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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 6131–6136

Synthesis of fused tetrahydro-β-carbolinequinoxalinones in 1-*n*-butyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)-imide ([bdmim][Tf_2N]) and 1-*n*-butyl-2,3-dimethylimidazolium perfluorobutylsulfonate ([bdmim][$PFBuSO_3$]) ionic liquids

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Received 8 March 2005; revised 27 June 2005; accepted 29 June 2005
Available online 14 July 2005

Abstract—Starting from tryptophan methyl ester, a three-step synthesis of fused tetrahydro-β-carbolinequinoxalinones in two new ionic liquids, [bdmim][Tf_2N] and [bdmim][$PFBuSO_3$], was described. Both ionic liquids can be readily prepared from commercially available starting materials in high yields. Unlike the commonly used [PF_6]-based ionic liquids that evidently undergo slow hydrolysis of the PF_6 anion with the concomitant release of HF, ionic liquids of [bdmim][Tf_2N] and [bdmim][$PFBuSO_3$] are not only chemically stable but also apparently inert to hydrolysis and therefore organic reactions carried out in both ionic liquids proceed smoothly with good yields. The overall isolated yields for this three-step synthesis of tetrahydro-β-carbolinequinoxalinones were 34–55%. To the best of our knowledge, the preparation of fused tetrahydro-β-carbolinequinoxalinones was unprecedented.

Ionic liquids are a class of highly polar solvents that are entirely constituted of ions.[1] They are liquid at low temperature (melting point typically below 100 °C),[2] and are often considered as recyclable and environmentally friendly substitutes for conventional organic solvents, mainly due to their attractive negligible vapor pressure, chemical and thermal stability, non-flammability, and high ionic conductivity. Because of these intriguing properties, ionic liquids have recently been found to be the solvents of choice for a large array of organic reactions.[1] When applicable, this non-volatile nature of ionic liquids ensures an effective product isolation by distillation. In addition, the high solubility of ionic liquids to many organic and inorganic compounds can in principle lead to enhanced rates, better selectivity, and improved yields in reactions.[1,3,4]

A number of ionic liquids are known from the literature.[1] Up to now, alkylimidazolium salts are still the most studied and best characterized ionic liquids. For example, 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) ionic liquid has been widely used by many researchers for a combination of reasons, including its ease of preparation, lack of vapor pressure, and, most significantly, hydrophobicity that presents an obvious advantage as a potential replacement for volatile organic solvents in developing green processes. Though useful in organic synthesis and popular in ionic liquid research, [bmim][PF_6] however is not totally stable chemically; it is well documented for the instability of PF_6 anion towards slow hydrolysis upon contact with moisture.[5]

Our idea of the present work to develop new and chemically inert ionic liquids as solvents for organic synthesis came from reports[5] that the popular [PF_6]-based ionic liquids have the propensity to decompose to release HF, HPO_2F_2, H_2PO_3F, and H_3PO_4, and also from our own experience[6] that the 'C2-unmodified' [bmim]-based ionic liquids are not compatible with the highly basic reaction conditions. In addition, various experimental observations of the chemical instability of hexafluorophosphate containing ionic liquids has been noted or discussed in the literature.[7] Moreover, Earle et al. have recently reported that certain ionic liquids are chemically reactive and can greatly influence the outcome of

Keywords: Ionic liquid; Organic synthesis; Tetrahydro-β-carbolinequinoxalinone.
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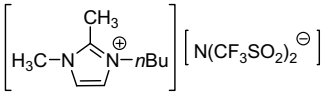
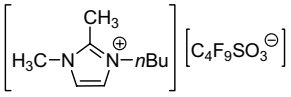
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.06.153

the electrophilic aromatic substitution reactions.[8] These disadvantages limited the application of ionic liquids to synthetic reactions. Therefore, there should be an urgent need to develop ionic liquids with new formulation. Fortunately, many valuable results from detailed to systematic studies of room temperature ionic liquids have been made available in the literature.[1] It is known, for example, that the diversity of possible cations and anions, along with the types of substituent groups on the cations, allows fine-tuning of melting points, hydrophobicity, and solvent properties of ionic liquids. In our program of ionic liquid research, we aim to develop new ionic liquids as direct replacements for conventional organic solvents in multistep organic synthesis and report here our preliminary progress towards preparing chemically stable ionic liquids for the synthesis of, for example, fused tetrahydro-β-carbolinequinoxalinones.

