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Heteroannulation of Nitroketene *N,S*-Arylaminoacetals with $POCl_3$: A Novel Highly Regioselective Synthesis of Unsymmetrical 2,3-Substituted Quinoxalines†

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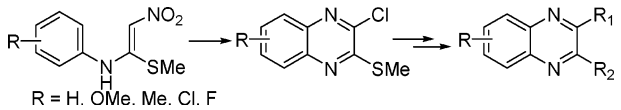
ABSTRACT



A novel regioselective route for the synthesis of substituted and fused 3-chloro-2-(methylthio)quinoxalines through $POCl_3$-mediated heteroannulation of a range of α-nitroketene *N,S*-anilinoacetals has been reported.

Quinoxaline and its derivatives are an important class of benzoheterocycles[1] displaying a broad spectrum of biological activities[2] which have made them privileged structures in combinatorial drug discovery libraries.[3] They have also found applications as dyes[4] and building blocks in the synthesis of organic semiconductors,[5] and they also serve as useful rigid subunits in macrocyclic receptors for molecular recognition[6] and chemically controllable switches.[7] These studies have resulted in the appearance of a large number of publications both in journals and patent literature related to the synthesis and physiochemical/biological properties of quinoxaline and their derivatives.[1,8] Although a number of methods are available for the synthesis of substituted quinoxalines,[1,8,9] a review of the literature revealed that while the parent molecules are easily prepared, the corresponding substituted compounds are considerably more challenging. Probably the most widely used method for the preparation of quinoxaline derivatives is by condensation of aryl-1,2-diamines with α-diketones, usually α-dicarbonyl compounds (Hinsberg

† Dedicated to Dr. S. Anand Kumar, Director, Astrazeneca Research Foundation, Bangalore, India, on his 70th Birthday.

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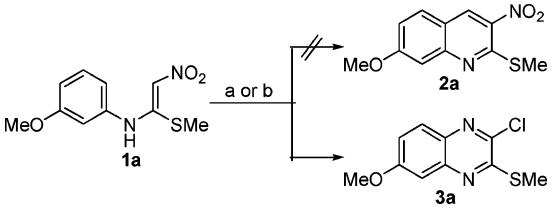
condensation) or their equivalents.[1,8a−f] However, a major drawback in this method is the lack of regioselectivity leading to formation of isomeric products with unsymmetrically substituted reactants.[4c,8f,9b] Among the various regioselective routes to quinoxaline and derivatives,[1,8−10] the method involving nucleophilic substitution on *o*-nitrohalobenzene by appropriately functionalized aliphatic amine followed by reductive cyclization of the resulting *o*-nitroaminobenzene derivatives has been most widely employed.[3] The other most promising route in terms of regiochemistry and generality is the intramolecular cyclization of α-aryliminophenylhydrazone[11] or oxime derivatives[12−14] of α-dicarbonyl compounds employing readily available substituted aniline precursors instead of 1,2-diaminobenzene or *o*-halonitrobenzene derivatives.[14] However, these potentially useful methods have not been thoroughly explored, and the existing few examples are rather limited in scope and suffer from several practical disadvantages such as extremely vigorous conditions or low yields.[11] During the course of our ongoing exploration on synthetic applications of polarized ketene *S,S*- and *N,S*-acetals as versatile building blocks for heterocycle synthesis,[15,16] we have now developed a novel, highly regioselective and efficient route to 2,3-substituted quinoxalines through *N*-heteroannulation of α-nitroketene *N,S*-anilinoacetals. The results of these studies are presented in this letter.

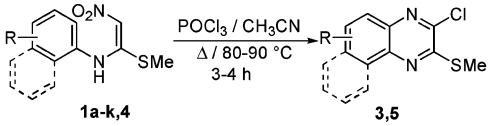
We have recently reported an efficient general route to 3-aroyl-2-(methylthio)quinolines through cyclocondensation of various α-oxo *N,S*-arylacetals with Vilsmeier reagents.[17] These studies motivated us to extend this method for the synthesis of 3-nitroquinolines by reaction of the corresponding nitroketene *N,S*-acetals with Vilsmeier reagent. However when the *N,S*-acetal **1a** was exposed to Vilsmeier reaction conditions, the product (60%) isolated was not the expected quinoline **2a** but was characterized as 3-chloro-7-methoxy-2-(methylthio)quinoxaline **3a** (Scheme 1). Subsequently, it was found that the reaction proceeded smoothly in the absence of DMF and under optimized conditions, the quinoxaline **3a** was obtained in improved yield (70%) when *N,S*-acetal **1a** was reacted with $POCl_3$ in acetonitrile at 80 °C. The reaction was extended to other substituted α-nitroketene *N,S*-acetals **1b**−**j** with a view to examine scope of the reaction for a general quinoxaline synthesis and the results are presented in the Table 1. In general, the nitro-

