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Microwave-Promoted Syntheses of Quinazolines and Dihydroquinazolines from 2-Aminoarylalkanone *O*-Phenyl Oximes

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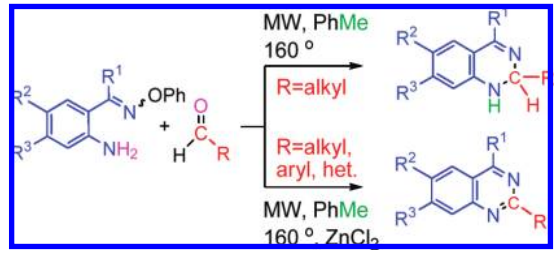

A wide range of biologically active compounds contain the quinazoline ring system. A new free-radical-based method of making functionalized quinazolines is described, which relies on microwave-promoted reactions of *O*-phenyl oximes with aldehydes. A small set of 2-aminoaryl alkanone *O*-phenyl oximes was prepared and shown to produce dihydroquinazolines when mixed with an aldehyde in toluene and subjected to microwave heating. When $ZnCl_2$ was included in the reaction mixture, fully aromatic quinazolines were produced in high yields by a rapid and convenient process. The method worked well with alkyl, aryl, and heterocyclic aldehydes and for a variety of substituents in the benzenic part of the molecule. Similar reactions employing ketones instead of aldehydes were less efficient. Although some dihydroquinazolines did form, they were accompanied by several byproducts. Surprisingly, in each case, one of the byproducts was a quinoline derivative, and a plausible mechanism to account for this rearrangement is proposed.

Introduction

Quinazoline derivatives are among the most potent tyrosine kinase and cellular phosphorylation inhibitors,[1] and they also show remarkable activity as antitubercular, antiviral, and anticancer agents.[2] They have been used as DNA ligands,[3] they bind to adenosine receptors,[4] and are potent antibacterial agents.[5] It is no surprise, therefore, that the quinazoline ring system forms the basis of many pharmaceutical, agrochemical, and veterinary products. The growing importance of quinazolines in medicine is highlighted by the huge sales of the drugs Erlotinib, which is used in the treatment of several types tumors,[6] and Prazosin, an α-adrenergic blocker.[7] Likewise, Iressa, an epidermal growth factor receptor inhibitor, was recently approved by the U.S. Food and Drug Administration for the treatment of lung cancer[8] (Figure 1). The quinazoline unit represents a useful natural product scaffold with demonstrated activities against numerous disorders. The transferable nature of its properties provides a strong rationale for the development of synthetic methods.

Not surprisingly, considerable progress in synthetic methodology applicable to quinazoline alkaloids has been made during the past decade.[9] The following are among the most important

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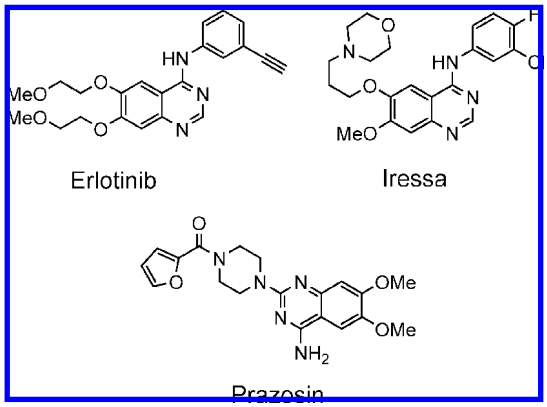

FIGURE 1. Popular drugs containing the quinazoline unit.

preparative methods relying on conventional wet organic methodology: (a) aza-Wittig and tandem aza-Wittig/6π-electrocyclization procedures[10] have been applied in preparations starting from *N*-imidoyl iminophosphoranes.[11] (b) Three-component systems consisting of an aldehyde, morpholine, and an aryl azide react to yield triazolines that are converted into quinazolines by ethanolic ammonia.[12] (c) Condensations of a cyano- or nitro-activated *o*-fluorobenzaldenyde with an amidine yield imines that undergo intramolecular nucleophilic aromatic substitution at the fluorine-substituted carbon, thus affording a variety of quinazolines.[12] (d) Amidines derived from 2-unsubstituted 4-arylaminoquinazolines are converted to 4-arylaminoquinazolines in good yields when heated with formic acid.[13] Furthermore, 2-amino-*N*′-phenylbenzimidamides react with aromatic aldehydes to yield 2-aryl-4-arylimino-2,3-dihydroquinazolines, which are easily oxidized to the corresponding quinazolines with potassium permanganate.[14] (e) A mild synthesis of 2,4-dihydroxyquinazolines uses 2-aminobenzonitrile and carbon dioxide in the presence of DBU.[15] (f) The intermediates formed from 2-aminobenzonitrile and Grignard reagents react with acid chlorides or anhydrides to afford quinazolines in moderate to good yields.[16] (g) 6-Substituted quinazoline-2,4-diones are readily prepared from anthranilamides by treatment with phosgene and can be converted to 2,4-dichloroquinazolines in excellent yields by refluxing in phosphorus oxychloride.[17] (h) A solid-supported method for the preparation of the 2,4-diaminoquinazoline ring system has also been developed.[18]

Microwave-assisted methods offer improved opportunities for reproducibility, rapid reaction optimizations, and the potential for discovery of new chemistry. Several examples of microwave-assisted syntheses of the quinazoline core have also been described. Anilines (protected as *N*-ethyl carbamates) with HMTA in TFA afforded quinazolines on microwave irradiation under pressure in a monomode reactor.[19] 4-Amino-2-arylquinazolines were obtained from cyano-aromatic compounds with anthranilonitrile in the presence of catalytic amounts of base.[20] Microwave-assisted reactions of *N*-(2-cyanophenyl)-*N*,*N*-dimethylformamidine derivatives and amines, with a catalytic amount of acetic acid, gave 4-aminoquinazolines in high yields.[21] Recently, a solvent- and catalyst-free approach toward the selective synthesis of quinazolines and benzo[*g*]quinazolines from *N*-arylamidines with various aldehydes has been developed.[22] 2,4-Disubstituted quinazolines were obtained from 2-aminoacylbenzenes by N-acylation and rapid cyclization in the presence of ammonium formate under microwave heating.[23] Microwave-assisted cyclizations of 2-aminoaryl imines with aldehydes provided good yields of novel 2,4-disubstituted quinazolines.[24] Microwave irradiations of solutions of *N*-arylimino-4-chloro-5*H*-1,2,3-dithiazoles, in the presence of sodium alkoxide, in the corresponding alcohol, gave good yields of quinazolines even on multigram scales.[25] Various derivatives of indolo- and benzimidazo[1,2-*c*]quinazolines were obtained by condensation of appropriate diamines with benzothiazole-2-carbonitrile substituted on the benzenic part.[26] Anthranilic acid condenses with formamide under open-vessel microwave conditions to yield quinazolinones.[27]