In this letter, two new hydrophobic and chemically stable ionic liquids, 1-*n*-butyl-2,3-dimethylimidazolium bis(trifluoromethylsulfonyl)imide ([bdmim][Tf_2N])[9] and 1-*n*-butyl-2,3-dimethylimidazolium perfluorobutylsulfonate ([bdmim][$PFBuSO_3$]), are described. Both ionic liquids can be conveniently prepared by direct quaternization of 1,2-dimethylimidazole; different anions can subsequently be introduced by anion exchange.[10] The [bdmim] cation was employed in the new ionic liquids for good reasons that the proton at the C2 carbon in [bmim] cations is chemically acidic and can be readily exchanged with D_2O at room temperature and neutral pH,[11] and under basic conditions this [bmim] cation readily reacts with various electrophiles such as aldehydes.[6] The [bdmim] cation is chemically inert under the above conditions, since its C2 carbon has been substituted and blocked by a methyl group. Fluoroanions of [Tf_2N] and [$PFBuSO_3$] were chosen in our new ionic liquid formulation because the strong delocalization of the negative charge in the fluoroanions weakens its interaction with the cation, eventually resulting in lower melting points of ionic liquids.[12] In addition, the organofluoro compounds are known to possess unique properties such as resistance to extremes of temperature and pressure, resistance to corrosive acids and bases, and inertness to oxidizing agents.[13] Furthermore, both sulfonate and sulfonimide functional groups present in ionic liquids are thought to be hydrolytically more stable than, for example, the ester linkage in organosulfate-based ionic liquids such as the hydrophilic [bmim][octylsulfate] at elevated temperatures. Both [bdmim][Tf_2N] and [bdmim][$PFBuSO_3$] ionic liquids are miscible with polar organic solvents—methanol, acetone, dichloromethane, ethyl acetate, and acetonitrile—and insoluble in less polar species such as diethyl ether, *n*-hexane, and toluene. Like ionic liquids incorporating PF_6, the two new ionic liquids are immiscible with water.



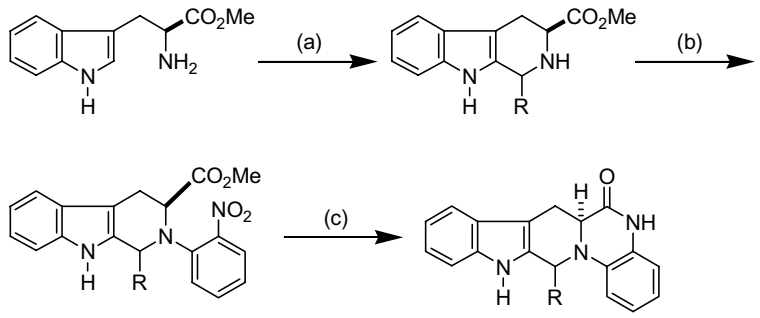
[bdmim][Tf_2N]



[bdmim][$PFBuSO_3$]

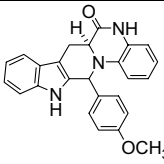
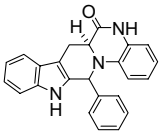
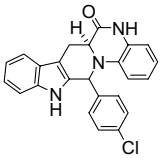
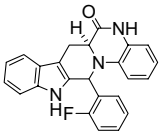
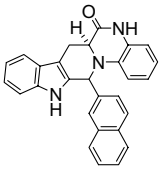
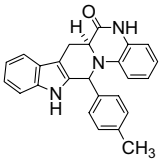
[bdmim][Tf_2N] is a liquid at ambient temperature. We were interested in the bis(trifluoromethylsulfonyl)imide-based ionic liquids because of their reported minimal water association with the liquid (<2%)[12,14] and unusual low melting points.[1b] We rationalized that, mainly due to its low viscosity, resistance to thermal and electrochemical reactions, and immiscibility with water and less polar organic solvents, the [bdmim][Tf_2N] ionic liquid should be a superb solvent for applications in organic synthesis. As the other choice, the [bdmim][$PFBuSO_3$] ionic liquid is a solid at room temperature (mp 59–61 °C), but becomes a clear liquid with modest heating or when small amounts of water (or organic solvents) are added. This was totally expected because previous reports have demonstrated that methylation at the C2 carbon of alkylimidazolium cation greatly increases the melting point of ionic liquids.[1,15]

