown in Fig. 1.[16] High yields of quinazolines **8a** and **8b** were obtained from **1** with the aliphatic aldehydes pent-4-enal and cyclohexanecarbaldehyde, respectively. The aromatic 4-nitrobenzaldehyde gave **8d** also in high yield (90%). Somewhat lower, but still useful, yields of quinazolines were obtained on starting with aromatic aldehydes containing electron donating substituents, as **8e** and **8f** demonstrate. Similarly, the annulation worked well with pyridine-2-carbaldehyde (→**8c**).

To probe the sensitivity of the reaction to substituents in the aryl ring, and at the 4-position of the quinazoline, *O*-phenyl oxime ethers of 2-aminobenzaldehyde, 5-bromo-2-aminoacetophenone and 4,5-dimethoxy-2-aminoacetophenone were prepared. The formation of quinazolines **8f**, **8g** and **8h** all in good yields (Fig. 1) showed that the reaction tolerates a good range of functionality in the aminoketones as well as in the partner aldehydes.

The change to aromatic quinazolines when $ZnCl_2$ is included might signal a change in mechanism. It is known from previous work[7,8] that the precursor *O*-phenyl oximes are completely dissociated to radicals in <30 min under the microwave conditions. To compete, any alternative mechanism would have to be faster than this.[17] Possibly the zinc bonds



Scheme 2 Possible role of zinc chloride in quinazoline formation.

to the imine nitrogen prior to cyclisation *i.e.* **9** and the subsequent ring closure gives amminium radical cation **10** in a process akin to an iminium salt cyclisation. The adjacent cation would considerably lower the pK_a of the H-atom at position 2 of the heterocycle **10**. Proton loss would then yield **11** in a process reminiscent of the Minisci reaction (Scheme 2).[18] Stabilised intermediate **11** might transfer an electron to the starting oxime ether to give **12** or be converted to **13** on exposure to oxygen during work-up. When the $ZnCl_2$ is not present, the C–H at position 2 is not acidic, and hence aromatisation to a quinazoline does not occur.[19]

Overall, this process is a two-stage synthetic route from 2-aminoarylalkenones *via* their *O*-phenyl oximes and thence by a one pot procedure with carbonyl compounds to dihydroquinazolines or quinazolines. The process is of wide scope and works well with alkyl, aryl and heterocyclic types of aldehyde. The reaction has several advantages over existing methods for quinazoline synthesis. It is rapid (30 min) and requires no acids, bases, or toxic metals. It is comparatively mild and high yielding. The *O*-phenyl oximes are easily made in one step and can be stored indefinitely. Unlike many other radical-mediated synthetic methods, no initiator is needed and hence no by-products from initiator fragments contaminate the system. There is evidently a promising future for microwave-assistance in reactions where the initial step is homolysis of a weak bond in a reactant molecule, *O*-phenyl oxime ethers being prime examples.

