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Intramolecular Arylation Reactions of Alkenes: A Flexible Approach to Chromans and Tetrahydroquinoline Derivatives

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A convenient approach for preparing heterocycles is based on the heteroatom as a tethering element and on an eventual cyclization by C−C bond-forming reaction.[1,2] Currently, many efforts in this area are focused in searching for new processes involving reactive organometallic species.[3] Herein, we present preliminary results on a metal-free preparation of representative heterocyclic skeletons, where the key cyclization step is an intramolecular arylation reaction of a heteroatom-linked alkene promoted by iodonium ion. Along this study IPy_2BF_4 was used as the source of iodonium ion[4] that efficiently promotes C−C bond-forming reactions,[5] affording iodinated 3,4-dihydro-2*H*-benzopyranes (chromans)[6] and 1,2,3,4-tetrahydroquinolines.[7] When different allylphenyl ethers **1** were treated with IPy_2BF_4 and variable amounts of HBF_4, a series of reactions took place, leading diastereoselectively to chroman skeletons. Interestingly, besides the expected carbocyclization to heterocycles **2**, an unexpected selective rearrangement to chromans **3** was observed (Table 1).

For internal alkenes, the reaction temperature provides a convenient control over the reaction manifold. At −40 °C, diastereoselective cyclizations took place, furnishing heterocycles **2**. Interestingly, at −90 °C chromans **3** were formed through a selective rearrangement−cyclization sequence. From **1b** this was the only product observed at −90 °C, while for **1a** it was obtained as a minor side product. Alternatively, **3a** was directly obtained from cyclization of **1d** (Scheme 1), showing that terminal alkenes do not undergo rearrangement at that temperature.[8]

From the 1,1-disubstituted alkene **1c**, only **3c** was accessible, with no evidence for the formation of the corresponding **2** even when reactions at higher temperature were assayed.[9] The same trend was also confirmed when more challenging polycyclization reactions were tested. From geraniol, the corresponding phenyl ether, **1f**, featured a trisubstituted alkene at the allyloxy moiety. Thus, the resulting heterocycle **4** arises from a selective sequence comprising rearrangement and formation, in this case, of two C−C bonds. Interestingly, **4** was also prepared in a faster and direct reaction from **1g** (Scheme 2).

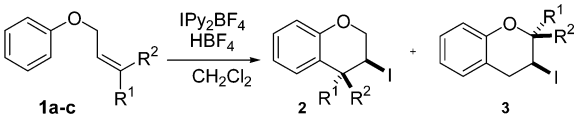
This methodology can be implemented to prepare nitrogenated heterocyclic compounds. *N*-Protected-*N*-allylaniline derivatives[10] **5** were smoothly cyclized to yield 1,2,3,4-tetrahydroquinolines **6** in a stereoselective way (Scheme 3). No evidence was obtained for the formation of related heterocyclic structures involving additional rearrangement of the allyl moiety, even when the reaction temperature was changed.

A relevant extension of this methodology is represented by the diastereoselective polycyclization sequence of the related nitrogen-containing precursor **5e** that furnishes **8** in a straightforward manner[11] (Scheme 4).

Simple homoallyl phenyl ether **9** is also an adequate partner for this process. Its reaction with the iodonium system led to chroman **10** in 76% yield, in this case as the result of an exocyclization mode. Upon dehydroiodination reaction, the exocyclic alkene **11** was fomed in 83% yield, as the sole reaction product (Scheme 5).[12]

As a proposal, a reaction path that explains the formation of the observed compounds might reasonably invoke formation of iodonium ions, for which some NMR evidence has been gathered.[13] Besides its assumption, additional involvement of readily available lone pairs of electrons at the neighboring heteroatom[14] might

Table 1. Synthesis[a] of Chromans **2** and **3**

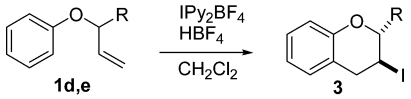


1a R^1: Me, R^2: H; **1b** R^1: Ph, R^2: H; **1c** R^1: Me, R^2: Me

1	HBF_4 (equiv)	t[b] (h)	T (°C)	2	3	yield[c] (%)
1a	1	30	−40	**2a**		92
1a	1	72	−85	**2a**	**3a**	64(10)[d]
1b	1.5	3	−40	**2b**		95
1b	1.5	12	−90		**3b**	95
1c	3	6	−90		**3c**	85

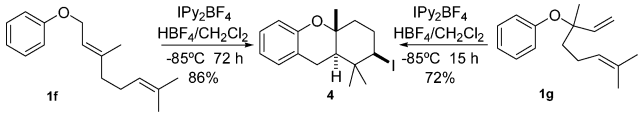
[a] Reactions conducted in CH_2Cl_2, using IPy_2BF_4 as the iodonium source (1.1 equiv). [b] Time for the complete disappearance of **1**. [c] Isolated yield of the chroman derivative. [d] Within brackets, isolated yield for **3a**.