Radical additions to imines and related compounds are gradually emerging as useful synthetic processes,[28] although imines can be difficult to handle because they are prone to hydrolysis and tautomerism. Attack at the carbon of the C=N bond is almost exclusively observed, especially for oxime ethers and hydrazones, where the stabilizing 3-electron π-bond in the adduct aminyl radical lowers the energy of the transition state. However, the competition between *5-exo* and *6-endo* cyclization of alkyl, aryl, and acyl radicals onto imines is intriguing. Warkentin and co-workers[29] studied the regioselectivity for the cyclization of an aryl radical onto an aldimine receptor and found a large *6-endo* preference (Scheme 1).

They provided evidence that formation of the C−C single bond was favored over the corresponding C−N bond by approximately 10 kcal/mol. In addition, the geometry inherent in the imine functional group, with a C−C=N angle of approximately 119°, is more suited to *endo* addition than is the

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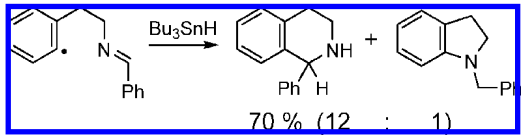
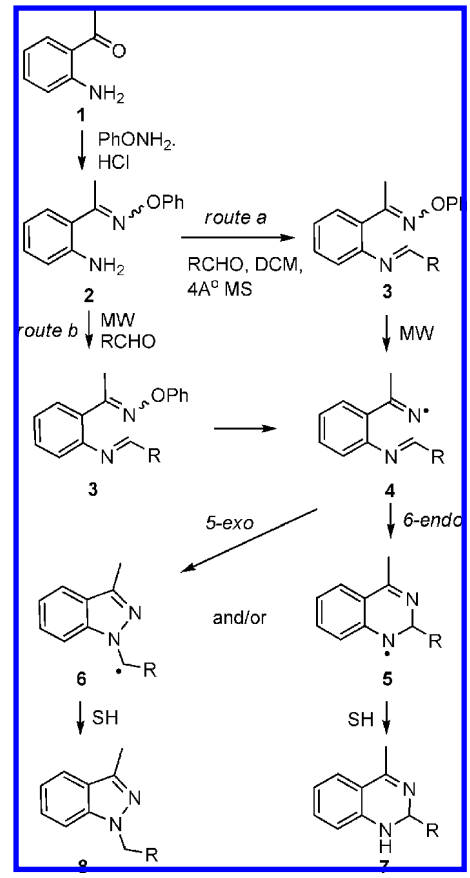
SCHEME 1. 6-*endo* Preference for Ring Closure of an Aryl Radical onto an Aldimine[29]



alkene group with a larger angle of approximately 125°. Despite numerous examples of radical additions to C═N bonds, there have been only a few cases where addition occurs at the nitrogen. In the case of imines, the "radical α-effect" is not possible, and thus it is surprising that addition does not occur more often at nitrogen, given the stabilization available through interaction of the adduct α-aminyl radical with the nonbonding electron pair on nitrogen. In the cases of additions at nitrogen known to date, additional stabilizing groups, conformational restriction, severe steric hindrance, or polar effects are present to encourage attack at nitrogen.[30] These and other examples[31] show that intramolecular additions of alkyl, aryl, vinyl, and acyl radicals onto imines constitute useful processes for syntheses of aza-heterocycles. Addition of iminyl radicals onto imines has not previously been reported, although the intramolecular version could constitute an attractive approach for the synthesis of diaza-heterocycles, such as quinazolines or benzopyrazoles.

Thermolyses of *O*-phenyl oxime ethers were shown to release simple dialkyl- and diaryl-iminyl radicals together with phenoxyl radicals.[32] Furthermore, we recently discovered that for alkenone *O*-phenyl and related oximes, microwave heating was a suitable method for release of unsaturated iminyl radicals that ring closed to afford a variety of aza-heterocycles in good yields.[33] 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, diaza-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 (**2**) can be made in good yield by treatment of ketone **1** with commercially available *O*-phenylhydroxylamine hydrochloride. Imines **3** could be made by condensation of **2** with aldehydes in the conventional way (route a, Scheme 2). However, it is known that microwave irradiation assists imine formation,[34] and the technique forms part of a standard method for syntheses of secondary amines.[35]

SCHEME 2. Sequential and One-Pot Reactions of 1-(2-Aminophenyl)ethanone *O*-Phenyl Oxime 2



We conjectured, therefore, that the imine-yielding step would also be promoted by microwaves and that there was the possibility of assimilating this with radical generation, thus enabling the whole sequence to be combined in one pot (route b, Scheme 2).

Competition between the 5-*exo* and 6-*endo* radical ring closures onto the C═N bond could lead to formation of **6** or **5**. It was likely, however, that the architecture of iminyl radical **4** would favor ring closure in the 6-*endo* mode because the resultant aminyl radical **5** would be strongly resonance-stabilized.

