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A Simple and Mild Synthesis of 1*H*-Isochromenes and (*Z*)-1-Alkylidene-1,3-dihydroisobenzofurans by the Iodocyclization of 2-(1-Alkynyl)benzylic Alcohols

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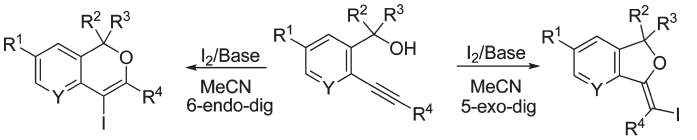

(Y = CH, N; R^1 = H, OMe, NO_2; R^2, R^3 = H, alkyl; R^4 = alkyl, aryl, thienyl)

A variety of iodo-substituted isochromenes, dihydroisobenzofurans, and pyranopyridines are readily prepared in good to excellent yields under mild conditions by the iodocyclization of readily available 2-(1-alkynyl)benzylic alcohols or 2-(1-alkynyl)-3-(hydroxymethyl)pyridines. Reactions are carried out in MeCN at 25 °C with 3 equiv of I_2 as the iodine source and $NaHCO_3$ (3 equiv) as the base. The regiochemical outcome of the reaction strongly depends on the substitution pattern of the starting material. In particular, the 5-*exo*-*dig* cyclization mode, leading to dihydroisobenzofurans, is observed in the case of substrates bearing a tertiary alcoholic group, owing to the *gem*-dialkyl effect, while the 6-*endo*-*dig* cyclization mode, leading to isochromene or pyranopyridines, is the usually preferred pathway in the case of substrates bearing a primary or secondary alcoholic group.

Introduction

The iodocyclization of alkynes has emerged as a powerful tool in organic synthesis.[1] Recently, we and others have utilized this methodology to accomplish efficient syntheses of a wide variety of interesting carbocyclic and heterocyclic compounds.[2−26] In general, these electrophilic cyclization

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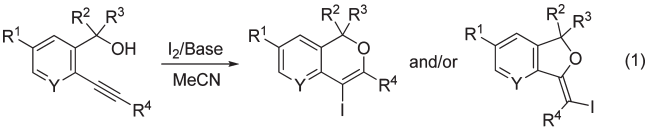
reactions are very clean and efficient, and tolerate a wide variety of functional groups. Furthermore, the iodine-containing products can be further diversified by using a number of subsequent palladium-catalyzed processes.

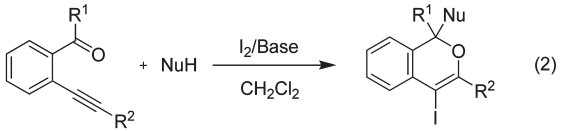
Herein we report a simple and efficient method for the synthesis of 1*H*-isochromene and/or (*Z*)-1-(1-iodoalkylidene)-1,3-dihydroisobenzofuran derivatives, based on the iodocyclization of readily available 2-(1-alkynyl)benzylic alcohols (eq 1). Isochromenes and 1,3-dihydroisobenzofurans are important heterocyclic compounds, and there are several examples of naturally occurring and biologically active compounds containing these ring systems.[27,28]



(1)

(Y = CH, N; R^1 = H, OMe, NO_2; R^2, R^3 = H, alkyl; R^4 = alkyl, aryl, thienyl)

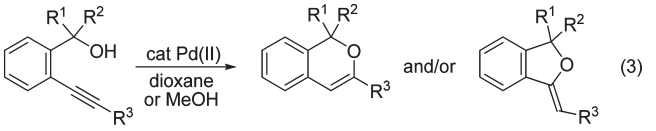
Over the years, several groups have reported a variety of synthetic approaches to isochromene and dihydroisobenzofuran derivatives by the heterocyclization of acyclic precursors.[29] In particular, we[30] and the Barluenga group[31] have independently reported the formation of 4-iodo-1*H*-isochromenes by the iodocyclization of 2-(1-alkynyl)benzaldehydes in the presence of suitable nucleophiles (eq 2).



