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An Easy Entry into 2-Halo-3-aryl-4(3*H*)-quinazoliniminium Halides from Heteroenyne-allenes

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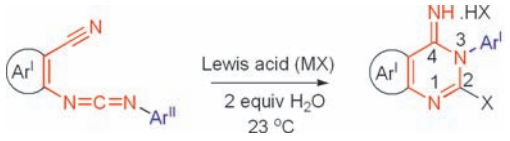
ABSTRACT



An efficient three-step synthesis of 2-halo-3-aryl-4(3*H*)-quinazoliniminium halides from commercially available materials is described. Upon reaction with hydrogen halides, generated *in situ* from a Lewis acid (MX) and trace water, a variety of easily accessible heteroenyne-allenes underwent facile intramolecular cyclization to afford the title compounds in good yields. The method is highly versatile and provides a general way to construct quinazoliniminium ring systems with a variety of different substitutions.

4(3*H*)-Quinazolinones **1** substituted at C-2 or/and N-3 (Figure 1) constitute an important family of compounds in heterocyclic chemistry and exhibit a broad spectrum of biological activities such as antihypertensive,[1] antimalarial,[2] antimicrobial,[3] anticonvulsive,[4] anticancer,[5] anti-inflammatory,[6] and analgesic effects.[7] As a result, quinazolinones and their derivatives are regarded as "privileged structures" that are capable of binding to multiple receptors with high affinity.[8] The 4(3*H*)-quinazolinone ring system **1** is also featured in several natural products. For instance, quinadoline A and B isolated from *Aspergillus* sp. FKI-1746 inhibit lipid droplet synthesis,[9] febrifugine obtained from a Chinese herb Dichroa febrifuga is an active component against malarial parasite,[10] luotonin A also from a Chinese herb *Peganum nigellastrum* is a Topoisomerase I poison,[11] and nigellastrines isolated from *Peganum*

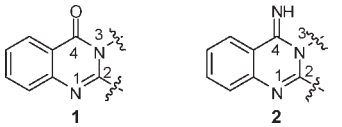


Figure 1. 4(3*H*)-Quinazolinone **1** and 4(3*H*)-quinazolinimine **2**.

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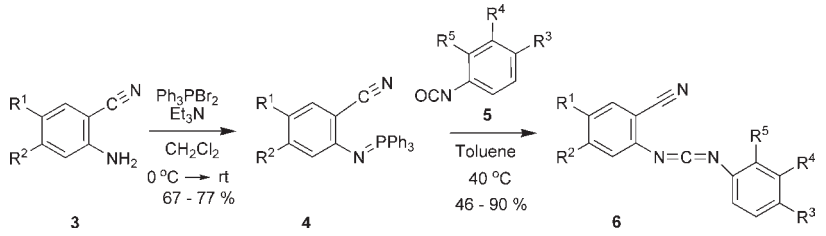
Scheme 1. General Method for the Synthesis of Heteroenyne-allenes **6**



Nigellastrum Bunge are acetylcholinesterase inhibitors.[12] This heterocycle and its derivatives have also been evaluated in electroluminescent devices and organic dyes.[13] The widespread applications of quinazolinones in medicinal and materials chemistry have triggered considerable synthetic efforts to construct these ring systems.[14]

One important building block for the synthesis of quinazolinones **1** and their derivatives is a 4(3*H*)-quinazolinimine scaffold **2** (Figure 1).[15a] Note that the ring system **2** is featured in compounds that exhibit cholinesterase inhibitory[15f,g,n] and antiproliferative activities.[16] Several methods to synthesize **2** are available in the literature.[15] A single step synthesis of quinazolinimines **2** has been reported in a three-component reaction between a carbonyl compound, amine, and 2-azido-5-nitro-benzonitrile.[17] However, none of the reported methods have been optimized and examined for versatility to construct a variety of functionalized 4(3*H*)-quinazolinimine scaffolds in a general way. Furthermore, some of the existing protocols require long reaction times,[15a] high temperatures,[15d] special setup, and workup conditions[15f,n] and produce low yields.[15g,o] During our attempts to induce a formal [4 + 2] cyclization from cyanoene-carbodiimides,[18] we discovered a new and alternative method to build **2** in the presence of a hydrogen halide, generated *in situ* from the reaction of a Lewis acid with trace water, which was further subjected to an optimization study. The advantages of this newly discovered method are the following: (1) It is highly versatile and allows the construction of a quinazoliniminium ring carrying a wide range of different substitutions, notably on N-3. (2) It provides access to 2-halo quinazoliniminiums that have not been previously explored. The presence of a halogen atom at C-2 offers possibilities to exploit this site into further chemistry for additional functionalization. As mentioned above, functionalization at N-3 or/and C-2 positions of these ring systems is extremely important from a drug discovery viewpoint, and in addition, (3) the reaction is carried out at room temperature and requires no special setup/workup to isolate the quinazoliniminium product.

