JOC*Note*

Dipolar Cycloaddition of Ethyl Isocyanoacetate to 3-Chloro-2-(methylthio)/ 2-(methylsulfonyl)quinoxalines: Highly Regio- and Chemoselective Synthesis of Substituted Imidazo[1,5-*a*]quinoxaline-3-carboxylates†

G. S. M. Sundaram, B. Singh, C. Venkatesh, H. Ila,* and H. Junjappa

Department of Chemistry, Indian Institute of Technology, Kanpur-208016, India

hila@iitk.ac.in

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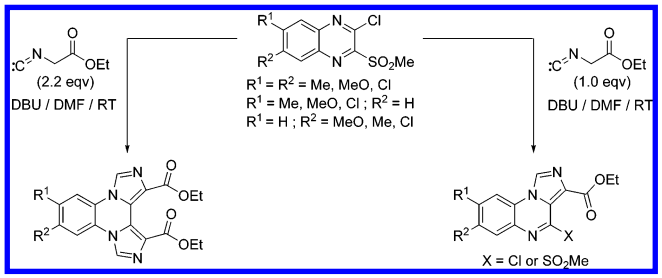
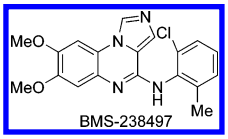


An efficient route for regio- and chemoselective synthesis of substituted 3-(carboethoxy)imidazo[1,5-*a*]quinoxalines and novel diimidazo[1,5-*a*:5′,1′-*c*]quinoxalines via base-induced cycloaddition of ethyl isocyanoacetate to unsymmetrically substituted 3-chloro-2-(methylthio)/2-(methylsulfonyl)quinoxalines has been reported.

Compounds containing azole-fused quinoxalines such as pyrrolo[1,2-*a*]quinoxalines,[1] imidazo[1,2-*a*]quinoxalines,[2] imidazo[1,5-*a*]quinoxalines,[3] [1,2,4]triazolo[4,3-*a*]quinoxalines,[2a,4,5] and 1*H*-imidazo[4,5-*b*]quinoxalines[6] are known to exhibit a wide range of biological activities. Among these compounds, imidazo-[1,5-*a*]quinoxalines and the related imidazo[1,5-*a*]quinoxalin-4-ones are common structural arrays that are found in a number of biologically important and therapeutically useful agents. Thus, they have been used as a template for the synthesis of GABA/benzodiazepine receptor agonists/antagonists,[7] cAMP and cGMP phosphodiesterase inhibitors,[8] A_1- and A_{2a}-adenosine receptor agonists,[9] and several other pharmacologically active compounds.[2a,10−12] More recently, 4-[(2-chloro-6-methylphenyl)-amino]-7,8-dimethoxyimidazo[1,5-*a*]quinoxaline (BMS-238497) has emerged as a novel and potent inhibitor of Src-family kinase $p56^{Lck}$, displaying excellent enzymatic activity against Lck (IC_{50} = 2 nM) and good potency in blocking T-cell proliferation (IC_{50} = 0.67 μM).[13−14]



Mainly two approaches have been reported in the literature for the construction of the imidazo[1,5-*a*]quinoxalin-4-one ring system. In the first approach, an appropriately substituted imidazole derivative is introduced into a substituted *o*-halonitrobenzene derivative followed by intramolecular cyclization of the resulting *ortho*-substituted imidazobenzene.[8,12,15] The second approach involves annulation of an imidazole ring to *N*-protected quinoxalin-2-one mediated by a dipolar cycloaddition of tosylmethyl or benzyl isocyanide as the key step.[3,7,16] Whereas the first approach is not feasible for the synthesis of imidazoquinoxalines with electron-donating substituents (OMe), the second approach suffers from several drawbacks such as a lack of regioselectivity encountered in the formation of quinoxalin-2-ones from unsymmetrical phenylene-1,2-diamines and poor chemoselectivity (*N* vs *O*-alkylation) observed in the *N*-protection step.[16] Also, the method requires not easily accessible, air-sensitive, unstable phenylene-1,2-diamines as initial precursors. During the course of our ongoing studies on polarized ketene *S*,*S*- and *N*,*S*-acetals,[17,18] we have recently reported a novel highly regioselective synthesis of unsymmetrical 2,3-substituted quinoxalines.[19] The overall strategy involves $POCl_3$-mediated heterocyclization of the readily accessible α-nitroketene *N*,*S*-anilino acetals, furnishing regiospecifically substituted 3-chloro-2-(methylthio)quinoxalines

† Dedicated to Prof. Miguel Yus on his 60th birthday.