(2)

R^1 = H, Me; NuH = MeOH, EtOH, $PhNMe_2$, PhOH; R^2 = alkyl, aryl, heteroaryl

We have also previously disclosed the Pd(II)-catalyzed cycloisomerization of 2-(1-alkynyl)benzylic alcohols to 1*H*-isochromenes and/or (*Z*)-1-alkylidene-1,3-dihydroisobenzofurans, depending on the nature of the substrate and the reaction conditions (eq 3).[29k]



(3)

R^1, R^2 = H, alkyl; R^3 = alkyl, aryl

The new methodology reported in this work is complementary to those previously reported procedures, and allows for the direct synthesis of 3-iodo-1*H*-isochromenes, (*Z*)-1-(1-iodoalkylidene)-1,3-dihydroisobenzofurans, and iodopyranopyridines by the iodocyclization of variously substituted 2-(1-alkynyl)benzylic alcohols or 2-(1-alkynyl)-3-(hydroxymethyl)pyridines under mild conditions (see eq 1).

Results and Discussion

2-(2-Phenylethynyl)benzyl alcohol (**1a**, Y = CH, R^1 = R^2 = R^3 = H, R^4 = Ph) was chosen as a model substrate for determining the optimum conditions for the iodocyclization reaction, using I_2 or ICl as the iodine source and MeCN, CH_2Cl_2, or EtOH as the solvent, in the presence of an inorganic ($NaHCO_3$, K_2CO_3, $KHCO_3$, NaH) or organic (morpholine) base. The results obtained are shown in Table 1.[32]

As can be seen from Table 1, the isochromene derivative **2a** derived from a 6-*endo-dig* cyclization was consistently obtained in higher yield than the dihydroisobenzofuran derivative **3a** derived from a 5-*exo-dig* cyclization. The optimal

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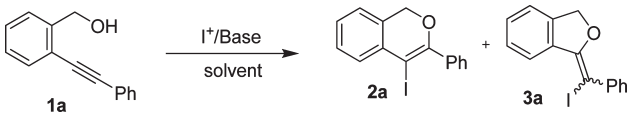
(32) The reaction did not occur in the absence of base, as shown by blank experiments.

TABLE 1. Iodocyclization of 2-(2-Phenylethynyl)benzyl Alcohol: Optimization Studies[a]



entry	I^+	base	time (h)	solvent	total yield (**2a** + **3a**)[b] (%)	**2a**/**3a** ratio[c]
1	2.0 I_2	2.0 $NaHCO_3$	72	CH_3CN	56	75/25
2	2.0 I_2	3.0 $NaHCO_3$	72	CH_3CN	56	71/29
3	3.0 I_2	3.0 $NaHCO_3$	15	CH_3CN	71	91/9
4	3.0 I_2	3.0 $NaHCO_3$	15	CH_2Cl_2	45	100/0
5	3.0 I_2	3.0 $NaHCO_3$	15	EtOH	45	100/0
6[d]	3.0 I_2	3.0 $NaHCO_3$	15	CH_3CN	33	64/36
7	3.0 I_2	3.0 K_2CO_3	24	CH_3CN	56	48/52
8	3.0 I_2	3.0 $KHCO_3$	24	CH_3CN	46	48/52
9	3.0 I_2	3.0 NaH	24	CH_3CN	10	100/0
10	3.0 I_2	3.0 morpholine	24	CH_3CN	-	-
11	3.0 ICl	3 $NaHCO_3$	1.5	CH_3CN	38	100/0
12	3.0 ICl	3 $NaHCO_3$	1.5	CH_2Cl_2	25	100/0

[a]Unless otherwise noted, all reactions were carried out on a 0.3 mmol scale in 6 mL of acetonitrile at 25 °C. [b]Isolated yield of **2a** + **3a**, based on starting **1a**. In most cases, an inseparable mixture of the two regioisomers was obtained from column chromatography. [c]The **2**:**3** ratio is based on ^{1}H NMR spectroscopic data. [d]The reaction was carried out in 2.5 mL of MeCN.

reaction conditions in terms of total yield for the iodocyclization of **1a** are those reported in entry 3 (substrate:I_2:$NaHCO_3$ molar ratio = 1:3:3, T = 25 °C, substrate concentration = 0.05 M in CH_3CN, time = 15 h).[33] Under these conditions, **1a** was converted into approximately a 10:1 mixture of **2a** and **3a** in a total yield of 71%. On the other hand, no formation of **3a** was observed with I_2 as the iodine source in CH_2Cl_2 or EtOH as the solvent (entries 4 and 5) or with ICl as the iodine source either in MeCN or in CH_2Cl_2 (entries 11 and 12, respectively). However, the yields of **2a** obtained under these conditions ranged from only 25% to 45%.