Scheme 1. Synthesis of Quinoxaline[a]

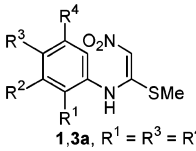
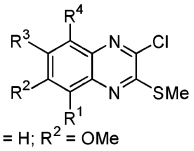
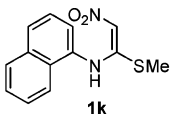
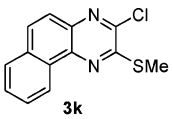
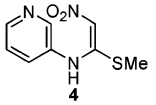
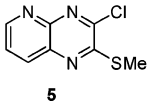


[a] Reagents and conditions: (a) DMF, $POCl_3$, $Cl_2CHCHCl_2$, 80−90 °C, 60%; (b) $POCl_3$, CH_3CN, 80 °C, 70%.

Table 1. Synthesis of Quinoxalines **3** and **5** by $POCl_3$-Promoted Cyclocondensation of α-Nitroketene *N,S*-Acetals



1a-k,4 → 3,5

Entry	*N,S*-acetals **1,4**	Quinoxaline **3,5**	% Yield
			
1	**1**,**3a**, $R^1 = R^3 = R^4 = H$; $R^2 = OMe$		70%
2	**b**, $R^1 = R^4 = H$; $R^2 = R^3 = OMe$		75%
3	**c**, $R^1 = R^3 = H$; $R^2 = R^4 = OMe$		71%
4	**1d**, $R^2 = R^3 = H$; $R^1 = OMe$; $R^4 = OMe$		
	3d, $R^2 = R^3 = H$; $R^1 = OMe$; $R^4 = Cl$		61%[a]
5	**1**,**3e**, $R^2 = R^4 = H$; R^1= Me; $R^3 = OMe$		62%
6	**f**, $R^1 = R^2 = R^3 = R^4 = H$		50%
7	**g**, $R^1 = R^2 = R^4 = H$; $R^3 = OMe$		57%
8	**h**, $R^1 = R^2 = R^4$= H; $R^3 = Cl$		50%
9	**i**, $R^1 = R^4 = H$; $R^2 = R^3 = Cl$		42%
10	**1j**, **3ja**, $R^1 = R^3 = R^4 = H$; $R^2 = F$		40%
	3jb, $R^1 = R^2 = R^3 = H$; $R^4 = F$		20%
11	 **1k**	 **3k**	80%
12	 **4**	 **5**	45%

[a] The 4-methoxy group in the product **3d** was found to be replaced by chlorine.

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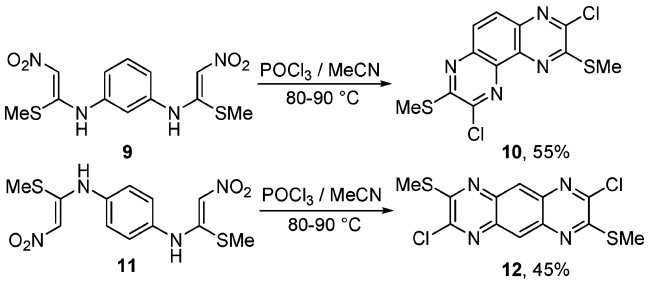
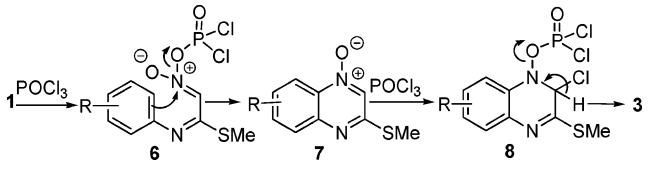
ketene *N*,*S*-acetals **1a**−**c** with an activating group para to the site of cyclization gave the corresponding 3-chloro-2-(methylthio)quinoxalines **3a**−**c** in high yields (entries 1−3), whereas moderate to good yields of the quinoxalines were obtained from the *N*,*S*-acetals **1d**−**j** (entries 4−10).The corresponding (4-fluoroanilino) *N*,*S*-acetal **1j** gave both the regioisomers of the quinoxalines **3ja** and **3jb** formed by heterocyclization at both para and ortho positions of fluorine substituent (entry 10). Interestingly, the *N*,*S*-acetal **1k** from 1-naphthylamine was transformed into the 3-chloro-2-(methylthio)benzo[*h*]quinoxaline(**3k**) in excellent yield (80%) under the standard reaction conditions (entry 11). Extension of the method to *N*,*S*-acetal **4** derived from 3-aminopyridine furnished the corresponding 3-chloro-2-(methylthio)pyrido-[2,3-*b*]pyrazine **5** in a moderate yield of 45% (Table 1, entry 12). To further explore the generality and scope of this new quinoxaline synthesis, the reaction was extended to bis-(nitroketene *N*,*S*-acetals) **9** and **11** which afforded the novel hitherto unknown pyrazinoquinoxalines **10** and **12** in 55% and 45% yields, respectively, under identical conditions (Scheme 2).