2-((Phenylimino)methyleneamino)-benzonitrile (**6a**) ($R^1 = R^2 = R^3 = R^4 = R^5 = H$) was prepared as reported in the literature (Scheme 1).[19] Briefly, the aza-Wittig reaction of 2-aminobenzonitrile (**3a**) ($R^1 = R^2 = H$) with triphenylphosphine dibromide in the presence of triethylamine yielded the iminophosphorane **4a** ($R^1 = R^2 = H$) (77%) which upon treatment with isocyanate **5a** ($R^3 = R^4 = R^5 = H$) generated **6a** (67%).

Treatment of **6a** with chlorotrimethylsilane (TMSCl) produced a single product in very good yield. The structure elucidation of this product was carried out by a combination of COSY, HSQC, and HMBC NMR experiments and high resolution mass spectrometry, which confirmed the presence of a 2-chloro-3-phenyl-4(3*H*)-quinazolinimine scaffold **7a** (Scheme 2, see Supporting Information for discussion of 2D spectra). The product was insoluble in most organic solvents such as methylene chloride, ethyl acetate, acetone, and hexane (except methanol), which suggested that the isolated compound may be the hydrochloride salt of the 2-chloro-3-aryl-4(3*H*)-quinazolinimine **7a**. Under the acidic conditions employed, the imines are expected to be protonated. The formation of the hydrochloride salt **7a** was further supported by the NMR signal

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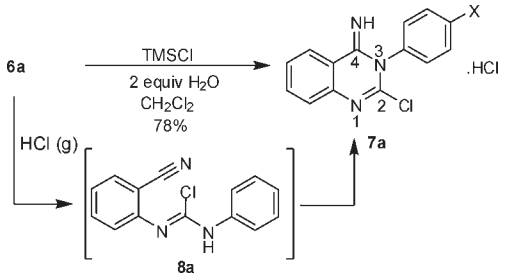
corresponding to C4, which was strongly deshielded (161.4 ppm) because of the presence of a nearby positive charge.[20]

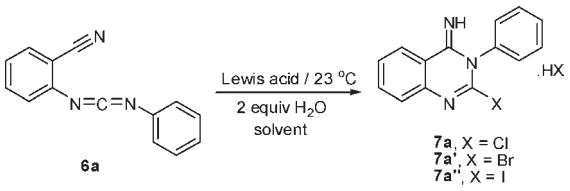
Scheme 2. Conversion of **6a** to 2-Chloro-3-phenyl-4(3*H*)-quinazoliniminium Chloride **7a** and the Proposed Intermediate **8a**



Based on a report by Pazdera et al.[15m] on the synthesis of 1,3-oxazolo[2,3-*b*]quinazolinimines, we hypothesized that the formation of quinazoliniminium salt **7a** from **6a** may involve the intermediacy of *N*′-(2-cyanophenyl)-*N*-phenylcarbamimidic chloride **8a** (Scheme 2). The formation of the latter would require the addition of HCl at the carbodiimide moiety of **6a**. Since TMSCl is regarded as a mild, convenient source of HCl, formed by the reaction with trace amounts of water,[21] it would provide the needed source of chloride ions in our reaction. When **6a** was treated with freshly distilled TMSCl for 72 h in a glovebox, quinazoliniminium salt **7a** was not formed, which further supports the hypothesis that the TMSCl reacts with the moisture in the solvent to form trace amounts of HCl, which eventually promotes the cyclization of **6a** to **7a** as depicted in Scheme 2. In a separate experiment, we also bubbled HCl gas through a solution of **6a** in methylene chloride for 10 min, and the reaction mixture was allowed to stir at room temperature for 24 h. The ^{1}H NMR spectrum of the product confirmed the formation of **7a**.