A variety of 2-(1-alkynyl)benzylic alcohols **1b**−**w** were then subjected to iodocyclization under the conditions of Table 1, entry 3. The results obtained are summarized in Table 2.

As can be seen from the results reported in Table 2, the regiochemistry of the process strongly depends on the substitution pattern of the substrate. Interestingly, the presence of an electron-donating group in the para position of a phenyl ring conjugated with the triple bond (R^4 = *p*-MeC_6H_4 or *p*-$MeOC_6H_4$, substrates **1b** and **1c**, respectively) led to preferential formation of the isochromene derivative (compare entries 2 and 3 with entry 1). In fact, the electron-donating effect of the para substituent should increase the electron density on C-1 of the arylethynyl group, thus favoring intramolecular nucleophilic attack of the hydroxyl group on C-2. As expected, this effect was not observed when the substituents are in the meta positions, as shown by the results obtained in the case of substrate **1d** (R^4 = 3,5-dimethoxyphenyl). In fact, iodocyclization of the latter led to a mixure of the isochromene and isobenzofuran derivatives (entry 4). A mixture of **2e** and **3e** was also obtained in the case of a *p*-chloro substituent (R^4 = *p*-ClC_6H_4, substrate **1e**, entry 5). On the other hand, the presence of a nitro group in the para position (R^4 = *p*-$O_2NC_6H_4$, substrate **1f**, entry 6) significantly augments the electrophilicity of C-1 of the arylethynyl group, thus reversing the selectivity of the reaction in favor of the 5-membered-ring product **3f**. A similar effect is observed when R^4 is a 3,5-*bis*(trifluoromethyl)phenyl substituent (substrate **1g**, entry 7). When the triple bond is substituted with a 3-thienyl, 1-cyclohexenyl, or butyl group, the reaction consistently follows a 6-*endo*-*dig* pathway, with selective formation of the corresponding isochromene derivatives **2h**−**j** (entries 8−10). Substrates bearing a sterically demanding substituent [R^4 = *tert*-butyl (**1k**) or TMS (**1*l***)] led to complex reaction mixtures. Also, the reaction did not proceed well with a terminal triple bond (R^4 = H, **1m**), and partial decomposition of the substrate occurred. Interestingly, the presence of either an electron-donating or an electron-withdrawing group meta with respect to the hydroxymethyl group (R^1 = OMe or NO_2, substrates **1n**−**p**) also tended to favor selective formation of the 6-membered-ring products **2n**−**p** (entries 11−13). Excellent yields of pyranopyridine derivatives **2q** and **2r** were obtained by 6-*endo*-*dig* iodocyclization of the corresponding 2-(1-alkynyl)-3-(hydroxymethyl)pyridines **1q** and **1r** (entries 14 and 15).

Substrates bearing a secondary alcoholic group (**1s** and **1t**) behaved similarly to substrates with a primary alcoholic group, as can be seen by comparing entries 16 and 17 (Table 2) with entries 1 and 2 (Table 2). On the other hand, substrates bearing a tertiary alcohol group (such as **1u**−**w**) selectively proceed by a 5-*exo*-*dig* cyclization, with formation of the corresponding dihydroisobenzofurans **3u**−**w** in good yields (70−82%, entries 18−20). This result is in agreement with what has been previously observed in the Pd(II)-catalyzed cycloisomerization of 2-(1-alkynyl)benzylic alcohols.[29k] The *gem*-dialkyl effect[34] may be responsible for the observed regioselectivity. In fact, in the presence of α,α-dialkyl substitution, the hydroxyl group is forced closer to the triple bond, thus favoring the 5-*exo*-*dig* pathway with respect to the 6-*endo*-*dig* pathway.