In this work, we demonstrated for the first time the synthesis of fused tetrahydro-β-carbolinequinoxalinones in both [bdmim][Tf_2N] and [bdmim][$PFBuSO_3$] ionic liquids. For compounds of tetrahydro-β-carbolinequinoxalinones, the structure of tetrahydro-β-carboline is a central core for many biologically important indole alkaloids[16] and the moiety of quinoxalinone often exhibits a wide spectrum of biological activities such as anti-HIV agents, antihypertensives, and ligands for a number of protein receptors.[17] Most recently, several new quinoxalinone-based antithrombotic agents were synthesized and reported as highly specific subnanomolar inhibitors for blood coagulation factor Xa.[18] Scheme 1 outlines our total synthesis of fused tetrahydro-β-carbolinequinoxalinones in ionic liquids.[19] Three reactions were incorporated in the synthesis: the Pictet–Spengler condensation[16,6a] used in step a, the nucleophilic aromatic substitution as step b, and the cyclization-upon-reduction reaction for the last step. With respect to the first step of synthesis, in our laboratory we have routinely employed the Pictet–Spengler reaction to construct tetrahydro-β-carbolines.[6a] Under our optimized condition in ionic liquid, it required only a short reaction time to complete the reaction (Table 1). As shown in Table 1, all aldehydes studied complete the Pictet–Spengler reaction in less than 2 h. The isolated yields for the Pictet–Spengler adducts were good to excellent (75–96%). Under our experimental condition, the desired products were isolated as a mixture of two diastereoisomers with the cis/trans ratios close to unity, that is, no apparent preference for a particular product isomer was resulted.[6a] The tetrahydro-β-carbolines obtained were directly used for the subsequent step of nucleophilic aromatic substitution reaction to set up for the core preparation of quinoxalinones. Quinoxalinones have been studied and prepared both in solution and on solid support.[20] Our quinoxalinone synthesis in ionic liquids first involved the direct coupling of 2-nitrofluorobenzene with sterically hindered and less reactive tetrahydro-β-carbolines. This problem of unusual low reactivity of the secondary amine of tetrahydro-β-carbolines has been previously encountered by us and others.[6a] After a few experimental trials, we were pleased to find that these *ipso*-fluoro displacement reactions proceeded smoothly to afford arylamines in both ionic



Scheme 1. Synthesis of tetrahydro-β-carbolinequinoxalinones. Reagents and conditions: (step a) L-tryptophan methyl ester (0.39 mmol), 10% TFA, ionic liquid (0.2 mL), aldehyde (4 equiv), 70 °C; (step b) 1-fluoro-2-nitrobenzene (2 equiv), DMAP (2 equiv), ionic liquid (0.2 mL), 70 °C; (step c) $SnCl_2$ (4 equiv), ionic liquid/ethanol (1:1, 0.2 mL), 70 °C.

Table 1. Synthesis of fused tetrahydro-β-carbolinequinoxalinones in ionic liquids of [bdmim][Tf_2N] and [bdmim][$PFBuSO_3$][a]

Entry	Products	Ionic liquid	Step a		Step b		Step c	
			Reaction time (h)	Yield[b] (%)	Reaction time (h)	Yield[b] (%)	Reaction time (h)	Yield[b] (%)
1		[bdmim][Tf_2N]	1.5	82	3	87	4	64
2		[bdmim][Tf_2N]	0.6	80	8	74	3.5	66
3		[bdmim][Tf_2N]	0.7	75	4	90	4	71
4		[bdmim][$PFBuSO_3$]	0.9	81	5	69	3.5	61
5		[bdmim][$PFBuSO_3$]	1.5	91	8	69	3	61
6		[bdmim][$PFBuSO_3$]	1	96	5	93	3	62

