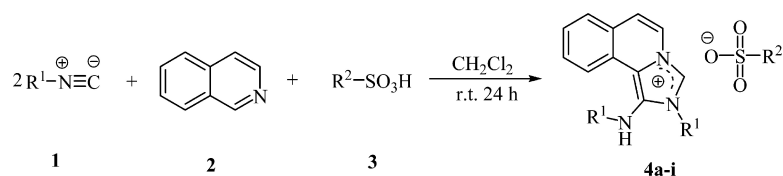


## Synthesis of 1-Aminoimidazo[5,1-a]isoquinolinium Salts Based on Multicomponent Reactions of Isocyanides

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# Synthesis of 1-Aminoimidazo[5,1-*a*]isoquinolinium Salts Based on Multicomponent Reactions of Isocyanides

Ahmad Shaabani,\* Ebrahim Soleimani, and Hamid Reza Khavasi

Department of Chemistry, Shahid Beheshti University, P.O. Box 19396-4716, Tehran, Iran

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A novel pseudo-four-component condensation yielding 1-aminoimidazo[5,1-*a*]isoquinolinium salts from isocyanides, isoquinoline, and sulfonic or bromic acids is described. The method offers several advantages including high yields of products and an easy experimental workup procedure.

## Introduction

Multicomponent reactions (MCRs), because of their productivity, simple procedures, convergence, and facile execution, are one of the best tools in combinatorial chemistry.<sup>1</sup> Therefore, the design of novel MCRs has attracted great attention from research groups working in various areas such as drug discovery, organic synthesis, and material science. MCRs that involve isocyanides are by far the most versatile reactions in terms of scaffolds and number of accessible compounds.<sup>2</sup> As a result; the number of new MCRs in recent years is growing rapidly.<sup>3</sup>

Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activity.<sup>4</sup> Imidazo[5,1-*a*]isoquinolinium salts are used as orally effective blood sugar lowering agents in the treatment of diabetes.<sup>5a</sup> Several methods have been reported for the synthesis of 1-aminoimidazo[5,1-*a*]isoquinoline. However, they all rely on multistep reactions; their yields are low, and the reaction times are very long.<sup>5</sup> For example, 3-dimethylamino-1-formylimidazo[5,1-*a*]isoquinoline **IV** was synthesized through a multistep pathway as illustrated by Scheme 1, Starting with isoquinoline **I**, which was subjected to oxidation to give isoquinoline-2-oxide (**II**). The reaction of **II** with TMSCN under reflux conditions in acetonitrile for 6 days afforded the cyano derivative **III**.<sup>6</sup> The Vilsmeier reaction of nitrile **III** afforded the expected product **IV** in 38% yield.<sup>5c</sup>

Although the reaction of isocyanides and pyridinium triflates has been previously reported,<sup>5g</sup> there is no literature precedence for the reaction of isocyanides and isoquinoline with various sulfonic acids or HBr under the MCRs strategy.

In continuation of our interest in isocyanide-based multicomponent reactions,<sup>7,8</sup> we report the synthesis of 1-aminoimidazo[5,1-*a*]isoquinolinium sulfonates via one-pot pseudo-four-component reaction of an isocyanide **1**, isoquinoline **2**, and

various sulfonic acids **3** in CH<sub>2</sub>Cl<sub>2</sub> at ambient temperature without the use any catalyst in high yields (Scheme 2).

## Results and Discussion

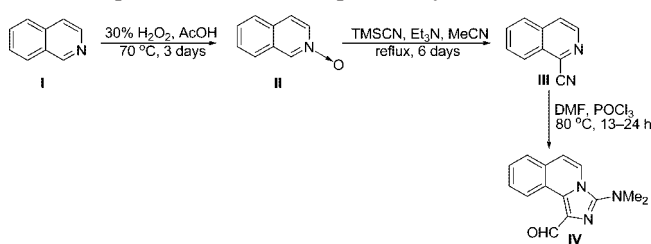
The structures of the products were deduced from their IR, mass, <sup>1</sup>H NMR, and <sup>13</sup>C NMR spectra. Finally, the structure of **4a** was confirmed unambiguously by single-crystal X-ray analysis (Figure 1). Note that the cyclohexyl carbon atoms have a high thermal parameter, which is common for such a group.<sup>7b</sup> We tried to refine these atoms in two positions with reducing occupancy, and although this model converged satisfactorily, the *R* value did not decrease. Apparently, the reported *R* value is the best refinement that we can achieve.