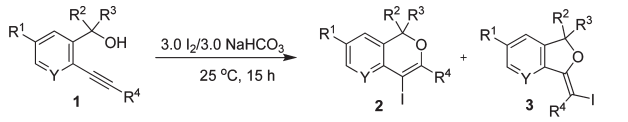
X-ray crystallographic experiments were performed in order to confirm the regiochemistry of the cyclized products.[35] Interestingly, the 1-alkylidene-1,3-dihydroisobenzofuran product

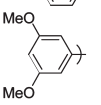
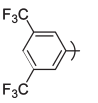
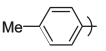
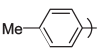
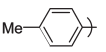
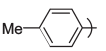
(33) Complex reaction mixtures were obtained when the reaction was carried out at temperatures higher than 25 °C (40−80 °C).

(34) Sammes, P. G.; Weller, D. J. *Synthesis* **1995**, 1205.

(35) The structures of iodocyclization products **2c** and **3u** were unequivocally confirmed by X-ray diffraction analysis. The structures of all other regioisomeric products **2** and **3** were determined by spectroscopic techniques, and confirmed by comparison with compounds **2c** and **3u**, respectively. See the Supporting Information for details.

TABLE 2. Synthesis of 3-Iodo-1*H*-isochromenes and 1-(1-Iodoalkylidene)-1,3-dihydroisobenzofurans by the Iodocyclization of 2-(1-Alkynyl)benzylic Alcohols[a]



entry	1	Y	R^1	R^2	R^3	R^4	isolated yield (%) 2	3
1	**1a**	CH	H	H	H		71[b] (10:1)[c]	
2	**1b**	CH	H	H	H		92	-
3	**1c**	CH	H	H	H		85	-
4	**1d**	CH	H	H	H		41	35
5	**1e**	CH	H	H	H		85[b] (3:1)[c]	
6	**1f**	CH	H	H	H		88[b] (1:3)[c]	
7	**1g**	CH	H	H	H		74[b] (1:4)[c]	
8	**1h**	CH	H	H	H		82	-
9	**1i**	CH	H	H	H		80	-
10	**1j**	CH	H	H	H	$CH_3CH_2CH_2CH_2$-	57	-
11	**1n**	CH	OMe	H	H		51	-
12	**1o**	CH	OMe	H	H		61	-
13	**1p**	CH	NO_2	H	H		92	-
14	**1q**	N	H	H	H		98	-
15	**1r**	N	H	H	H		92	-
16	**1s**	CH	H	Bu	H		76[b] (3:1)[c]	
17	**1t**	CH	H	Bu	H		72	-
18	**1u**	CH	H	Et	Et		-	70
19	**1v**	CH	H	Et	Et		-	70
20	**1w**	CH	H	Bu	Et		-	82

[a]Unless otherwise noted, all reactions were carried out on a 0.3 mmol scale in 6 mL of acetonitrile. The reactions were allowed to stir at room temperature for 15 h. All yields are isolated yields after column chromatography. [b]An inseparable mixture of the two regioisomers was obtained from column chromatography. [c]The **2**:**3** ratio is based on ^{1}H NMR spectroscopic data.

3u was found to be the *Z*-isomer, instead of the *E*-isomer that would be expected from an *anti*-5-*exo-dig* cyclization (Figure 1). This *Z*-stereochemistry was also found in other 5-membered-ring products (by ^{1}H NMR spectral data correlation with **3u**).

Given the unexpected stereochemistry, an immediately reasonable hypothesis was that the predicted stereoisomer is originally formed, and then equilibrates to the observed

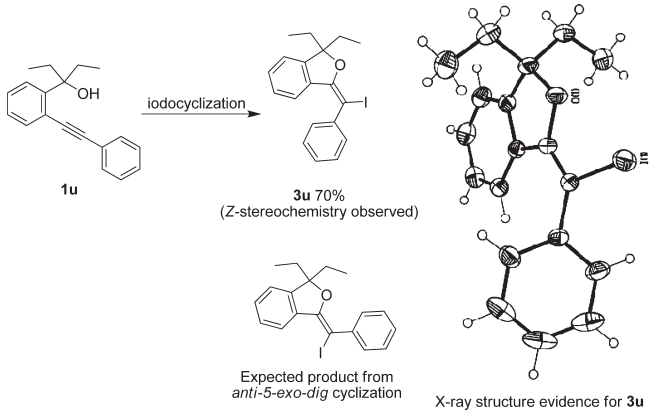


FIGURE 1. X-ray evidence for the structural assignment of 1-alkylidene-1,3-dihydroisobenzofurans.