[a] The reaction conditions: (step a) L-tryptophan methyl ester (0.39 mmol), 10% TFA, ionic liquid (0.2 mL), aldehyde (4 equiv), 70 °C; (step b) 1-fluoro-2-nitrobenzene (2 equiv), DMAP (2 equiv), ionic liquid (0.2 mL), 70 °C; (step c) $SnCI_2$ (4 equiv), ionic liquid/ethanol (1:1, 0.2 mL), 70 °C.
[b] Isolated yield.

liquids at 70 °C with respectable yields (69–93%) (Table 1). Conventional methods for arylamine synthesis typically involve the use of excessive bases and polar solvents such as DMF or DMSO; they often took days at ambient temperature[21] or much longer hours at high temperatures to complete the reactions.[22] It is noted that our approach of using ionic liquid as the reaction medium was effective with sterically hindered and substituted tetrahydro-β-carbolines.[23] Moreover, if this nucleophilic aromatic substitution reaction was conducted in

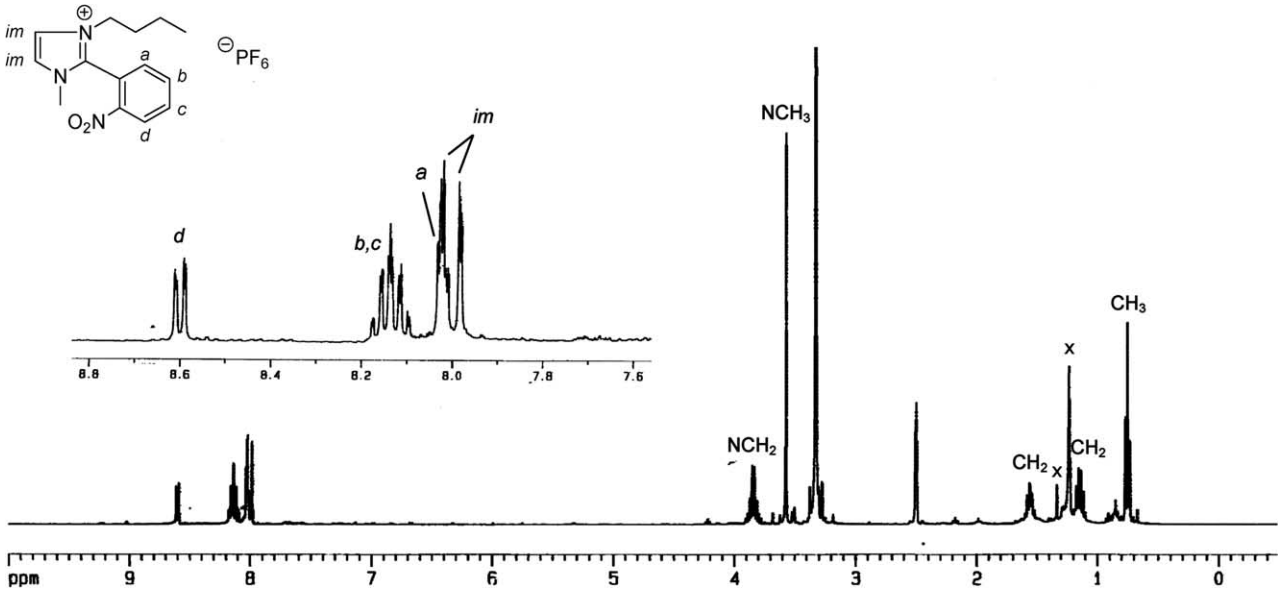


Figure 1. ^{1}H NMR spectrum of the 1-fluoro-2-nitrobenzene conjugated [bmim][PF_6] adduct in DMSO-d_6.