As indicated in Table 1, the scope of the reaction was explored by the reaction of various alkyl and aryl isocyanides and sulfonic acids to produce 1-aminoimidazo[5,1-*a*]isoquinolinium sulfonates.

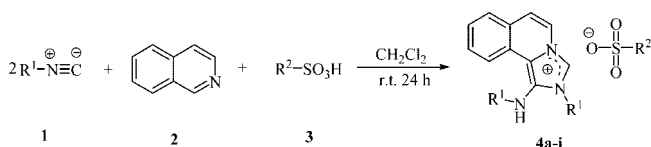
The variability of the MCR with respect to the amine component was also investigated. However, pyridinium and 1,10-phenantroquinolinium sulfonates were generated, and nucleophilic attack by isocyanide does not occur (Scheme 3).

The reaction proceeds under mild conditions and is compatible with a wide range of functional groups. Two

**Scheme 1.** Synthesis of 3-Dimethylamino-1-formylimidazo[5,1-*a*]isoquinoline via Multistep Pathway



**Scheme 2.** Synthesis of 1-Aminoimidazo[5,1-*a*]isoquinolinium Sulfonates via One-Pot Pseudo-Four-Component Reaction of Isocyanide, Isoquinoline, and Sulfonic Acid



\* To whom correspondence should be addressed. Phone: +98-21-29902800. Fax: +98-21-22431663. E-mail: a-shaabani@cc.sbu.ac.ir.