isomer. This would imply that the observed *Z*-isomer would need to be more stable than the expected *E*-isomer. To substantiate this idea, computations were carried out at MP2 and B3LYP levels of theory with use of a 6-31G(d) basis set on carbon and hydrogen atoms, and an approximately equivalent electron core potential and valence basis set on I. (Details are given in the Supporting Information). At both levels of theory, the *Z*-isomer was favored, by 3.6 and 3.9 kcal/mol, with use of B3LYP and MP2, respectively.

On the basis of these observations, the following reaction mechanism can be proposed for the iodocyclization of **1** (Scheme 1).[36] Coordination of an I^+ equivalent to the alkyne leads to electrophilic activation of the alkyne carbon−carbon triple bond[1] generating iodonium intermediate **A**. Nucleophilic attack by the hydroxyl group may then take place by either of two intramolecular cyclization modes (*anti*-6-*endo-dig* or *anti*-5-*exo-dig*, paths a and b, respectively) to give intermediates **B** or **B′**, respectively. Deprotonation of intermediate **B** leads to the isochromene product **2** that is isolated as the major product in most cases. However, dihydroisobenzofuran derivative **3′** with *E* stereochemistry derived from intermediate **B′** was not isolated. Presumably, isomerization of the initially formed *E*-isobenzofuran (**3′**) leads to the more stable *Z*-isomer (**3**). A few examples of the isomerization of substituted cis alkenes to the more stable corresponding trans isomers in the presence of iodine are known.[37] To demonstrate the feasibility of the isomerization, *cis*-stilbene was subjected to our reaction conditions and partial isomerization was observed. The ratio of cis:trans stilbene was found to be 1:0.6 at 10 h and 1:0.9 at 19 h by ^{1}H NMR spectral data. The possibility that $E \rightarrow Z$ isomerization occurs through the formation of intermediate **B″** (deriving from **B′** via proton shift) followed by stereospecific deprotonation cannot be ruled out, however.

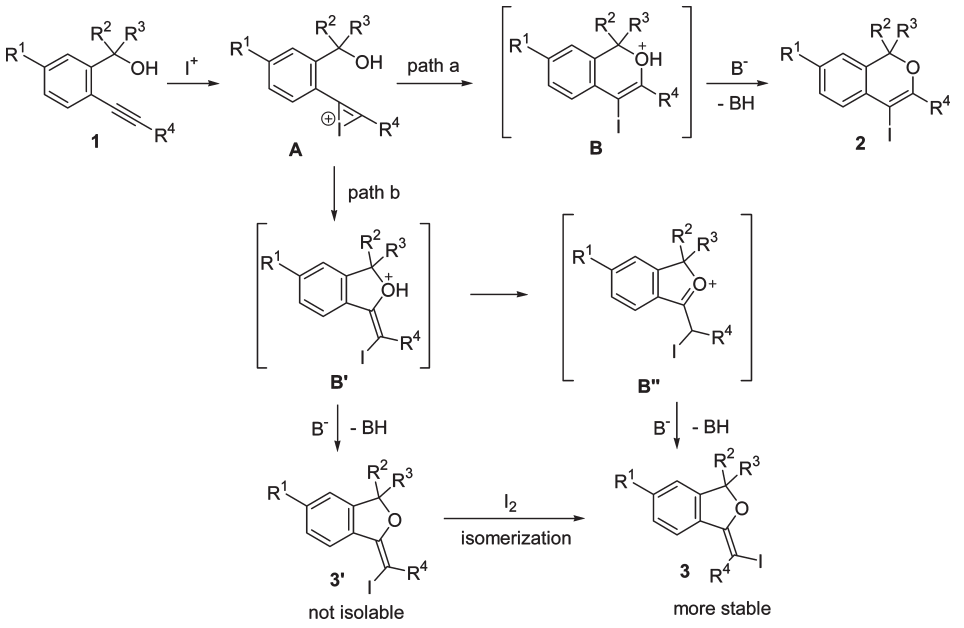
Conclusions

A simple and mild synthesis of 6- and 5-membered iodoheterocyclic ether derivatives (**2** and **3**, respectively) via

(36) The possibility of base-promoted cyclization, followed by iodination of the resulting vinylic ethers, was examined. The 2-(1-alkynyl)benzylic alcohol substrates **1a**, **1s**, and **1w** were subjected to our usual cyclization conditions omitting iodine. In all of these cases, no cyclization was observed and the starting materials were recovered.