the commonly used [bmim][PF_6] ionic liquid under the same experimental condition, the desired arylamine products were obtained with low yields (20% and 19% for entries 2 and 6 in step b reaction, respectively) and found to be contaminated with the 1-fluoro-2-nitrobenzene-conjugated [bmim][PF_6] adduct (**1**). The chemical nature of adduct **1** could be readily verified and unambiguously confirmed by proton NMR (Fig. 1). The disappearance of the C-2 proton signal at δ 9.07 ppm clearly indicated the site of conjugation of [bmim][PF_6] with the electrophilic 1-fluoro-2-nitrobenzene. This chemical reactivity of [bmim][PF_6] ionic liquid to electrophilic compounds under basic conditions has previously been reported.[4,6b] We performed the last, cyclization-upon-reduction reaction (step 3 in Scheme 1) without the aid of additional bases. Our results indicated that, under the standard reduction condition by tin chloride and the subsequent intramolecular cyclization, the desired tetrahydro-β-carbolinequinoxalinones were readily formed as sole products in moderate overall isolated yields (34–55%). Furthermore, under the experimental conditions developed in this study, only minute amounts of ionic liquids were used to dissolve all required starting materials and, in such high concentrations, the total synthesis of tetrahydro-β-carbolinequinoxalinones could therefore be readily achieved in short reaction time. Accordingly, two new ionic liquids developed in this work apparently are chemically stable to all reagents and conditions employed in this study and therefore should emerge as useful replacements for the popular PF6-based ionic liquids and other volatile organic solvents commonly used in organic synthesis.

In this study, we report two new ionic liquids, [bdmim][Tf_2N] and [bdmim][$PFBuSO_3$], that appear to fulfill the requirement as inert solvents in organic synthesis. We have demonstrated that both ionic liquids were well suited for the three-step synthesis of fused tetrahydro-β-carbolinequinoxalinones. These new ionic liquids open exciting perspectives of use as solvents for synthetic applications of many heterocycles and non-heterocycles of biological significance. Furthermore, these ionic liquids may enable new applications that are not possible with conventional solvents.

Acknowledgments

We gratefully acknowledge support of this work through grants from the National Science Council (NSC93-2113-M-194-019, NSC92-2751-B-001-014, and NSC92-2218-E-194-015).