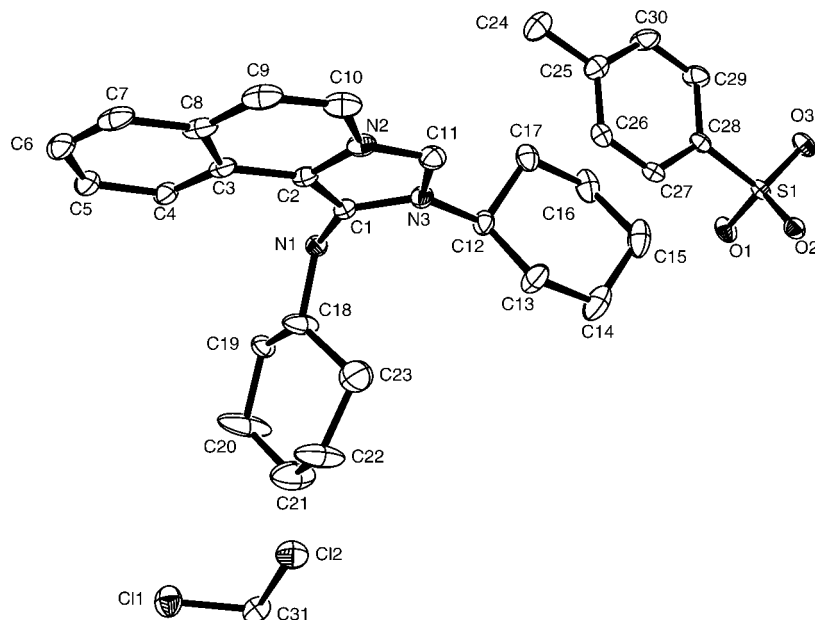


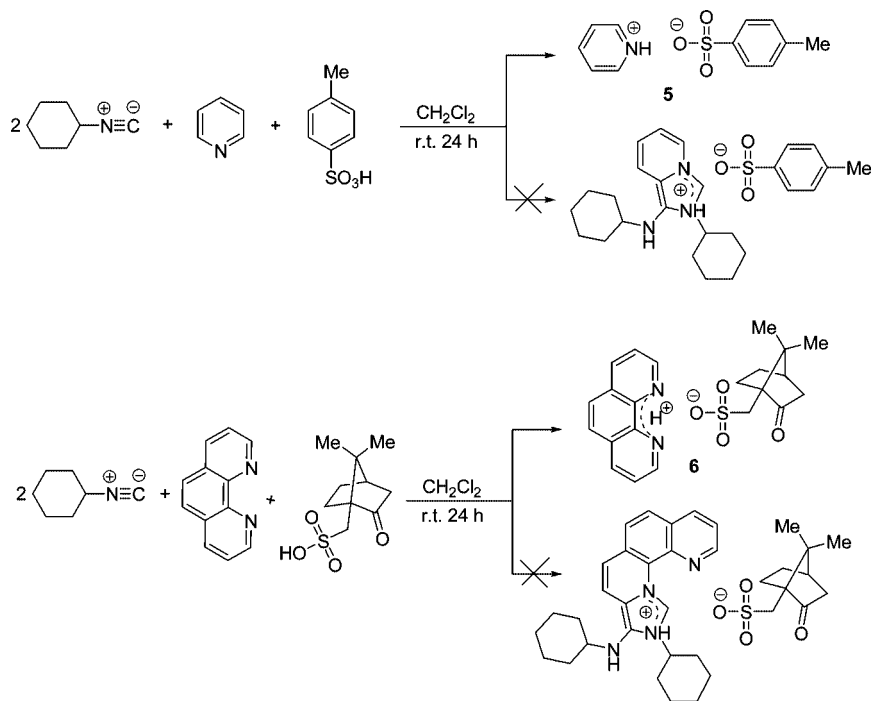
Figure 1. Single-crystal X-ray structure of **4a**.

Table 1. Multicomponent Synthesis of 1-Aminoimidazo[5,1-*a*]isoquinolinium Sulfonates

entry	isocyanide	sulfonic acid	product	yield (%)
1	cyclohexyl	<i>p</i> -toluenesulfonic acid	<b>4a</b>	90
2	<i>tert</i> -butyl	<i>p</i> -toluenesulfonic acid	<b>4b</b>	80
3	benzyl	<i>p</i> -toluenesulfonic acid	<b>4c</b>	88
4	1,1,3,3-tetramethyl-butyl	<i>p</i> -toluenesulfonic acid	<b>4d</b>	83
5	2,6-dimethyl-phenyl	<i>p</i> -toluenesulfonic acid	<b>4e</b>	75
6	cyclohexyl	(-)-camphorsulfonic acid	<b>4f</b>	91
7	2,6-dimethyl-phenyl	(-)-camphorsulfonic acid	<b>4g</b>	77
8	cyclohexyl	phenylsulfonic acid	<b>4h</b>	96
9	cyclohexyl	methansulfonic acid	<b>4i</b>	86

substituents in the products can be varied independently of each other. Representative examples of this reaction are shown in Figure 2.