The intramolecular cyclization of 2-((phenylimino)-methyleneamino)-benzonitrile **6a** was carefully examined in the presence of various other Lewis acids (Table 1). The reaction proceeded smoothly in the presence of TMSBr and TMSI to afford the corresponding 2-halo-3-aryl-quinazoliniminium halides **7a**′ and **7a**″, respectively (Table 1, entries 2–3). $ZnCl_2$, $SnCl_4$, and $TiCl_4$ also yielded the expected product **7a** (Table 1, entries 4–6). However, the reaction with $BF_3 \cdot OEt_2$ and $FeCl_3$ gave a complex mixture of products (Table 1, entries 7–8). The best Lewis acid was the initially tested TMSCl in which the 2-chloro-3-phenyl-quinazoliniminium chlorides **7a** were obtained in excellent yields in 48 h at room temperature (Table 1, entry 1). Note that the reaction with $TiCl_4$ proceeded much faster than

Table 1. Optimization of the Reaction Conditions



entry	solvent	Lewis acid	time (h)	product **7**	yield (%)
1	CH_2Cl_2	TMSCl	48	**7a**	84
2	CH_2Cl_2	TMSBr	60	**7a**′	61
3	CH_2Cl_2	TMSI	60	**7a**″	55
4	CH_2Cl_2	$ZnCl_2$	48	**7a**	65
5	CH_2Cl_2	$SnCl_4$	24	**7a**	62
6	CH_2Cl_2	$TiCl_4$	5	**7a**	70
7	CH_2Cl_2	$BF_3 \cdot OEt_2$[a]	4	None	
8	CH_2Cl_2	$FeCl_3$[a]	24	None	
9	$ClCH_2CH_2Cl$	TMSCl	48	**7a**	77
10	THF	TMSCl	48	**7a**	75
11	Toluene	TMSCl	48	**7a**	76

[a] A complex mixture of products formed which were not identified.

the reaction with TMSCl, but the yield of the quinazoliniminium salt obtained was low (Table 1, entry 6). Given the easier handling of TMSCl, this Lewis acid certainly seems to be the best choice to induce this cyclization. Using TMSCl, we also studied the influence of different solvents, e.g., 1,2-dichloroethane, tetrahydrofuran, and toluene. The yields of **7a** were found to be unaffected in these three solvents (Table 1, entries 9–11); however, these were slightly lower than those obtained in methylene chloride (Table 1, entry 1).

Under the optimized conditions the scope of this protocol was further explored by using a variety of 2-((arylimino)methyleneamino)-benzonitriles **6b**–**h**. These were prepared from the corresponding benzonitriles **3** and phenylisocyanates **5** using the strategy described above (Scheme 1). As shown in Table 2, almost all of the substrates produced the 2-chloro-3-aryl-quinazoliniminium chlorides in good yields. Our results demonstrated that the cyclization reaction was insensitive to the electronic nature of the substituent present on the phenyl ring attached to N-1 of the carbodiimide functional group (see Table 2 for numbering). The presence of an electron-donating methoxy group (**6b**), electron-withdrawing ethyl ester (**6c**), and a weakly electron-withdrawing chloro group (**6d**) at the *para* position of this phenyl ring produced the expected quinazoliniminium salts in good yields (Table 2, entries 2–4). Changing the position of the chloro substituent on the phenyl ring to the *meta* position (**6e**) also proceeded efficiently (Table 2, entry 5). Sterically hindered ortho-substituted derivative **6f** also successfully underwent cyclization using this method, although it afforded somewhat reduced yields (Table 2, entry 6). The effect of the substitution on the aromatic ring attached to N-3 of the

(20) The addition of triethylamine to a suspension of **7a** in methylene chloride resulted in the immediate dissolution of the solid. The upfield signal shifts in the ^{1}H NMR spectrum confirmed the formation of a free imine base of **7a**. The latter reverted back to the salt form **7a** by the addition of TMSCl as confirmed by ^{1}H NMR spectroscopy