Scheme 2



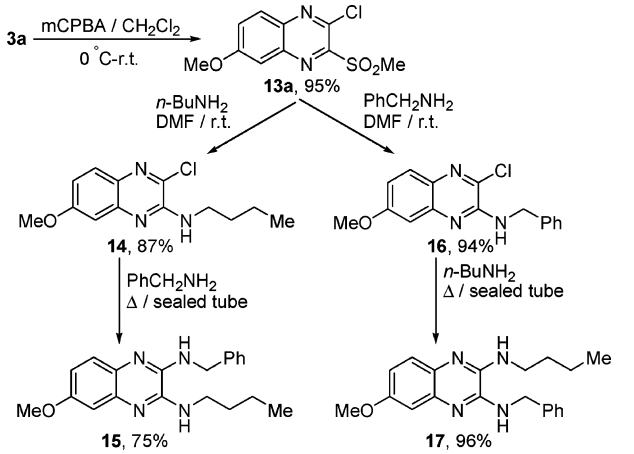
The probable mechanism[18] for the conversion of *N*,*S*-acetals **1** to quinoxalines **3** involves initial formation of quinoxaline *N*-oxide **7** by dehydrative cyclization of **1** followed by subsequent chlorination at 3-position and extrusion of oxygen through intermediate **8** (Scheme 3).

Scheme 3



With a number of substituted quinoxalines in hand, we next focused our attention on the development of regioselective routes for 2,3-substituted quinoxalines through sequential nucleophilic substitution of 3-chloro- and 2-methylthio groups by various hetero and carbon nucleophiles. It is pertinent to note that nucleophilic substitution on 2,3-dichloroquinoxalines with various nucleophiles usually yields a regioisomeric mixture of substituted quinoxalines.[9b,19,20] However, our studies revealed displacement of only 3-chloro group by various nucleophilic species (amines, phenol, alcohols, thiols, etc.) in the quinoxaline **3a**, whereas the 2-methylthio group remained inert even under drastic conditions. The quinoxalines **3a** and **3g** were therefore transformed into the corresponding more labile 3-chloro-2-(methylsulfonyl)quinoxalines **13a** and **13g** in high yields by oxidation with *m*-CPBA. Subsequently, it has been possible to tune up the reactivity of 2-chloro- and 3-(methylsulfonyl) groups in **13a** and **13g** toward displacement by various nucleophiles in a sequential manner, and the results of our preliminary studies are presented in the Schemes 4 and 5. Thus, the

Scheme 4



treatment of the quinoxaline **13a** with *n*-butylamine at room temperature afforded the corresponding 2-(*n*-butylamino)-3-chloro-7-methoxyquinoxaline **14** in excellent yield. Subsequent treatment of **14** with benzylamine in a pressure tube gave the corresponding 3-(benzylamino)-2-(*n*-butylamino)-7-methoxyquinoxaline **15** in 75% yield with high regiocontrol (Scheme 4). Similarly, the regioisomeric 2-(benzylamino)-3-(*n*-butylamino)-7-methoxyquinoxaline **17** could be obtained in high yield from **13a** through sequential displacement of 2-(methylsulfonyl) and 3-chloro groups by respective amines (Scheme 4). Similarly, the 2-cyano-3-(*N*-benzylpiperazino)-6-methoxyquinoxaline **19** displaying selective $5HT_3$ antagonist activity on guinea pig peripheral receptors[2c] and its 2-(*N*-