### Scheme 3. Synthesis of Pyridinium and 1,10-Phenantroquinolinium Sulfonates

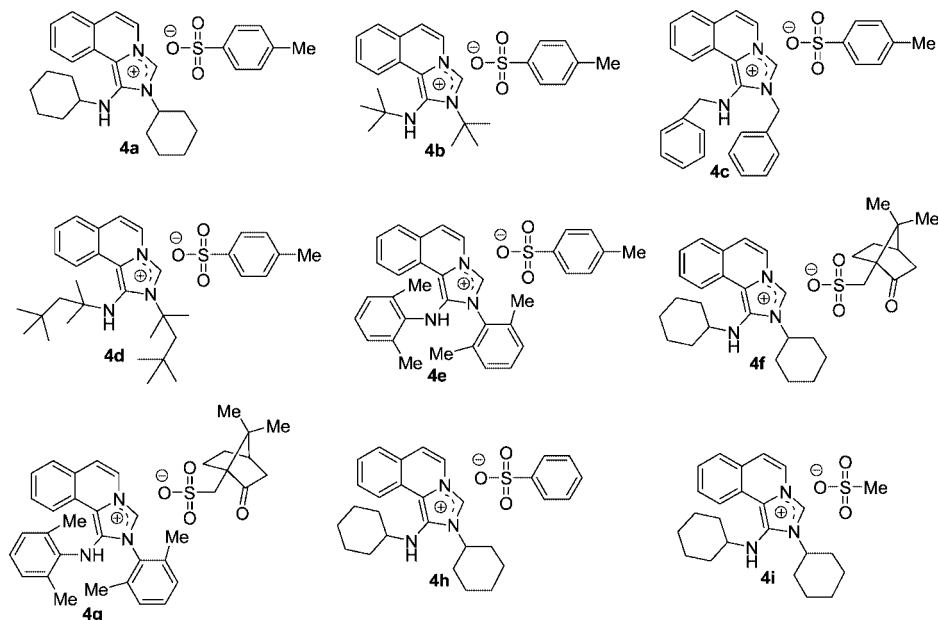


To illustrate the need for sulfonic acid, the reaction of cyclohexyl isocyanide and isoquinoline was studied in the absence of sulfonic acid. Under these conditions, no product was obtained even after 24 h. Obviously, sulfonic acid is an important component of the reaction.

We were able to also demonstrate that 2-cyclohexyl-1-cyclohexylamino-imidazo[5,1-*a*]isoquinolin-2-ium bromide **7** successfully synthesized by the reaction of cyclohexyl isocyanide with isoquinoline and HBr in 53% yield (Scheme 4).

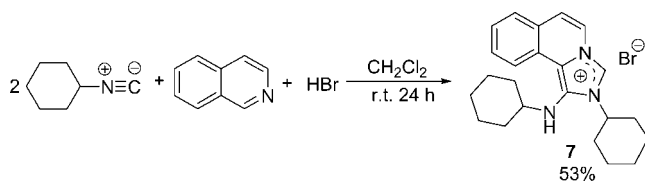
The possible mechanism of the formation of product is shown in Scheme 5.

To clarify the proposed mechanism, a mixture of reactants (0.1 mmol) was dissolved in CDCl<sub>3</sub> (0.7 mL) in a 5 mm NMR tube, and the progress of the reaction was monitored



**Figure 2.** Structure of products **4a–i**.

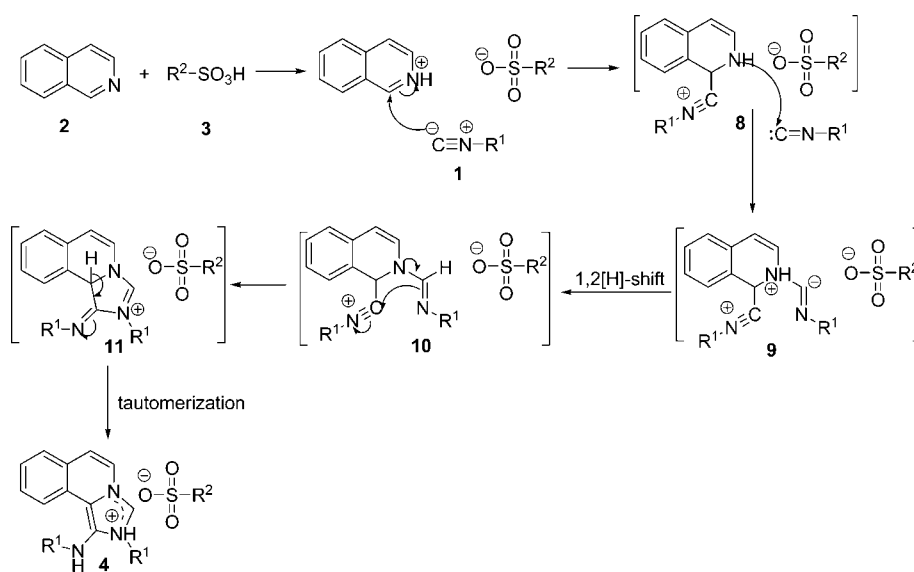
**Scheme 4.** Synthesis of 2-Cyclohexyl-1-cyclohexylamino-imidazo[5,1-*a*]isoquinolin-2-ium Bromide



by recording the  $^1\text{H}$  NMR of mixture after approximately 5, 80, 180, and 255 min. The starting compound (isoquinoline), intermediate (isoquinolinium sulfonate), and product (compound **4a**) can be easily distinguished in the  $^1\text{H}$  NMR spectra by means of the characteristic signals of the  $\text{N}=\text{CH}_\alpha$  ( $\delta = 9.27$  ppm),  $\text{NH}^+=\text{CH}_\alpha$  ( $\delta = 9.81$  ppm), and  $\text{N}=\text{CH}-\text{N}$  ( $\delta = 10.13$  ppm) protons, respectively.