Furthermore, the *5-exo* approach of the nucleophilic iminyl radical to the nitrogen atom of the imine would be polarity-mismatched.[36] Together these two effects might lead to regiospecific 6-*endo* cyclization, despite the possible 3-electron π-bonding interaction in **6** (Scheme 2). We report in this paper that dihydroquinazolines and quinazolines can indeed be prepared in good to excellent yields by microwave-promoted reactions of **2** and related oxime ethers with a range of aldehydes and ketones. Part of this research has previously been published as a preliminary communication.[37]

Results and Discussion

Optimization of Dihydroquinazoline Preparation. The *O*-phenyl oxime ether **2** was prepared in 76% yield as a mixture of *E* and *Z* isomers by stirring 2-aminoacetophenone **1** with

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TABLE 1. Microwave-Assisted Reactions of Pent-4-enal with 2[a] at 160 °C[b]

entry	solvent	time (min)	IL	yield **7a**[c] (mol %)
1	toluene	15	$emimPF_6$	68
2	toluene	20	$emimPF_6$	74
3	toluene	25	$emimPF_6$	90
4	toluene	30	$emimPF_6$	94
5	toluene	35	$emimPF_6$	88
6	toluene	30	$emimPF_6$	81
7	*i*-PrOH	30	none	91
8	*t*-BuOH	30	none	83

[a] [**2**] = 0.15 M except for entry 6 where [**2**] = 0.2 M [b] In each case **7a** (R = but-3-enyl) was accompanied by PhOH, but no **8** was obtained. [c] **7a** (R = but-3-enyl).

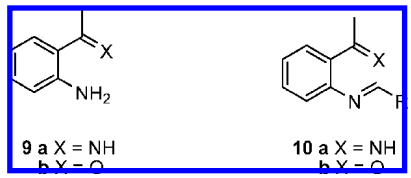


FIGURE 2. Potential products from premature H-atom abstractions.

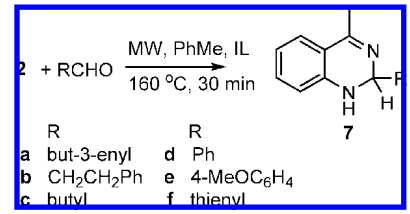
O-phenylhydroxylamine hydrochloride in pyridine at rt. The fact that two isomers were present did not matter because both released the same iminyl radical on scission of their N−O bonds. To test the annulation sequence of Scheme 2 and find the best reaction conditions, pent-4-enal (1 equiv) and oxime ether **2** (1 equiv) in various solvents, with and without $emimPF_6$ (1-ethyl-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate) as ionic liquid (IL), were irradiated with microwaves (nominally 300 MHz) in a Biotage Initiator closed reactor. A temperature of 160 °C was chosen on the basis of previous microwave-assisted reactions of oxime ethers.[33] As Table 1 shows, with toluene as H-atom donor solvent, dihydroquinazoline **7a** (R = but-3-enyl) was indeed formed.

The one-pot protocol incorporating hydrogen abstraction from toluene gave essentially quantitative production of **7a** with an equal amount of phenol in 30 min (entry 4). The latter is formed by H-abstraction from solvent by the co-produced phenoxyl radicals and was easily separated.

If H-atom abstraction from solvent, by an iminyl radical generated before imine formation, had been important, then **9a** or its hydrolysis product **9b** should have been obtained (Figure 2). Similarly, if H-atom abstraction from solvent by radical **4** had been faster than ring closure, then **10a** or its hydrolysis product **10b** should have been detected. In practice none of **9a,b** or **10a,b** was observed.

Imine production from **2** and an aldehyde will take place via a series of equilibria involving hemiaminal formation, water loss, and various protonation/deprotonation steps. The absence of **9a,b** shows that the equilibria must be fast in comparison with radical generation. Evidently, the imine intermediate was rapidly trapped by the cyclization step, but the fast imine formation equilibria ensured a constant supply until reactant depletion set in. At the same time, the plain fact that none of the benzopyrazole **8** was detected confirmed the regiospecific character of the ring closure. This can be accounted for by the strong resonance stabilization effect in **5** and the "polarity-mismatch" involved in formation of **6** (see above). The kinetics of this type of ring closure have not been studied. However, the known rate constants for 6-*endo-trig* cyclizations of C-centered radicals onto C=N bonds[36] and for iminyl radicals onto C=C bonds[38] suggest **4** → **5** would be a fast process at

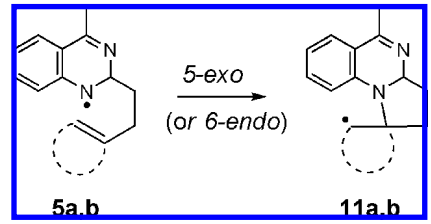
TABLE 2. Microwave-Assisted Reactions of 2 with Aldehydes



entry	aldehyde	dihydroquinazoline	yield (mol %)
1	pent-4-enal	**7a**	94
2	3-phenylpropanal	**7b**	92
3	pentanal	**7c**	91
4	benzaldehyde	**7d**	72
5	4-methoxy-benzaldehyde	**7e**	[51][a]
6	thiophene-2-carbaldehyde	**7f**	[46][a]

[a] Yield determined by ^1H NMR spectroscopy.

SCHEME 3. Potential Tandem Reaction of Aminyl Radical Intermediates

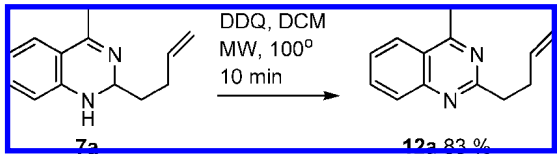


160 °C with a rate constant at least equal to that of a C-centered radical onto a C=C bond and probably greater because of the resonance stabilization in **5**. This is consistent with the absence of compounds **10a,b** (Figure 2) in the product mixtures.

The use of hydrogen donor solvents such as toluene or isopropanol allowed the iminyl radical sufficient lifetime to cyclize. Good yields were obtained in both solvents, although isopropanol was less convenient because its low boiling point led to the microwave vial being exposed to high pressures. The ionic liquid $emimPF_6$ was used together with toluene because of the poor microwave absorption properties of this solvent. Entries 1−5 show that at 160 °C the reaction needed an irradiation time of 30 min to achieve complete conversion but that at longer times side reactions/degradative processes set in. However, for larger concentrations of precursor **2** in toluene (entry 6) the yield fell off in 30-min reactions.