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Notes and references

1. J. P. Michael, *Nat. Prod. Rep.*, 2003, **20**, 476.
2. (*a*) J. H. Chan, J. S. Hong, L. F. Kuyper, M. L. Jones, D. P. Baccanari, R. L. Tansik, C. M. Boytos, S. K. Rudolf and A. D. Brown, *J. Heterocycl. Chem.*, 1997, **34**, 145; (*b*) S. L. Gackenheimer, J. M. Schaus and D. R. Gehlert, *J. Pharmacol. Exp. Ther.*, 1995, **274**, 1558; (*c*) R. O. Dempcy and E. B. Skibo, *Biochemistry*, 1991, **30**, 8480.
3. P.-P. Kung, M. D. Casper, K. L. Cook, L. Wilson-Lingardo, L. M. Risen, T. A. Vickers, R. Ranken, L. B. Blyn, J. R. Wyatt, P. D. Cook and D. J. Ecker, *J. Med. Chem.*, 1999, **42**, 4705.
4. A. C. Tinker, H. G. Beaton, N. Broughton-Smith, T. R. Cook, S. L. Cooper, L. Fraser-Rae, K. Hallam, P. Framley, T. McInally, D. J. Nicholls, A. D. Pimm and A. V. Wallace, *J. Med. Chem.*, 2003, **46**, 913.
5. R. J. Abdel-Jalil, W. Völter and M. Saeed, *Tetrahedron Lett.*, 2004, **45**, 3475.
6. For reviews of quinazoline synthetic methods see: (*a*) D. J. Connolly, D. Cusack, T. P. O'Sullivan and P. J. Guiry, *Tetrahedron*, 2005, **61**, 10153; (*b*) K. Undheim and T. Benneche, in *Comprehensive Heterocyclic Chemistry II*, ed. A. J. Boulton, Pergamon, Oxford, 1998, vol. **6**, pp. 93.
7. J. A. Blake, D. A. Pratt, S. Lin, J. C. Walton, P. Mulder and K. U. Ingold, *J. Org. Chem.*, 2004, **69**, 3112.
8. F. Portela-Cubillo, J. S. Scott and J. C. Walton, *Chem. Commun.*, 2007, 4041.
9. For alternative methods of generating iminyl radicals see: (*a*) S. Z. Zard, *Synlett*, 1996, 1149; (*b*) L. E. Kaim and C. Meyer, *J. Org. Chem.*, 1996, **61**, 1556; (*c*) K. Takai, N. Katsura and Y. Kunisada, *Chem. Commun.*, 2001, 1724; (*d*) J. Boivin, E. Fouquet and S. Z. Zard, *Tetrahedron Lett.*, 1991, **32**, 4299; (*e*) J. Boivin, A.-M. Schiano and S. Z. Zard, *Tetrahedron Lett.*, 1992, **33**, 7849; (*f*) M. Kitamura, Y. Mori and K. Narasaka, *Tetrahedron Lett.*, 2005, **46**, 2373; (*g*) M. Yoshida, M. Kitamura and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 2003, **76**, 2003; (*h*) R. Alonso, P. J. Campos, B. Garcia and M. A. Rodriguez, *Org. Lett.*, 2006, **8**, 3521; (*i*) T. Mikami and K. Narasaka, *Chem. Lett.*, 2000, 338; (*j*) D. Nanni, P. Pareschi, C. Rizzoli, P. Sgarabotto and A. Tundo, *Tetrahedron*, 1995, **51**, 9045; (*k*) R. Leardini, H. McNab, M. Minozzi and D. Nanni, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1072.
10. The option of the aminyl radical **4b** undergoing a second 5-*exo*-trig cyclisation onto the butenyl chain to afford a tricyclo-radical, with final production of a tetrahydropyrrolo[1,2-*a*]quinazoline, is a clear possibility for this species. However, none of this product was detected and evidently H-atom abstraction by **4b** from the toluene solvent is too fast for the second cyclisation to compete.
11. (*a*) J. Hine, M. S. Cholod and W. K. Chess Jr, *J. Am. Chem. Soc.*, 1973, **95**, 4270; (*b*) J. Hine and Y. Chou, *J. Org. Chem.*, 1981, **46**, 649.
12. S. Kim, K. S. Yoon and Y. S. Kim, *Tetrahedron*, 1997, **38**, 73.
13. M.-H. Le Tadic-Biadatti, A.-C. Callier-Dublanchet, J. H. Horner, B. Quiclet-Sire, S. Z. Zard and M. Newcomb, *J. Org. Chem.*, 1997, **62**, 559.
14. A. G. Fallis and I. M. Brinza, *Tetrahedron*, 1997, **53**, 17543.
15. A. Pouilhes, Y. Langlois and A. Chiaroni, *Synlett*, 2003, 1488.
16. Experimental details for the preparation of **8d** are typical of the methodology for all the quinazolines. 4-Nitrobenzaldehyde (66 mg, 0.44 mmol) was added to a solution of 1-(2-aminophenyl)-ethanone *O*-phenyl oxime **1** (100 mg, 0.44 mmol) in toluene (0.15 M), containing anhydrous $ZnCl_2$ (17 mg, 0.13 mmol) and emimPF_6 (100 mg, 0.46 mmol) in a microwave vessel (2–5 cm^3). The vessel was sealed and subjected to microwave irradiation for 30 min at 160 °C in a Biotage Initiator system (nominally 300 MHz). After cooling, the ionic liquid was filtered off and the toluene was removed under reduced pressure. The residue was purified by flash column chromatography (5% EtOAc–hexane) affording 4-methyl-2-(4-nitrophenyl)quinazoline **8d** as a yellow solid (105 mg, 90%). Mp 168–179 °C; ν_{max}/cm^{-1} = 1597, 1569, 1548, 1340; ^{1}H NMR (400 MHz, $CDCl_3$), δ_H 2.96 (s, 3H, CH_3), 7.58 (ddd, J = 8.2, 7.6, 1.2 Hz, 1H, CH), 7.84 (ddd, J = 8.5, 7.0, 1.4 Hz, 1H, CH), 8.02 (d, J = 7.8 Hz, 1H, CH), 8.04 (d, J = 7.8 Hz, 1H, CH), 8.26 (d, J = 9.0 Hz, 2H, CH), 8.72 (dt, J = 9.0, 2.0 Hz, 2H, CH); ^{13}C NMR δ_C 21.5 (CH_3), 122.3 (C), 122.6, 124.3, 126.9, 128.4, 128.3, 133.0 (CH), 143.0, 148.1, 149.2, 156.8, 167.8 (C); HRMS calcd for $C_{15}H_{12}N_3O_2$ (MH^+) 266.0930, found 266.0936. Dihydroquinazolines were prepared in essentially the same way, except that the zinc chloride was omitted.
17. Electrocyclic ring closures of imines **2** to 3-phenoxy-2,3-dihydroquinazolines followed by elimination of $PhOR^1$ or $PhOR^2$ could give the quinazoline products. However, precedents suggest it is unlikely both these steps could be fast enough to compete with the radical process (see ref. 20).
18. (*a*) F. Fontana, F. Minisci, M. C. N. Barbosa and E. Vismara, *J. Org. Chem.*, 1991, **56**, 2866; (*b*) F. Minisci, F. Recupero, C. Punta, C. Gambarotti, F. Antonietti, F. Fontana and G. F. Pedulli, *Chem. Commun.*, 2002, 2496.
19. We thank an anonymous referee for suggesting this mechanism.
20. B. M. Trost and A. C. Gutierrez, *Org. Lett.*, 2007, **9**, 1473.