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10. Preparation and characterization of [bdmim][$PFBSO_3$] and [bdmim][Tf_2N] ionic liquids: To a round-bottomed flask containing 1,2-dimethylimidazole (15.0 g, 156 mmol) was added 1-bromobutane (18.5 mL, 172 mmol). The mixture was stirred and refluxed at 80 °C for 2 h. Using iodine for compound visualization, TLC could be employed to monitor the progress of the reaction. The resulting viscous reaction solution was cooled to room temperature and mixed with water (20 mL), and then washed with ethyl acetate (3 × 20 mL). The residual ethyl acetate present in aqueous solution was removed by heating to 60 °C under reduced pressure. The lyophilization of the aqueous solution afforded the 1-*n*-butyl-2,3-dimethylimidazolium bromide ([bdmim][Br]) with good isolated yield (88%, 32.8 g).
Synthesis of [bdmim][$PFBuSO_3$]: To a solution containing [bdmim][Br] (8 g, 34 mmol) and water (20 mL) was added potassium nonafluorobutanesulfonate (11.6 g, 34 mmol). The mixture was allowed to proceed the ion exchange for 12 h at room temperature. Two phases were formed in the mixture solution. The resulting solution was diluted with dichloromethane (20 mL) and then washed with water (3 × 20 mL). Removal of the solvent under reduced pressure afforded the 1-*n*-butyl-3-methylimidazolium perfluoro-1-butanesulfonate ([bdmim][$PFBuSO_3$]) with good isolated yield (88%, 13.2 g); mp 59–61 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.89 (t, 3H, $J = 7.40$ Hz, CH_3), 1.23–1.32 (m, 2H, CH_2), 1.66–1.73 (m, 2H, CH_2), 2.57 (s, 3H, CH_3), 3.73 (s, 3H, NCH_3), 4.09 (t, 2H, $J = 7.24$ Hz, NCH_2), 7.59 (d, 1H, $J = 1.96$ Hz, C═CH), 7.63 (d, 1H, $J = 2.00$ Hz, C═CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 9.3, 13.4, 19.1, 31.4, 34.8, 47.5, 105.0–120.0 (m, C_4F_9), 121.1, 122.5, 144.5; FAB-HRMS m/z $[M]^+$ calcd = 153.1386, obsd = 153.1392.
Synthesis of [bdmim][Tf_2N]: To a solution containing [bdmim][Br] (8.0 g, 34 mmol) and water (20 mL) was added bistrifluoromethanesulfonimide lithium salt (9.85 g, 34 mmol). The mixture was allowed to proceed the ion exchange for 12 h in room temperature. Two phases were formed in the mixture solution. The resulting solution was diluted with dichloromethane (20 mL) and then washed with water (3 × 20 mL). Removal of solvent under reduced pressure afforded the 1-*n*-butyl-3-methylimidazolium bistrifluoromethanesulfonimide ([bdmim][Tf_2N]) with excellent isolated yield (98%, 15.1 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.90 (t, 3H, $J = 7.28$ Hz, CH_3), 0.90–1.33 (m, 2H, CH_2), 1.64–1.72 (m, 2H, CH_2), 2.57 (s, 3H, CH_3), 3.74 (s, 3H, NCH_3), 4.09 (t, 2H, $J = 7.24$ Hz, NCH_2), 7.59 (d, 1H, $J = 1.96$ Hz, C═CH), 7.62 (d, 1H, $J = 2.00$ Hz, C═CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 9.3, 13.5, 19.0, 31.3, 34.8, 47.5, 118.1, 119.7 (q, $J_{CF} = 320$ Hz, CF_3), 121.0, 122.5, 144.4; FAB-HRMS m/z $[M]^+$ calcd = 153.1386, obsd = 153.1390.
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19. General procedure for the synthesis of tetrahydro-β-carbolinequinoxalinones. L-Tryptophan methyl ester hydrochloride (0.393 mmol) was dissolved in an ionic liquid (0.2 mL; [bdmim][Tf_2N] or [bdmim][$PFBuSO_3$]) containing 10% (v/v) trifluoroacetic acid. The aldehyde (1.57 mmol) was added in one portion to the stirred mixture at 70 °C and the reaction was allowed to proceed until tryptophan methyl ester was completely consumed as indicated by TLC (for reaction time, see Table 1). To this crude reaction mixture was added ether, the products were extracted with water, and the resulting aqueous solution was lyophilized to afford solid tetrahydro-β-carboline products with isolated yields ranging from 75% to 96%. The obtained Pictet–Spengler adduct was then mixed with *N*,*N*-dimethyl pyridine (2 equiv) in ionic liquid (0.2 mL; [bdmim][Tf_2N] or [bdmim][$PFBuSO_3$]). To the reaction solution, 1-fluoro-2-nitrobenzene (0.136 mmol) was added to proceed the nucleophilic aromatic substitution reaction. The reaction was carried out at 70 °C (for reaction time, see Table 1). After the completion of the substitution reaction, the nitro aryl products were directly purified by flash chromatography to give a yellow solid with good to excellent yields (74–93%).
The yellow nitro aryl compounds were dissolved in the solution of ionic liquid/ethanol (1:1, v/v; 0.2 mL) containing $SnCl_2$ (4 equiv) to carry out the final cyclization-upon-reduction reaction at 70 °C (for reaction time, see Table 1). The reaction was allowed to proceed until the nitro compounds were completely consumed and cyclized as monitored by TLC. Upon completion of the total three-step synthesis, the solution mixture containing the desired tetrahydro-β-carbolinequinoxalinones was concentrated under reduced pressure and purified by silica gel flash chromatography (ethyl acetate/hexane = 2:3). The final tetrahydro-β-carbolinequinoxalinone products were afforded as a colorless solid with overall isolated yields of 34–55%.
20. For the synthesis of quinoxalin-2-ones in solution, see: (a) Willardsen, J. A.; Dudley, D. A.; Cody, W. L.; Chi, L.; McClanahan, T. B.; Mertz, T. E.; Potoczak, R. E.; Narasimhan, L. S.; Holland, D. R.; Rapundalo, S. T.; Edmunds, J. J. *J. Med. Chem.* **2004**, *47*, 4089–4099; (b) Chen, B.-C.; Zhao, R.; Bednarz, M. S.; Wang, B.;

Sundeen, J. E.; Barrish, J. C. *J. Org. Chem.* **2004**, *69*, 977–979; For the solid-phase synthesis of quinoxalin-2-ones, see: (a) Lee, J.; Murray, W. V.; Rivero, R. A. *J. Org. Chem.* **1997**, *62*, 3874–3879; (b) Morales, G. A.; Gorbett, J. W.; DeGrado, W. F. *J. Org. Chem.* **1998**, *63*, 1172–1177; (c) Mazurov, A. *Tetrahedron Lett.* **2000**, *41*, 7–10.

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