* To whom correspondence should be addressed. Fax: 91-0512-2597436, 91-0512-2590260.

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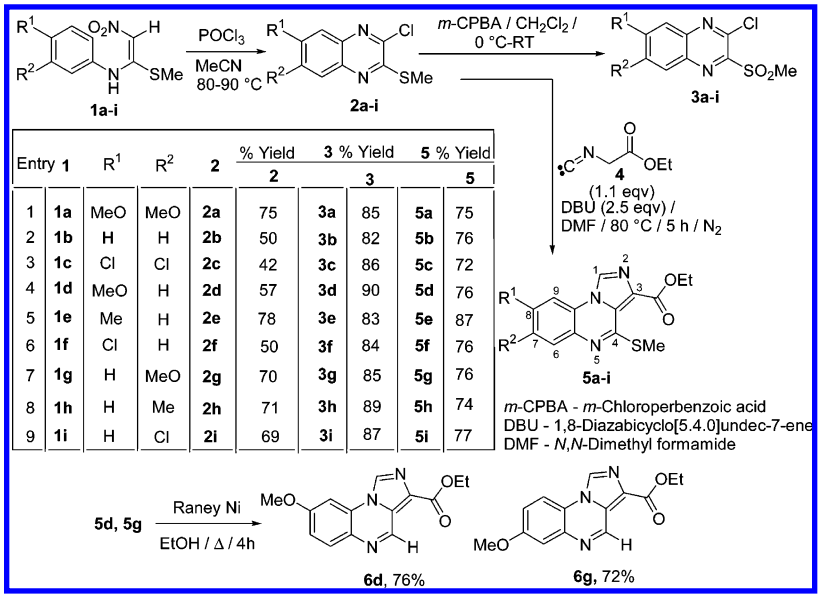
SCHEME 1

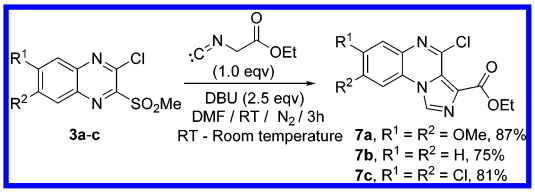


Entry	1	R^1	R^2	2	% Yield 2	3	% Yield 3	5	% Yield 5
1	**1a**	MeO	MeO	**2a**	75	**3a**	85	**5a**	75
2	**1b**	H	H	**2b**	50	**3b**	82	**5b**	76
3	**1c**	Cl	Cl	**2c**	42	**3c**	86	**5c**	72
4	**1d**	MeO	H	**2d**	57	**3d**	90	**5d**	76
5	**1e**	Me	H	**2e**	78	**3e**	83	**5e**	87
6	**1f**	Cl	H	**2f**	50	**3f**	84	**5f**	76
7	**1g**	H	MeO	**2g**	70	**3g**	85	**5g**	76
8	**1h**	H	Me	**2h**	71	**3h**	89	**5h**	74
9	**1i**	H	Cl	**2i**	69	**3i**	87	**5i**	77

in moderate to excellent yields depending on the nature of the substituents on the aniline ring.[19] This new heteroannulation protocol avoids phenylene-1,2-diamines as precursors, and the 3-chloro and 2-methylthio (or 2-methylsulfonyl) functionalities in these newly synthesized quinoxalines can be smoothly replaced by various heteronucleophiles or carbon nucleophiles in a highly regio- and chemoselective fashion via sequential nucleophilic substitution or metal-catalyzed cross-coupling, yielding a wide range of unsymmetrically 2,3-substituted quinoxalines with high regiocontrol.[19] In continuation of these studies, we became interested in investigating dipolar cycloaddition of these newly synthesized 3-chloro-2-(methylthio)/2-(methylsulfonyl)quinoxalines with activated methyl isocyanides with a view to develop a regioselective synthesis of unsymmetrically substituted imidazo[1,5-*a*]quinoxalines because of the broad spectrum of biological activity displayed by this class of compounds. We have successfully achieved this goal, and herein we describe the results of our studies.