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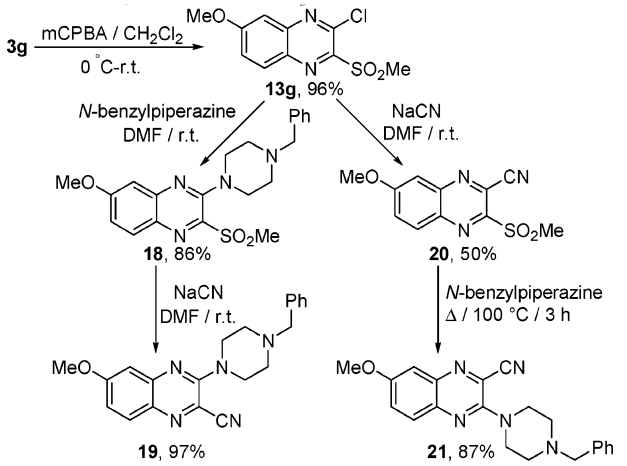
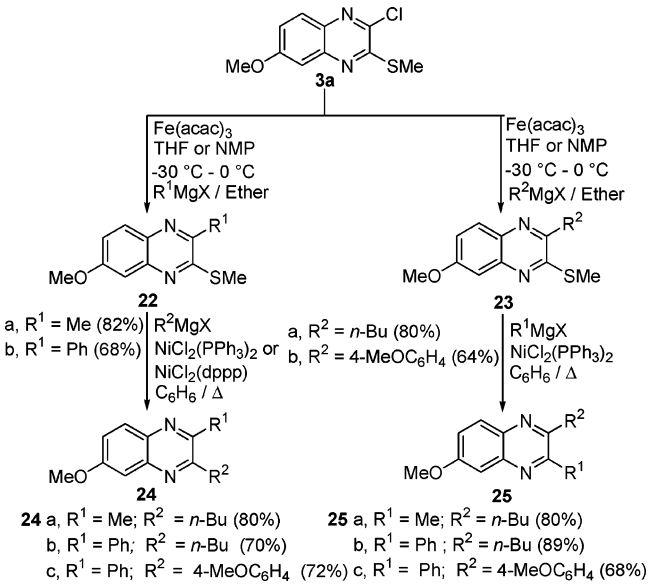
Scheme 5. Synthesis of $5HT_3$ Antagonists



benzylpiperazino)-3-cyano regioisomer **21** could be synthesized from the corresponding 3-chloro-6-methoxy-2-(methylsulfonyl) quinoxaline **13g** in excellent yields through sequential nucleophilic displacement by *N*-benzylpiperazine and cyanide ion (Scheme 4).

Finally, the 3-chloro and 2-methylthio groups in quinoxaline **3a** could be displaced by alkyl or aryl groups by sequential iron-[21] and nickel-catalyzed[22] cross-coupling reactions with the appropriate Grignard reagents as shown in Scheme 6. Thus, we could accomplish the synthesis of both the regioisomers of the hitherto inaccessible unsymmetrical 2-(*n*-butyl)-3-methyl- or 3-(*n*-butyl)-2-methyl- (**24a** and **25a**), 2-(*n*-butyl)-3-phenyl- or 3-(*n*-butyl)-2-phenyl- (**24b** and **25b**), and 2-(4′-methoxyphenyl)-3-phenyl- or 3-(4′-methoxyphenyl)-2-phenyl-7-methoxyquinoxalines (**24c** and **25c**) in high yields with full regiocontrol following the sequential reactions (Scheme 6).

Scheme 6. Regioselective Synthesis of Unsymmetrical Dialkyl/Diaryl Quinoxalines



In summary, we have developed a novel highly regioselective approach for the synthesis of substituted and fused 3-chloro-2-(methylthio)quinoxalines through $POCl_3$ mediated heteroannulation of readily accessible α-nitroketene *N*,*S*-anilinoacetals. The newly developed methodology is general and provides quinoxalines in moderate to excellent yields depending on the nature of the substituent on the aniline ring. The presence of 3-chloro and 2-(methylthio) or 2-(methylsulfonyl) functionalities further makes them useful substrates for the synthesis of wide range of unsymmetrical 2,3-substituted quinoxalines with high regiocontrol via either sequential nucleophilic substitution by various nucleophiles or via metal catalyzed C−C bond formation. Our efforts in this direction are underway and will be reported in due course.

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Supporting Information Available: Analytical and spectroscopic data of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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