Syntheses of 2-Substituted-4-methyldihydroquinazolines. To discover the scope of the annulation, oxime ether **2** was reacted with a range of commercially available aldehydes under the optimal conditions established above; the results are in Table 2. Reactions with aliphatic aldehydes (entries 1−3) delivered the corresponding dihydroquinazolines in very high yields, and no unreacted starting materials were found. Imine formation, iminyl radical generation, 6-*endo* radical cyclization onto the C=N bond, and H-atom abstraction from the solvent seemed to be extremely efficient (Table 2). In the reaction of pent-4-enal or of 3-phenylpropanal with **2**, intermediate aminyl radicals **5a,b** will be formed by the first ring closure. The option of undergoing subsequent *5-exo-* or *6-endo*-cyclization steps to afford polycyclo-radicals **11a,b** (Scheme 3) is a clear possibility for these species. However, none of the products derived from **11a,b** were detected, even when the reaction of **5b** was carried out in the poor-H-atom-donor solvent *t*-BuPh, and evidently H-atom abstraction by radicals **5a,b** is too fast for the second ring-closure step to compete. This result was not too surprising

SCHEME 4. DDQ Oxidation of a Dihydroquinazoline



because neutral aminyl radicals are not very reactive, and it is known that their additions to alkenes are often reversible.[39]

Reactions of **2** with aromatic aldehydes were next examined under the same conditions. Microwave irradiation with benzaldehyde gave a 72% yield of the corresponding dihydroquinazoline (entry 4). The ^{1}H NMR spectrum of the total product mixture showed quantitative production of phenol, but also benzaldehyde, imine **9a**, and the corresponding ketone **9b** were present. 4-Methoxybenzaldehyde and thiophene-2-carbaldehyde gave dihydroquinazolines **7e** and **7f** in 51% and 46% yield, respectively, as determined by NMR spectroscopy (entries 5 and 6). In both cases the ^{1}H NMR spectrum showed a complex mixture of components including the starting aldehydes as well as imine **9a** and ketone **9b**. However, phenol was formed quantitatively as was expected (Table 2). For the aromatic aldehydes, the presence of unreacted starting materials suggested that the first step of the sequence, the formation of imine **3**, was not complete. We inferred therefore, than an improvement in the imine forming condensation would lead to an increase in the dihydroquinazoline yields.

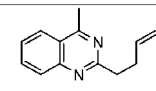
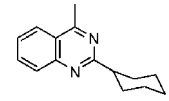
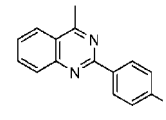
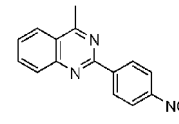
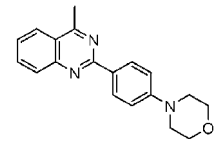
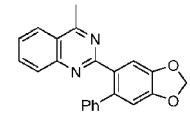
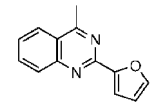
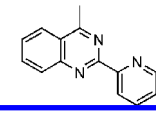
The dihydroquinazolines tended to slowly oxidize to the corresponding quinazolines over a period of days when stored in air at room temperature. The oxidation of dihydroquinazoline **7a** was studied by continuously bubbling oxygen through a solution of **7a** in $CDCl_3$ at 50 °C, the course of the oxidation being monitored by ^{1}H NMR spectroscopy (Table 3). Autoxidation was virtually complete in 48 h, but side processes had set in, and various minor unidentified byproducts were present in the total reaction mixture. It was desirable to find an oxidation protocol that could bring about this conversion in high yield and short reaction time. Microwave irradiation of dihydroquinazoline **7a** in DCM and in the presence of DDQ for 10 min at 100 °C gave the fully aromatic quinazoline **12a** in good yield (Scheme 4).

TABLE 3

	time (h)			
	4	8	24	48
yield of quinazoline **12a** (%)	28	32	42	88

Syntheses of 2-Substituted-4-methylquinazolines. The dehydration step of imine formation is acid-catalyzed, and the rates of individual steps depend on pH.[40] It is known that imine formation via microwave irradiation is promoted by inclusion of zinc chloride.[41] We hoped, therefore, that addition of $ZnCl_2$ as a promoter would improve the product yields when less reactive carbonyl compounds were employed. Pent-4-enal was reacted with oxime ether **2** in the presence of $ZnCl_2$ using the usual microwave reaction conditions. An excellent product yield was obtained, but the surprising outcome was that the quinazoline **12a** was formed directly rather than the dihydroquinazoline. Reactions with 0.1, 0.3, and 0.5 equiv of $ZnCl_2$ indicated that 0.3 equiv was the optimal amount, and this was adopted as standard in subsequent preparations.

TABLE 4. Preparation of Quinazolines by Microwave-Assisted Reactions of 2 with Aldehydes in the Presence of $ZnCl_2$[a]

Entry	RCHO	Quinazoline	Yield[b] mol %
1	pent-4-enal	 **12a**	91
2	cyclohexane carboxaldehyde	 **12b**	80
3	4-bromo-benzaldehyde	 **12c**	85
4	4-nitro-benzaldehyde	 **12d**	90
5	4-morpholino-benzaldehyde	 **12e**	77
6	6-phenyl-piperonal	 **12f**	58
7	furfural	 **12g**	76
8	picolinaldehyde	 **12h**	71

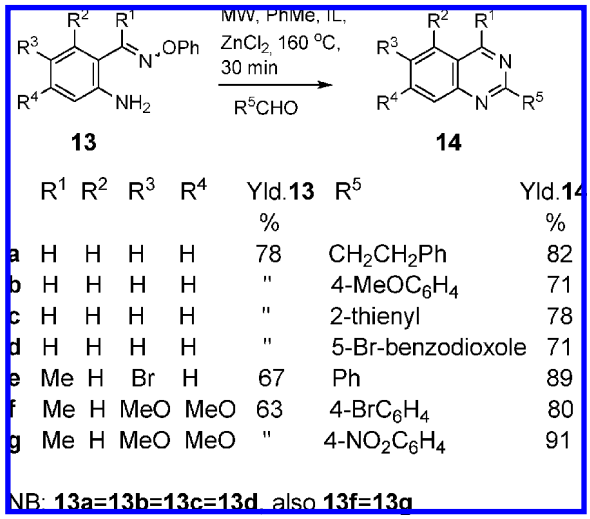
[a] 30-min reactions in PhMe at 160 °C with emimPF$_6$ and $ZnCl_2$ (0.3 equiv). [b] Isolated yields.