The desired substituted 3-chloro-2-(methylthio)quinoxalines **2a**−**i** were prepared according to our reported procedure via intramolecular cyclization of nitroketene *N*,*S*-anilino acetals **1a-i** in the presence of $POCl_3$ in acetonitrile at 70−80 °C (Scheme 1).[19] All the 3-chloro-2-(methylthio)quinoxalines **2a**−**i** were transformed into 2-(methylsulfonyl)quinoxalines **3a**−**i** via mCPBA oxidation at room temperature. We selected ethyl isocyanoacetate (**4**) as a dipolarophile for cycloaddition studies with a few selected 3-chloro-2-(methylthio)quinoxalines **2** (Scheme 1). Thus,

SCHEME 2



the reaction of **2a** with **4** was optimized in the presence of various bases (NaH, K^+-*t*-BuO^-, DBU, *n*-BuLi, NaHMDS) and solvents. The best results were obtained when **2a** was reacted with **4** in the presence of DBU in DMF at 80 °C for 4−5 h, furnishing only one product (75%) which was characterized as ethyl 7,8-dimethoxy-4-(methylthio)imidazo[1,5-*a*]quinoxaline-3-carboxylate (**5a**) on the basis of spectral and analytical data (Scheme 1). The product **5a** is apparently formed by dipolar cycloaddition of ethyl isocyanoacetate to the more activated 3,4-N═C−Cl bond of **2a**, whereas no reaction is observed with the 1,2-N═C−SMe bond. A similar trend was also observed when other substituted quinoxalines **2b**−**i** were reacted with **4** under identical conditions, yielding substituted 4-(methylthio)imidazo[1,5-*a*]quinoxaline-3-carboxylates **5b**−**i** in high yields (Scheme 1). Two of the imidazoquinoxalines, **5d** and **5g**, were subjected to Raney Ni dethiomethylation, yielding the regioisomeric 4-unsubstituted 8-methoxy-substituted (**6d**) and 7-methoxy-substituted (**6g**) imidazo[1,5-*a*]quinoxalines in good yields (Scheme 1).

The quinoxalines **3a**−**i** having a more activated 2-(methylsulfonyl) functionality were next subjected to cycloaddition with ethyl isocyanoacetate with a view to examine the effect of the substituents on the chemo- and regioselectivity of the reaction (Schemes 2 and 3).[20] Thus, the reaction of symmetrically substituted 3-chloro-6,7-dimethoxy-2-(methylsulfonyl)quinoxaline (**3a**) with ethyl isocyanoacetate (1.0 equiv) was found to be very facile, proceeding smoothly at room temperature with the disappearance of the starting materials within 3 h. Workup and analysis of the reaction mixture showed formation of only one major product (87%), which, after isolation, was character-

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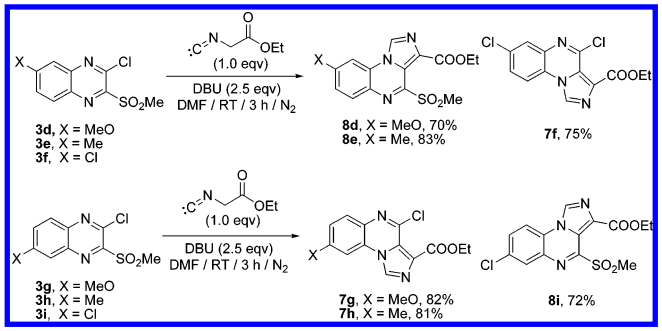
SCHEME 3