The  $^1\text{H}$  NMR experiment did not help to elucidate the possibly intermediate in proposed mechanism; however, the NMR data clearly showed that the first reaction step is

**Scheme 5.** Proposed Mechanism

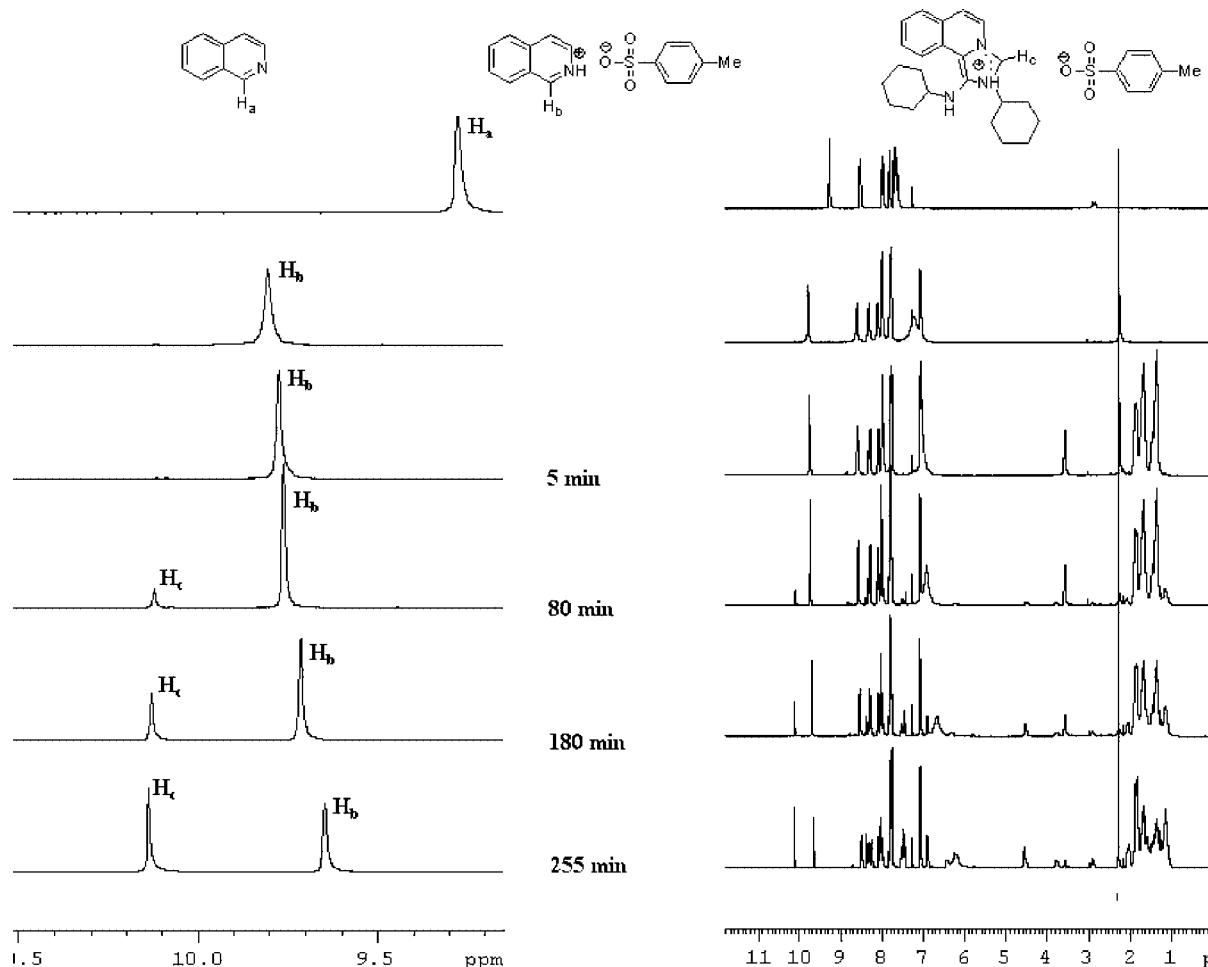


protonation of isoquinoline with PTSA and that the second is the nucleophilic addition of isocyanide to the activated  $\text{NH}^+=\text{CH}_\alpha$  bond of isoquinolinium sulfonate (Figure 3).