To assess the scope of this new process, oxime ether **2** was reacted with a range of aldehydes in the presence of 0.3 equiv of $ZnCl_2$ (Table 4). High yields of quinazolines **12a,b** were obtained with aliphatic aldehydes (entries 1 and 2) and with aromatic aldehydes containing electron-withdrawing substituents in the 4-position (entries 3 and 4). Somewhat lower but still useful yields of quinazolines were obtained from aromatic aldehydes containing electron-releasing substituents (entries 5 and 6). The low yield of entry 6 may be due to the high steric hindrance in the formation of the imine intermediate. The slightly better yields for aromatic aldehydes with electron-withdrawing groups might be due to an increase in the electrophilic character of the carbonyl group, which would favor the nucleophilic addition of **2**.

The annulations also worked well with heterocyclic aldehydes including furfural and picolinaldehyde, which gave novel and potentially useful quinazolines **12 g,h** (entries 7 and 8).

(38) Le Tadic-Biadatti, M.-H.; Callier-Dublanchet, A.-C.; Horner, J. H.; Quiclet-Sire, B.; Zard, S. Z.; Newcomb, M. *J. Org. Chem.* **1997**, *62*, 559–563.
(39) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1295–1310.
(40) (a) Hine, J.; Cholod, M. S.; Chess, W. K., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 4270–4276. (b) Hine, J.; Chou, Y. *J. Org. Chem.* **1981**, *46*, 649–652.
(41) Pouilhes, A.; Langlois, Y.; Chiaroni, A. *Synlett* **2003**, 1488–1490.

SCHEME 5. Preparation of Functionalized Quinazolines



	R1	R2	R3	R4	Yld.13 %	R5	Yld.14 %
a	H	H	H	H	78	CH_2CH_2Ph	82
b	H	H	H	H	"	4-$MeOC_6H_4$	71
c	H	H	H	H	"	2-thienyl	78
d	H	H	H	H	"	5-Br-benzodioxole	71
e	Me	H	Br	H	67	Ph	89
f	Me	H	MeO	MeO	63	4-BrC_6H_4	80
g	Me	H	MeO	MeO	"	4-$NO_2C_6H_4$	91

NB: **13a=13b=13c=13d**, also **13f=13g**

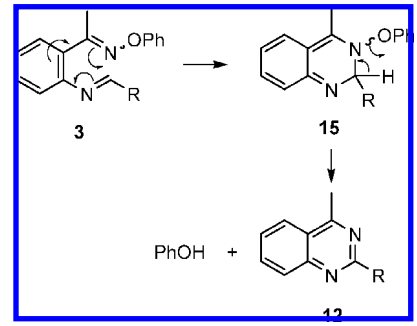
The efficiency of the reaction was also investigated for a set of *O*-phenyl oxime ethers having different functionality in the amino-aryl ring. The *O*-phenyl oxime ether **13a** was prepared in good yield (78%) from the condensation of 2-aminobenzaldehyde and *O*-phenyl hydroxylamine hydrochloride in pyridine. 5-Bromo-2-aminoactophenone was obtained by treatment of 2-aminoacetophenone with NBS in the presence of sulfonic-acid-functionalized silica as a heterogeneous catalyst.[42] The standard condensation gave the corresponding bromo-oxime ether **13e** in 67% yield. The 1-(2-amino-4,5-dimethoxyphenyl)ethanone *O*-phenyl oxime **13f** was obtained from condensation of the commercially available 4,5-dimethoxy-2-acetophenone with phenyl hydroxylamine hydrochloride. The reaction mixture was stirred for 24 h at rt, but a disappointing 46% yield resulted. The reaction was also carried out at 50 °C for 3 h, but numerous byproducts were formed, probably from scission of the N−O bond. The best result of the condensation (63%) was achieved by stirring the starting materials for 48 h at rt in pyridine. The slowness of this reaction may be due to the presence of three electron-releasing groups in the acetophenone ring.

Microwave irradiation of the unsubstituted oxime ether **13a** with aliphatic, aromatic, and heterocyclic aldehydes gave good yields of 2-substitued quinazolines (Scheme 5, **a**−**d**). The interesting building block **14d** is of special interest. Reaction of 6-bromopiperonal with the oxime ether **13d** gave the quinazoline **14d** in 71% yield, despite the presence of the large Br atom and a good electron-donating substituent, the dioxole, in the aromatic aldehyde. Both factors could have inhibited imine formation by steric hindrance and electronic effects respectively. The result demonstrated the healthy flexibility of this one-pot process. Similarly, the bromo-oxime ether **13e** and benzaldehyde afforded the 6-bromo-substituted quinazoline **14e** in an excellent yield (Scheme 5). Furthermore, dimethoxy-oxime ether **13f** reacted with 4-bromo- and 4-nitro-benzaldehydes, giving quinazolines **14f** and **14g** in high yields of 80% and 91%, respectively.

The possibility of making 4-phenyl quinazolines was also examined. In this case, 2-aminobenzophenone was reacted with *O*-phenyl hydroxylamine hydrochloride in pyridine to prepare the precursor oxime ether **13** (R^1 = Ph, R^2 = R^3 = R^4 = H). The reaction was carried out at rt for 24, 48, and 72 h and at 50 °C for 4 h. Unfortunately only a minimal conversion to the desired phenyl-derivative was achieved. This lack of success may be due to steric hindrance between one of the phenyl groups of the 2-aminobenzophenone and the phenyl hydroxylamine.

(42) Das, B.; Ventateswarly, K.; Krishnaiah, M.; Holla, H. *Tetrahedron Lett.* **2006**, *47*, 8693–8697.

SCHEME 6. Possible Electrocyclization Route to Quinazolines



Mechanism of Quinazoline Formation. Formation of the fully aromatic product suggested that inclusion of the Lewis acid $ZnCl_2$ might have caused a change in the mechanism and electrocyclic ring closure is worth considering. Imine **3** might electrocyclize to give the dihydroquinazoline intermediate **15** followed by the elimination of PhOH (Scheme 6). Recently, Trost and co-workers reported somewhat related syntheses of substituted pyridines via 6π-electrocyclizations of oxime-dienes with subsequent elimination of water under microwave irradiation.[43]

However, our precursor *O*-phenyl oximes are known to completely dissociate to radicals in <30 min under the microwave conditions,[33] so any alternative mechanism would have to be faster than this. It is unlikely both electrocyclization and phenol elimination could be fast enough to compete with the radical process. Note also that phenol was formed quantitatively in reactions with ketones, where this molecule cannot be produced by elimination from the 2,2′-disubstituted dihydroquinazoline analogous to **15** (see below). None of the quinazoline was observed in the absence of $ZnCl_2$, and therefore, the Lewis acid must play an important role in the mechanism. Recently, Lewis acids have been shown to catalyze 6-π electrocyclizations,[44] so the mechanism of Scheme 6 could not be entirely ruled out.