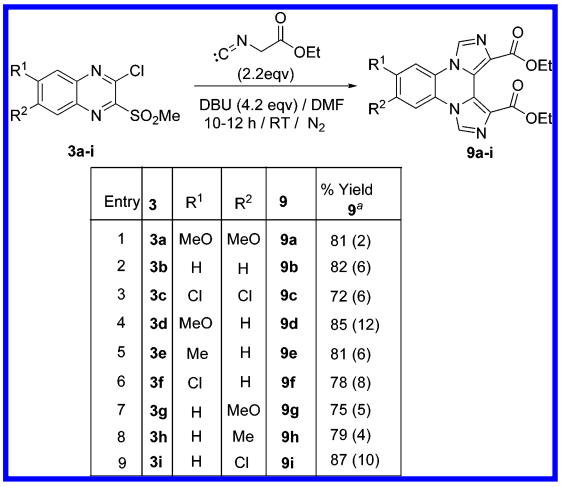


ized as ethyl 4-chloro-6,7-dimethoxy-imidazo[1,5-*a*]quinoxaline-3-carboxylate (**7a**) on the basis of spectral and analytical data (Scheme 2). Similarly, the corresponding unsubstituted quinoxaline **3b** and 6,7-dichloro-2-(methylsulfonyl)-3-chloroquinoxaline (**3c**) also furnished only regioisomeric imidazo[1,5-*a*]quinoxalines **7b**,**c** as the main products, which are evidently derived by cycloaddition of ethyl isocyanoacetate anion to the 1,2-N═C—SO_2Me bond of the quinoxalines **3b**,**c** in a highly chemoselective fashion (Scheme 2).

A further detailed investigation of cycloaddition studies on unsymmetrically substituted 3-chloro-2-(methylsulfonyl)quinoxalines **3d**−**i** displayed an interesting substituent effect on the chemo- and regioselectivity of the reaction. Thus, the quinoxalines **3d** and **3e** having an electron-donating methoxy or methyl group in the 6-position reacted with ethyl isocyanoacetate (1 equiv) under the earlier described conditions to give exclusively 4-(methylsulfonyl)imidazo[1,5-*a*]quinoxalines **8d**,**e** (formed by cycloaddition of **4** to the 3,4-N═C—Cl bond), whereas the corresponding 7-methoxy-substituted (**3g**) and 7-methyl-substituted (**3h**) 2-(methylsulfonyl)quinoxalines, on the other hand, underwent cycloaddition to the 1,2-N═C—SO_2Me double bond in a highly chemoselective fashion, furnishing the regioisomeric products imidazo[1,5-*a*]quinoxalines **7g** and **7h** in 82% and 81% yields, respectively (Scheme 3). Interestingly, the order of chemoselectivity was found to be reversed in the case of 6-chloro- and 7-chloro-2-(methylsulfonyl)quinoxalines **3f** and **3i**, which on reaction with 1 equiv of ethyl isocyanoacetate under standard reaction conditions afforded the respective 4,7-dichloroimidazo[1,5-*a*]quinoxaline-3-carboxylate **7f** (75%) and the corresponding 7-chloro-4-(methylsulfonyl) derivative **8i** (72%), which are apparently derived from cycloaddition of **4** to the 1,2-N═C—SO_2Me and 3,4-N═C—Cl double bonds of **3f** and **3i**, respectively (Scheme 3).

These observations can be explained in terms of the electronic effects of various substituents present in the quinoxalines **3a**−**i**. Thus, in the case of unsubstituted and symmetrically substituted quinoxalines **3a**−**c**, the electron-withdrawing effect of the 2-(methylsulfonyl) group appears to predominate over that of the 3-chloro substituent, thus directing the cycloaddition of the ethyl isocyanoacetate anion to the 1,2-double bond of quinoxalines **3a**−**c**, yielding 4-chloroimidazoquinoxalines **7a**−**c** exclusively in high yields (Scheme 2). On the other hand, the presence of electron-releasing 6-methoxy or 6-methyl groups increases the electron density at the 2-position of the quinoxalines **3d**,**e**, resulting in the attack of the ethyl isocyanoacetate anion on the more electrophilic 3,4-N═C—Cl bond to give the products imidazoquinoxalines **8d**,**e** exclusively in excellent yields (Scheme 3). Formation of the products **7g**,**h** from the 7-methoxy- and 7-methylquinoxalines **3g**,**h** can also be explained in a similar manner. On the other hand, reversal of the regio- and chemoselectivity observed in the cycloaddition of 6- and 7-chloro-substituted quinoxalines **3f** and **3i** to give **7f** and **8i**, respectively, appears to be probably due to predominance of the electron-withdrawing effect of the chloro group over its +M effect.