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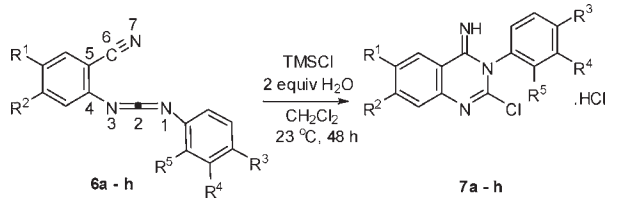
carbodiimide functional group of **6** on the cyclization was also examined. The reaction **6g** and **6h** with TMSCl proceeded efficiently, and the quinazoliniminium salts were obtained in good yields (Table 2, entries 7, 8).

Table 2. Investigation of the Scope of Cyclization of Heteroenyne-allenes **6** to 2-Chloro-3-aryl-quinazoliniminium Chlorides **7**



entry	**6**	R^1	R^2	R^3	R^4	R^5	yield (%)
1	**6a**	H	H	H	H	H	**7a:** 84
2	**6b**	H	H	OMe	H	H	**7b:** 60
3	**6c**	H	H	COOEt	H	H	**7c:** 72
4	**6d**	H	H	Cl	H	H	**7d:** 78
5	**6e**	H	H	H	Cl	H	**7e:** 74[a]
6	**6f**	H	H	H	H	Cl	**7f:** 56[a]
7	**6g**	Me	H	H	H	H	**7g:** 75
8	**6h**	H	Me	H	H	H	**7h:** 77

[a] Reaction required 60 h for completion.

As a final confirmation of the structure assignment of **7**, a single crystal X-ray structure analysis of 2-chloro-3-(4-methoxyphenyl)quinazolin-4(3*H*)-iminium chloride **7b** (Figure 2) was also obtained. The primary structure directing interactions in the crystal lattice of this salt are the four hydrogen bonds involving the two chloride ions and N–H's of the iminium moieties present on the two adjacent molecules (Figure 1s, Supporting Information). These interactions result in the formation of dimers (Figure 1s, Supporting Information). According to the graph set notation,[22] these hydrogen bonding interactions create an $[R^2_4\ (8)]$ motif. The adjacent dimers interact through halogen–halogen bonds of type I (interaction angle θ_1(C–Cl---Cl) = θ_2(Cl---Cl–C) = 117.74°).[23] The Cl–Cl bond length is 3.389 Å, which is slightly shorter than the sum of their van der Waals radii.[24]

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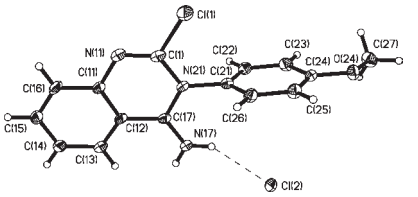

Figure 2. ORTEP diagram of **7b**.

In summary, we have reported a facile intramolecular cyclization of heteroenyne-allenes **6** to 2-halo-3-aryl-4(3*H*)-quinazoliniminium halides **7** upon reaction with a hydrogen halide, generated *in situ* from a Lewis acid and trace water. Since cyclization appears to be insensitive to the electronic nature of substituents present on the heteroenyne-allenes, this method offers a general way to produce quinazoliniminium salts **7** with desired substitutions on the aromatic rings by a careful choice of the corresponding benzonitriles **3** or isocyanates **5** during the synthesis of precursors **6**, making this method potentially useful for the development of libraries of heterocycles with possible biological and materials properties. It also seems plausible that these quinzoliniminium salts can be elaborated at C-2 through nucleophilic substitution or palladium-catalyzed cross-coupling to investigate the structure–activity relationship in drug discovery. These further investigations will be reported in due course.

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Supporting Information Available. General procedures; experimental procedures and spectroscopic data for **4a**, **4g**,**h**, **6a**–**h**, **7a**–**7h**, **7a**′, and **7a**″; ^{1}H and ^{13}C NMR spectra of all new compounds; COSY, HSQC, and HMBC spectra of **7a**; X-ray data and cif file of **7b**; discussion of 2D spectra of **7a** leading to its structural characterization. This material is available free of charge via the Internet at http://pubs.acs.org.