A radical-based mechanism in which the $ZnCl_2$ bonds to the iminyl nitrogen is outlined in Scheme 7. Bonding of zinc to the imine intermediate, followed by thermolysis of the N−O bond, would generate the iminyl radical **16**. Subsequent ring closure would lead to amminium radical cation **17** in a process akin to an iminium salt cyclization. The adjacent cation would considerably lower the pK_a of the H-atom at the 2-position of the heterocycle. Proton loss would then yield **18** in a process reminiscent of the Minisci reaction.[45] Stabilized intermediate **18** might transfer an electron to the starting oxime ether to give **19** or be converted to **19** on exposure to oxygen during workup. When the $ZnCl_2$ is not present, the C−H at the 2-position is far less acidic, and hence aromatization to a quinazoline does not occur.

(43) Trost, M.; Gutierrez, A. C. *Org. Lett.* **2007**, *9*, 1473–1476.

(44) Bishop, L. M.; Barbarow, J. E.; Bergman, R. G.; Trauner, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8100–8103.

(45) (a) Fontana, F.; Minisci, F.; Barbosa, M. C. N.; Vismara, E. *J. Org. Chem.* **1991**, *56*, 2866–2869. (b) Minisci, F.; Recupero, F.; Punta, C.; Gambarotti, C.; Antonietti, F.; Fontana, F.; Pedulli, G. F. *Chem. Commun.* **2002**, 2496–2497.

SCHEME 7. Possible Role of $ZnCl_2$ in Quinazoline Formation

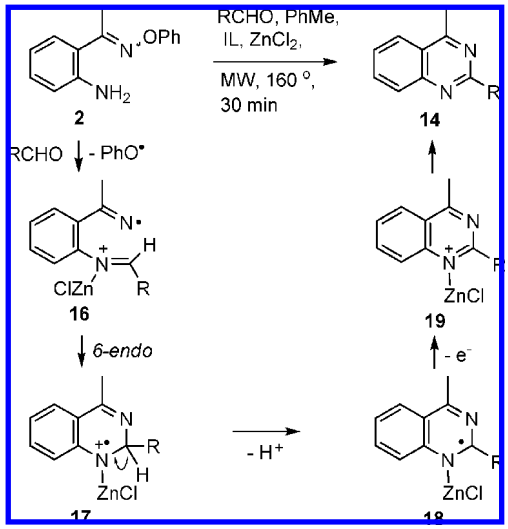
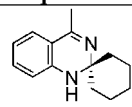
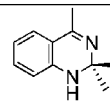
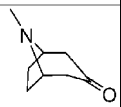
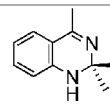


TABLE 5. Yields of Dihydroquinazolines from Reactions of Ketones with 2

Entry	Ketone	Conditions[a,b]	Dihydro-quinazoline	Yield[c] mol %
1		A	 **20a**	78
2	"	B	"	82
3	acetone	A	 **23a**	36[d]
4	"	B	"	45[d]
5		A	 **23a**	20[d]
6	"	B	"	21[d]

[a] MW at 160 °C for 30 min of 0.1 M solns. in PhMe with $emimPF_6$. [b] A: without $ZnCl_2$. B: with 0.3 equiv of $ZnCl_2$. [c] Isolated yields except as indicated. [d] Determined from ^1H NMR of total reaction mixtures.

Microwave-Promoted Reactions of 2 with Ketones. It was anticipated that 2,2′-disubstituted dihydroquinazolines could be prepared by the analogous reaction of oxime ether **2** with ketones. The ring-closed aminyl radical should abstract hydrogen from toluene solvent to give the 2,2′-disubstituted dihydroquinazoline together with an equal amount of phenol in the same way as shown in Scheme 2. The absence of an H-atom at the 2-position of these dihydroquinazolines would prevent their oxidation to quinazolines. To assess the scope and limitations of this annulation, reactions of **2** with several ketones were carried out in toluene, without (A) and with (B) $ZnCl_2$ under microwave irradiation (Table 5).

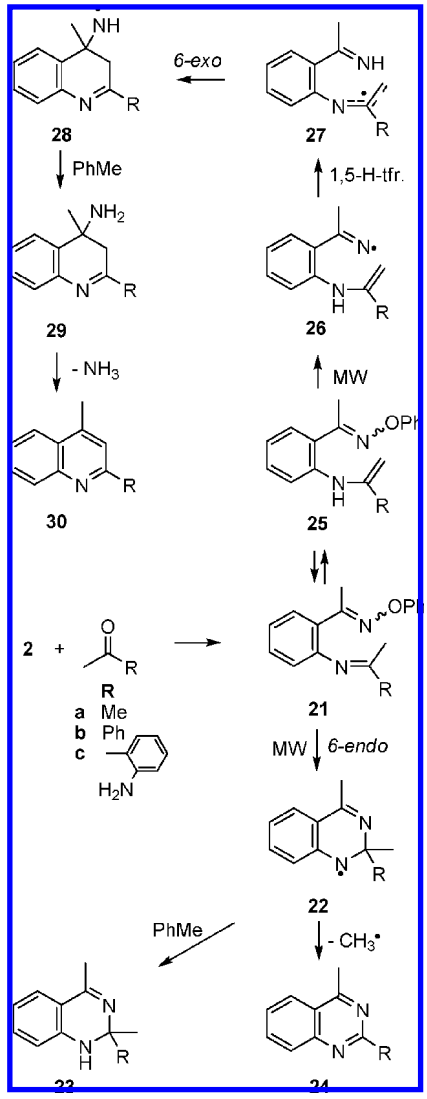
A promising result was achieved from reaction of **2** with cyclohexanone, which afforded an excellent yield of the spirodihydroquinazoline **20a**, with and without $ZnCl_2$ (entries 1 and 2). When the reaction was carried out with acetone, yields of the dihydroquinazoline **23a** were dramatically lower at 36% and 45% in the absence and presence of $ZnCl_2$, respectively (entries 3 and 4). The total reaction mixture of the Lewis acid mediated process was studied by ^1H NMR and GC/MS, which showed a complex mixture including phenol, imine **9a**, ketone **9b**, and six additional major peaks. The spectrum of the first eluted component ($M^+ = 158$) matched the library spectrum of 2,4-dimethylquinazoline **24a** (91% confidence level). The second eluted component ($M^+ = 174$) was probably the dihydroquinazoline **23a**. The quantitative formation of phenol was also of note. Its presence supported the generation of the phenoxyl radical and hence the radical mechanism. If a 6π-electrocyclization had taken place, analogous to that shown in Scheme 6, anisole should have been produced in the elimination step. However, no anisole was detected by GC/MS or ^1H NMR spectroscopy. Elimination of a methyl radical from aminyl radical **22** under the MW conditions probably accounts for the experimental finding of the fully aromatic quinazoline **24a** (Scheme 7). A major surprise was that the mass spectrum of the third eluted component ($M^+ = 157$) matched the library spectrum of 2,4-dimethylquinoline **30a** (94% confidence level). The fourth component remained unidentified, but the final two components with longer retention time had mass spectra identical to those of quinazoline **24c** and quinoline **30c** (see below). Mixtures from reactions of oxime ether **2** with the alkaloid tropinone were also studied, but NMR and GC/MS showed that none of the desired dihydroquinazoline was formed. Surprisingly, 2,2,4-trimethyl-1,2-dihydroquinazoline **23a** was isolated in 21% yield. This implies major degradation of tropinone and/or the initial products under microwave irradiation.