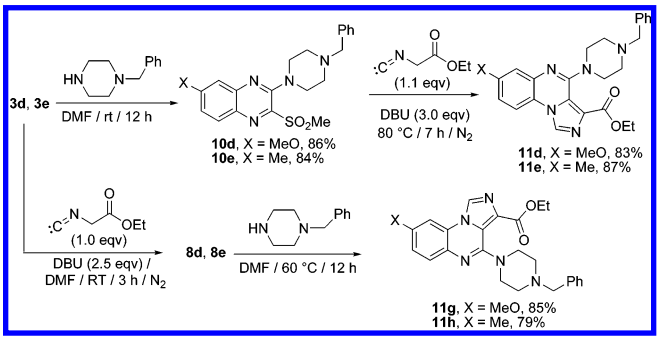
SCHEME 4



Entry	3	R^1	R^2	9	% Yield 9[a]
1	**3a**	MeO	MeO	**9a**	81 (2)
2	**3b**	H	H	**9b**	82 (6)
3	**3c**	Cl	Cl	**9c**	72 (6)
4	**3d**	MeO	H	**9d**	85 (12)
5	**3e**	Me	H	**9e**	81 (6)
6	**3f**	Cl	H	**9f**	78 (8)
7	**3g**	H	MeO	**9g**	75 (5)
8	**3h**	H	Me	**9h**	79 (4)
9	**3i**	H	Cl	**9i**	87 (10)

[a] Yields in parentheses represent yields of **9** obtained in reaction of **3** with 1.0 equiv of ethyl isocyanoacetate.

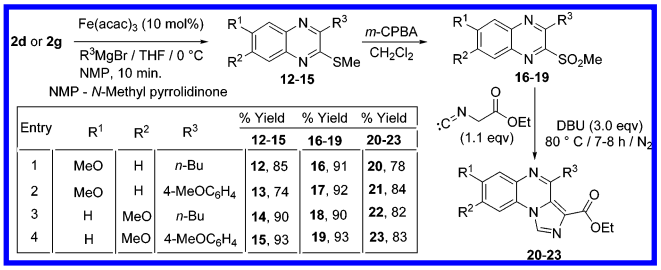
SCHEME 5



In all the reactions of substituted 3-chloro-2-(methylsulfonyl)-quinoxalines with 1 equiv of ethyl isocyanoacetate, formation of minor products (2−10%) was observed, which were characterized as the bis(imidazo)quinoxalinedicarboxylates **9a**−**i** on the basis of their spectral and analytical data. These hitherto unreported tetracyclic diimidazo[1,5-*a*:5′,1′-*c*]quinoxalines **9a**−**i** were obtained as exclusive products in excellent yields when the quinoxalines **3a**−**i** were reacted with 2.2 equiv of ethyl isocyanoacetate for a prolonged time (10−12 h) at room temperature (Scheme 4).

To further demonstrate the scope and versatility of this procedure for regiospecific synthesis of unsymmetrically substituted imidazo[1,5-*a*]quinoxalines, regioisomeric 4-(cycloamino)- and 4-alkyl/arylimidazo[1,5-*a*]quinoxalines were synthesized as shown in Schemes 5 and 6. Thus, the cycloaddition of ethyl isocyanoacetate (1.1 equiv) to 3-(*N*-benzylpiperazino)-6-methoxy-2-(methylsulfonyl)- and 3-(*N*-benzylpiperazino)-6-methyl-2-(methylsulfonyl)quinoxalines **10d,e** under the earlier described conditions afforded the corresponding 7-substituted 4-(*N*-benzylpiperazino)-imidazo[1,5-*a*]quinoxaline-3-carboxylates **11d** and **11e** in excellent yields (Scheme 5). The *N*-benzylpiperazino-substituted quinoxalines **10d,e** were prepared in good yields by chemoselective nucleophilic displacement on the corresponding 3-chloro-2-(methylsulfonyl)quinoxalines **3d** and **3e**. Alternatively, the regioisomeric 4-(*N*-benzylpiperazino)-8-methoxy- and

SCHEME 6



Entry	R^1	R^2	R^3	% Yield 12-15	% Yield 16-19	% Yield 20-23
1	MeO	H	*n*-Bu	**12**, 85	**16**, 91	**20**, 78
2	MeO	H	4-MeOC_6H_4	**13**, 74	**17**, 92	**21**, 84
3	H	MeO	*n*-Bu	**14**, 90	**18**, 90	**22**, 82
4	H	MeO	4-MeOC_6H_4	**15**, 93	**19**, 93	**23**, 83

4-(*N*-benzylpiperazino)-8-methylimidazo[1,5-*a*]quinoxalines **11g** and **11h** could be obtained by direct nucleophilic displacement of the 4-methylsulfonyl group in the previously synthesized 8-substituted imidazoquinoxaline derivatives **8d** and **8e**, respectively, by *N*-benzylpiperazine (Scheme 5).