In conclusion, we have developed a new and efficient approach to the synthesis of a wide range of 1-aminoimidazo[5,1-*a*]isoquinolinium salts from various isocyanides with isoquinoline in the presence of various sulfonic acids. The reaction has been shown to display good functional group tolerance and is high yielding, and product isolation is very straightforward. We hope that this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry programs.

## Experimental Section

**Typical Procedure for Preparation of Toluene-4-sulfonate 2-Cyclohexyl-1-cyclohexylamino-imidazo[5,1-*a*]isoquinolin-2-ium (**4a**).** To a magnetically stirred solution of isoquinoline (0.13 g, 1 mmol) and *p*-toluenesulfonic acid



**Figure 3.** 300 MHz  $^1\text{H}$  NMR spectrum of isoquinoline, isoquinolinium sulfonate, and reaction mixture after approximately 5, 80, 180, and 255 min.

(0.19 g, 1 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) was added cyclohexyl isocyanide (0.22 g, 2 mmol). The resulting mixture was stirred for 24 h at room temperature. The solvent was removed under vacuum, and the residue was crystallized from a  $\text{CH}_2\text{Cl}_2$ /ethyl acetate (1:2) mixture and washed with ethyl acetate. Product **4a** was obtained in the form of colorless crystals (0.47 g, yield 90%). mp: 171–173 °C. IR (KBr) ( $\nu_{\text{max}}$   $\text{cm}^{-1}$ ): 3230 (NH), 2925, 2852, 1639, 1617, 1453, 1209. MS  $m/z$  (%): 347 ( $\text{M}^+ - \text{MeC}_6\text{H}_4\text{SO}_3^-$ , 5), 265 (100), 222 (20), 183 (85), 155 (75), 129 (50), 107 (25), 91 (55), 67 (75), 39 (70).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  (ppm) 1.17–2.02 (20H, m, 10 $\text{CH}_2$  of two cyclohexyls), 2.31 (3H, s,  $\text{CH}_3$ ), 2.93 (1H, m,  $\text{CH-N}$  of cyclohexyl), 3.80 (1H, brs, NH), 4.52 (1H, m,  $\text{CH-N}$  of cyclohexyl), 6.92 (1H, d,  $^3J_{\text{HH}} = 7.1$  Hz, H-Ar), 7.10 (2H, d,  $^3J_{\text{HH}} = 7.6$  Hz, H-Ar), 7.52–7.59 (3H, m, H-Ar), 7.82 (2H, d,  $^3J_{\text{HH}} = 7.6$  Hz, H-Ar), 8.34 (1H, d,  $^3J_{\text{HH}} = 7.4$  Hz, H-Ar), 8.51 (1H, d,  $^3J_{\text{HH}} = 7.1$  Hz, H-Ar), 10.34 (1H, s,  $\text{CH=N}^+$ ).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  (ppm) 21.30 ( $\text{CH}_3$ ), 24.4, 25.0, 25.4, 25.7, 33.8, 34.1 (C-cyclohexyls), 55.8 ( $\text{CH-N}$  of cyclohexyl), 58.0 ( $\text{CH-N}$  of cyclohexyl), 118.2, 119.8, 122.2, 122.8, 123.4, 125.1, 126.0, 127.5, 128.0, 128.5, 128.8, 129.1, 129.3, 139.3, 143.6 (C-Ar). Anal. Calcd for  $\text{C}_{30}\text{H}_{37}\text{N}_3\text{O}_3\text{S}$ : C, 69.33; H, 7.18; N, 8.09. Found: C, 69.21; H, 7.25; N, 8.01.

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**Supporting Information Available.** Experimental procedures, IR, mass,  $^1\text{H}$ , and  $^{13}\text{C}$  NMR for all compounds, crystallographic data, and ORTEP/X-ray structures for **4a** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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