(37) (a) Muizebelt, W. J.; Nivard, R. J. F. *Chem. Commun.* **1965**, 148. (b) Windmon, N.; Dragojlovic, V. *Tetrahedron Lett.* **2008**, *49*, 6543.

SCHEME 1. Proposed Mechanistic Pathways for the Iodocyclization of 2-(1-Alkynyl)benzylic Alcohols (1)



iodocyclization of readily available 2-(1-alkynyl)benzylic alcohols **1** is reported. The nature of the substituents in the starting material governs the regiochemistry of the reaction products. The 5-membered-ring products obtained (1-alkylidene-1,3-dihydroisobenzofurans **3**) exhibit unexpected *Z*-stereochemistry, and are presumably derived from the initially formed less stable *E*-isomers through iodine-mediated isomerization.

Experimental Section

Substrates **1a**−**w** were prepared by Sonogashira coupling between the appropriate *o*-halobenzylic alcohol or hydroxymethylpyridine and a terminal alkyne, as described in the Supporting Information. All products have been fully characterized by spectroscopic techniques and, in the case of 4-iodo-3-(4-methoxyphenyl)-1*H*-isochromene (**2c**) and 1,1-diethyl-3-(iodophenylmethylene)-1,3-dihydroisobenzofuran (**3u**), by X-ray diffraction analysis also, as detailed in the Supporting Information. A typical procedure for iodocyclization is given below.

Typical Procedure for Iodocyclization. We report here a typical procedure for the preparation of 4-iodo-3-*p*-tolyl-1*H*-isochromene (Table 2, entry 2). Details for the preparation of all other products can be found in the Supporting Information. To a solution of 2-(*p*-tolylethynyl)benzyl alcohol (**1b**, 67 mg, 0.30 mmol) in CH_3CN (6.0 mL) was added $NaHCO_3$ (76 mg, 0.90 mmol), followed by I_2 (228 mg, 0.90 mmol), at room temperature with stirring. The resulting mixture was allowed to stir at room temperature for 15 h. The excess I_2 was removed by adding a satd aq solution of $Na_2S_2O_3$, followed by stirring for 5−10 min. The phases were separated, and the aqueous phase was extracted with Et_2O (2 × 10 mL). The collected organic phases were dried (Na_2SO_4) and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (hexane−EtOAc from 95:5 to 9:1) to give 4-iodo-3-*p*-tolyl-1*H*-isochromene (**2b**) as a yellow solid (96.0 mg, 92%): mp 43−44 °C; IR (KBr) 1590 (m), 1509 (m), 1477 (m), 1452 (m), 1265 (s), 1183 (w), 1084 (s), 919 (m), 819 (m), 737 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 7.6 Hz, 1H), 7.33 (t, J = 7.7 Hz, 1H), 7.21 (d, J = 7.6 Hz, 3H), 6.97 (d, J = 6.2 Hz, 1H), 5.20 (s, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 140.0, 133.7, 133.5, 130.3, 128.6, 128.5, 128.4, 127.4, 123.3, 121.2, 72.8, 69.5, 21.5; GC-MS, m/z 348 (M^+, 100), 347 (7), 222 (4), 221 (4), 220 (3), 194 (5), 193 (8), 192 (6); HRMS calcd for $C_{16}H_{13}IO$ 348.00111, found 348.00173.

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Supporting Information Available: General experimental methods, preparation of substrates, general procedures for the iodocyclization reactions, characterization data, copies of ^1H and ^{13}C NMR spectra for all previously unreported compounds, and X-ray crystallographic data for compounds **2c** and **3u**. This material is available free of charge via the Internet at http://pubs.acs.org.