Microwave irradiation of **2** with acetophenone under the usual conditions gave again a complex mixture of compounds. The GC/MS showed the presence of unreacted starting material, phenol, imine **9a**, and ketone **9b**, together with six additional major components and several minor ones. The first and second of these ($M^+ = 221$ and 220, respectively) were probably dihydroquinazoline **23b** and quinazoline **24b**. The mass spectrum of the third component ($M^+ = 219$) matched the library spectrum of 2-phenyl-4-methylquinoline **30b** at the 95% confidence level. There were two additional components with longer retention times ($M^+ = 234$, 235 respectively), which we identify as quinazoline **24c** and quinoline **30c** respectively (Scheme 8). The presence of unreacted ketone, imine **9a**, and its hydrolysis product **9b** in the total reaction mixture confirmed that imine formation was not very efficient. This may be due to the high sensitivity of the imine condensation to steric hindrance.

To explain the formation of these compounds, it was conjectured that precursor **2** could react with the ketone **9b** to give the imine **21c**. Subsequent generation of the iminyl radical and 6-*endo* cyclization onto the imine could give aminyl radical **22c**. Dihydroquinazoline **23c** would be obtained by hydrogen abstraction from the solvent. The related quinazoline **24c** was presumably formed by elimination of a methyl radical (Scheme 8).

The most intriguing aspect of this reaction was the apparent formation of products containing the quinoline ring, i.e., **30a**−**c**. A tentative mechanism to account for this is also shown in Scheme 8. Imines **21** will be in equilibrium with their enamine tautomers **25**. Generation of iminyls **26** could be followed by favored [1,5]-hydrogen migrations giving the aza-allyl radicals **27**; 6-*exo* ring closures of **27** onto the newly formed imine bonds would produce aminyl radicals **28**. Hydrogen abstraction from

SCHEME 8. Mechanism for Reaction of 2 with Ketones



the solvent and subsequent elimination of ammonia could then yield the quinolines **30** (Scheme 8).

This mechanism for formation of quinazoline **24c** and quinoline **30c** implied that oxime ether **2** might react on its own, without any ketone being present, under the usual microwave reaction conditions in toluene with ionic liquid and $ZnCl_2$. When this control experiment was carried out, the 2-(4-methylquinazolin-2-yl)aniline **24c** was isolated in 41% yield; dihydroquinazoline **23c** could not be isolated, but a minor peak in the GC/MS with the correct mass confirmed that it was formed. The quinoline **30c** was also isolated in 18% yield and its identity confirmed from its NMR spectra.

Ketone **9b** is formed either by hydrolysis of imine **9a** or by direct hydrolysis of precursor **2**. It should therefore be a minor component, particularly in the early stages of the reaction. If the mechanism of Scheme 8 is correct, oxime ether **2** condenses with **9b** to give imine **21c** even though 1 equiv of the added ketone (acetone or acetophenone) is present. A tentative explanation of this selectivity may be that the aryl-amino group, as well as imine nitrogen, might interact with the $ZnCl_2$ present in the reaction medium to favor **21c** against intermediates **21b** (or **21a**) (Figure 3).

It was clear from the results described above that reaction of oxime ether **2** with ketones did not constitute a general method

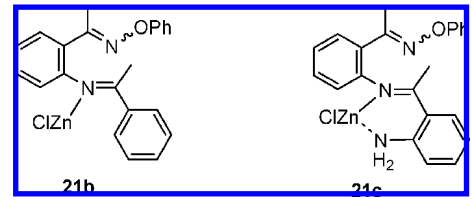


FIGURE 3. Imines from **2** with acetophenone and 1-(2-aminophenyl)ethanone.

for the syntheses of disubstituted dihydroquinazolines. The reactions generally gave complex mixtures of numerous compounds. It was also shown that when reactions were carried out with more sterically demanding ketones, such as acetophenone, the complexity of the total reaction mixture increased as a result of the poor efficiency of imine formation.

Conclusions

The results show that 2-(aminoaryl)alkanone *O*-phenyl oximes are excellent precursors for quinazoline derivatives. They react in one pot, with aliphatic aldehydes, in microwave-assisted reactions yielding dihydroquinazolines. When more sterically demanding aldehydes were used, the yield dropped dramatically. The precursor *O*-phenyloximes are easily made in one step from the corresponding carbonyl and *O*-phenyl hydroxylamine in good yields and can be stored indefinitely. Nevertheless, it was found that electronic and steric hindrance effects played an important role in the success of this condensation reaction.