Finally, the application of our method for the synthesis of regioisomeric 4-alkyl/aryl-7- or 8-methoxyimidazo[1,5-*a*]quinoxalines **20**−**23** is depicted in Scheme 6. The desired regioisomeric 3-alkyl/aryl-6-methoxy-2-(methylsulfonyl)- and 3-alkyl/aryl-7-methoxy-2-(methylsulfonyl)quinoxalines **16**−**19** were prepared by our earlier reported procedure[19] via iron-catalyzed cross-coupling of *n*-butyl- and (4-methoxyphenyl)magnesium halides on the quinoxalines **2d** and **2g** followed by mCPBA oxidation of the resulting 3-alkyl/aryl-2-(methylthio)quinoxalines **12**−**15** to the corresponding 2-(methylsulfonyl)quinoxalines **16**−**19**, respectively. Subsequent cycloaddition of ethyl isocyanoacetate on 3-alkyl/aryl-6-methoxy-2-(methylsulfonyl)quinoxalines **16** and **17** or the corresponding 7-methoxy analogues **18** and **19** furnished the regioisomeric 4-alkyl/arylimidazoquinoxalines **20** and **21** or **22** and **23** in excellent yields (Scheme 6).

In summary, we have developed a highly regio- and chemoselective approach for the synthesis of substituted 3-(carboethoxy)-imidazo[1,5-*a*]quinoxalines via base-induced cycloaddition of ethyl isocyanoacetate to unsymmetrically substituted 3-chloro-2-(methylthio)/2-(methylsulfonyl)quinoxalines. It should be noted that the earlier cycloaddition routes to this heterocyclic template involve reaction of either tosylmethyl or benzyl isocyanides with the activated 3,4-double bond of *N*-substituted quinoxalin-2-ones, furnishing only imidazo[1,5-*a*]quinoxaline-4-one derivatives, whereas there is no report of direct cycloaddition of activated methyl isocyanides to the −C═N bond of the quinoxalines. Also the previous methods suffer from several limitations such as poor regio- and chemoselectivity and air sensitivity of electron-rich phenylene-1,2-diamine precursors. Whereas 3-chloro-2-(methylthio)quinoxalines **2a**−**i** undergo exclusive cycloaddition to the 3,4-N═C−Cl bond, in the case of substituted 3-chloro-2-(methylsulfonyl)quinoxalines **3a**−**i**, the regio- and chemoselectivity is governed by the nature and position of the substituent on the benzene ring of quinoxaline. The cycloaddition of 2 equiv of ethyl isocyanoacetate to both the 1,2- and 3,4-N═C bonds of 3-chloro-2-(methylsulfonyl)-quinoxalines affords novel hitherto unreported diimidazo[1,5-*a*:5′,1′-*c*]quinoxalines in excellent yields. The methodology is also useful for regioselective synthesis of alkyl/aryl- and amino-substituted imidazo[1,5-*a*]quinoxalines which can be derivatized for creating further points of diversity on the quinoxaline template.

Exprimental Section

General Procedure for the Base-Induced Cycloaddition Reaction of Ethyl Isocyanoacetate to 3-Chloro-2-(methylthio)-quinoxalines 2a−**i**. An oven-dried 100 mL two-necked flask was charged with the corresponding 2,3-disubstituted quinoxalines (1.5 mmol), ethyl isocyanoacetate (1.65 mmol), and DMF (10 mL) under a N_2 atmosphere and the solution stirred for 5 min at room temperature. DBU (3.75 mmol) was added to this stirring solution, and the resulting mixture was heated at 80 °C for 5 h (monitored by TLC). It was then cooled and poured into water (100 mL). The mixture was extracted with chloroform (3 × 50 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, adsorbed onto silica gel, and purified using hexane−EtOAc as the eluent to give 3-(carboethoxy)imidazo[1,5-*a*]quinoxalines 5a−i in good yields.

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Supporting Information Available: Additional experimental procedures and spectral characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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