When $ZnCl_2$ was included in the mixture, quinazolines were obtained instead of dihydroquinazolines. The process is of wide scope and works well with alkyl, aryl, and heterocyclic types of aldehydes. The reaction has all the advantages associated with microwave chemistry. The process is rapid, high-yielding, reproducible, neutral, and comparatively mild. The methodology was successful in syntheses of quinazolines with high steric demand such as 4-methyl-2-(6-phenylbenzo[*d*][1,3]dioxol-5-yl)quinazoline **12f** and 2-(6-bromobenzo[*d*][1,3]dioxol-5-yl)quinazoline **14f**. Quinazolines with heterocycles as substituents were also prepared in good yields. On the other hand, although this methodology was extremely effective for the preparation of quinazolines from aldehydes, it does not appear to be a suitable method in the preparation of dihydroquinazolines from ketones. Apart from the reaction with cyclohexanone, complex mixtures of several compounds were obtained instead.

Experimental Section

Typical Procedure for Preparation of *O*-Phenyl Oximes: 1-(2-Aminophenyl)ethanone *O*-Phenyl Oxime (2). *O*-Phenyl hydroxylamine hydrochloride (2.15 g, 15 mmol) was dissolved in anhydrous pyridine (40 mL) under N_2 at room temperature, and 1-(2-aminophenyl)ethanone (2.0 g, 15 mmol) was added in one portion. The resulting solution was stirred at rt overnight, and the progress of the reaction was monitored by TLC (EtOAc/ hexane, 1:2). Upon completion, the reaction mixture was poured into water (40 mL) and extracted with EtOAc (3 × 30 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) affording a dark orange oil (2.54 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (3H, s, CH_3), 5.72 (2H, s, NH_2), 6.80 (2H, m, CH), 7.10 (1H, tt, J = 7.2, 1.1 Hz, CH), 7.22 (1H, t, J = 7.7 Hz, CH), 7.28 (2H, m, CH), 7.39 (2H, t, J = 7.2 Hz, CH), 7.49

(1H, dd, J = 7.7, 1.4 Hz, CH); ^{13}C NMR δ 14.1 (CH_3), 114.8, 118.8, 117.0 (CH), 117.6 (C), 122.3, 129.4, 129.5, 130.3 (CH), 146.2, 159.4, 160.4 (C); IR 3474, 3345, 1613, 1593 cm^{-1}; HRMS calcd for $C_{14}H_{15}N_2O$ (MH^+) 227.1183; found 227.1184.

Typical Procedure for 4-Methyldihydroquinazoline Preparations: 2-(But-3-enyl)-4-methyl-1,2-dihydroquinazoline (7a). Pent-4-enal (37.0 mg, 0.44 mmol) was added to a solution of 1-(2-aminophenyl)ethanone *O*-phenyl oxime **2** (100 mg, 0.44 mmol) in toluene (0.15 M) and emimPF_4 (100 mg, 0.46 mmol) in a microwave vessel (2−5 mL). 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 (25% EtOAc/hexane) affording the desired product as a yellow oil (83.1 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (2H, m, CH_2), 2.20 (2H, m, CH_2), 2.23 (3H, s, CH_3), 3.90 (1H, s, NH), 4.77 (1H, t, J = 5.8 Hz, CH), 4.92 (1H, m, CH_2), 5.01 (1H, dq, J = 17.0, 1.8 Hz, CH_2), 5.80 (1H, m, CH), 6.45 (1H, dd, J = 8.0, 0.8 Hz, CH), 6.63 (1H, td, J = 7.6, 1.1 Hz, CH), 7.1 (1H, m, CH), 7.21 (1H, dd, J = 7.7, 1.3 Hz, CH); ^{13}C NMR δ 21.0 (CH_3), 28.11, 34.5 (CH_2), 67.9, (CH), 112.9 (CH), 114.1 (CH_2), 117.0 (CH), 117.5 (C), 125.3, 131.7 (CH), 137.6 (CH), 144.7, 161.9 (C); IR 3302, 1611 cm^{-1}; HRMS calcd for $C_{13}H_{17}N_2$ (MH^+) 201.1392; found 201.1390.

Typical Procedure of Oxidation of Dihydroquinazolines to Quinazolines: 2-(But-3-enyl)-4-methylquinazoline (12a). A solution of 2-(but-3-enyl)-4-methyl-1,2-dihydroquinazoline (**7a**) (50 mg, 0.25 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (68 mg, 0.30 mmol) in DCM (4 mL) was placed in a microwave vial and was irradiated for 10 min at 100 °C. The solvent was removed under reduced pressure. The residue was purified by column chromatography (5% EtOAc/hexane), giving the desired product as a brown oil (49 mg, 83%).

Typical Procedure for $ZnCl_2$-Promoted Quinazoline Preparations: 2-(But-3-enyl)-4-methylquinazoline (12a). Pent-4-enal (36.9 mg, 0.44 mmol) was added to a solution of 1-(2-aminophenyl)ethanone *O*-phenyl oxime (100 mg, 0.44 mmol) in toluene (0.15 M) containing anhydrous $ZnCl_2$ (17 mg, 0.13 mmol) and emimPF_4 (100 mg, 0.46 mmol) in a microwave vessel (2−5 mL). The vessel was sealed and subjected to microwave irradiation for 30 min at 160 °C in a Biotage Initiator system. 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 the desired product as a yellow oil (79.0 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.60 (2H, q, J = 8.0 Hz, CH_2), 2.87 (3H, s, CH_3), 3.09 (2H, m, CH_2), 4.92−5.01 (2H, m, CH_2), 5.88 (1H, m, CH), 7.48 (1H, ddd, J = 8.2,6.9, 1.2 Hz, CH), 7.76 (1H, ddd, J = 8.4, 6.9, 1.4 Hz, CH), 7.88 (1H, d, J = 8.3 Hz, CH), 7.98 (1H, d, J = 8.3 Hz, CH); ^{13}C NMR δ 22.0 (CH_3), 38.8 (CH_2), 39.3 (CH_2), 115.2 (CH_2), 122.5 (C), 125.0, 126.7, 128.5, 133.6 (CH), 137.9 (CH), 149.9, 166.1, 168.1 (C); IR 1617, 1561 cm^{-1}; HRMS calcd for $C_{13}H_{15}N_2$ (MH^+) 199.1235: found 199.1234

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Supporting Information Available: General procedures. Preparation and characterization of dihydroquinazolines and quinazolines. ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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