Scheme 1. Metal-Free Arylation of Terminal Alkenes To Give Chromans

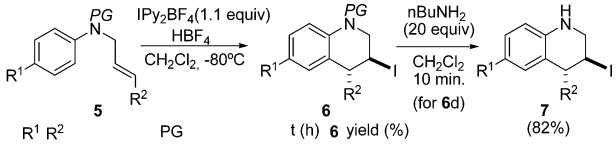


1d R: Me (3 equiv HBF_4, 8h) **3a** (85%)
1e R: Ph (1.5 equiv HBF_4, 4h) **3b** (81%)

Scheme 2. Iodonium-Triggered Polycyclizations of Allylphenyl Ethers



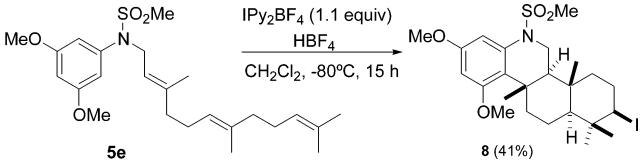
Scheme 3. Iodonium-Promoted Tetrahydroquinoline Derivatives



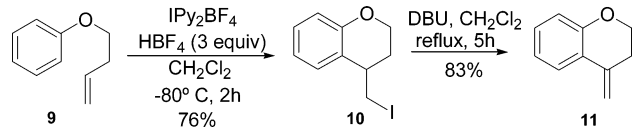
5	R^1	R^2	PG	t (h)	6	yield (%)
5a	H	Me	Ms	15	**6a**	80
5b	H	Ph	Ms	15	**6b**	65
5c	H	Ph	Ts	4	**6c**	84
5d	I	Ph	2,4-dinitrobenzenesulfonyl	1.5	**6d**	75

10.1021/ja0397299 CCC: $27.50

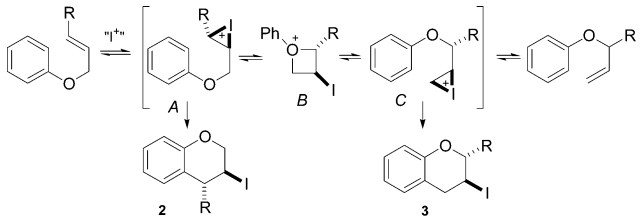
Scheme 4. Diastereoselective Polycyclization to an Azahomosteroid



Scheme 5. Formal Heck-like Approach to Chroman **11**



Scheme 6. Mechanistic Proposal for the Synthesis of Chromans **2,3**



account well for the stereoselectivity of the in situ observed rearrangement and/or iodination−cyclization events, as depicted in Scheme 6.[15]

Thus, the possibility of an equilibrium among intermediate species *A*, *B*, and *C*, might play a crucial role to explain some relevant facts accompanying the reported synthesis of chromans, namely an unusual skeletal isomerization,[16] besides the observed regio- and stereoselectivity.[17,18]

In summary, the reported results show not only promising and differentiating signs but also a nice structural complement to the use of transition metals to assemble relevant heterocyclic cores. Well-established chemistry of carbon−iodine bond would be a nice addition to this strategy for easily preparing derivatives of bioactive basic cores. Overall, simple synthetic tools are to be considered and tested, resulting in yet unexplored attractive preparative alternatives to obtain valuable compounds from readily available starting materials.

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Supporting Information Available: Experimental procedures and characterization data for compounds **2**, **3**, **6**−**8**, **10**, and **11** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) The intermediate species resulting from the addition of a source of halonium ions to alkenes have been widely used in organic synthesis. However, their application to promote C−C bond formation has been scantly documented. For early illustrative examples of synthesis of carbocycles using this methodology, see: (a) González, A. G.; Martín, J. D.; Pérez, C.; Ramírez, M. A. *Tetrahedron Lett.* **1976**, 137. (b) Kato, T.; Ichinose, I.; Kamoshida, A.; Kitahara, Y. *J. Chem. Soc., Chem. Commun.* **1976**, 518. (c) Martin, J. D.; Pérez, C.; Ravelo, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 7801. (d) Barluenga, J.; González, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1546.

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(8) **1d** and **1e** are terminal alkenes that react in this process at reasonably fast rates. In sharp contrast to this trend, allylphenyl ether cannot be cyclized to the parent 3-iodochroman using this approach.

(9) In this case, running the reaction at higher temperature gave rise to mixtures containing variable amounts of the fluoroiodinated adduct, $PhOCH_2CH(F)CMe_2I$.

(10) The use of *N*-methyl-*N*-allylaniline as starting material did not result in the desired heterocycle. Protection of the secondary amines as sulfonyl derivatives provided satisfactory model compounds.

(11) All new heterocycles gave NMR (^1H and ^{13}C), MS, and analytical data in good agreement with the proposed structures (see Supporting Information).

(12) This process offers a clean alternative to the use of Heck-type conditions to prepare **11**. Thus, 4-*o*-iodophenoxy-1-butene reacted at 80 °C for 5 h with $Pd(OCOCF_3)_2$ (5 mol %), P(2-furyl)$_3$ (10 mol %), and EtN^iPr_2(1.5 equiv), in supercritical CO_2, to furnish the desired heterocycle **10** as the major component (78:22) of a mixture of regioisomers, that also contains the related endocyclic alkene (4-methyl-chromene), see: Shezad, N.; Clifford, A. A.; Rayner, C. M. *Tetrahedron Lett.* **2001**, *42*, 323.

(13) A test NMR experiment for **1b** at −80 °C showed the appearance of a mixture of intermediates whose signals might be compatible with the proposed intermediacy of **A** and **C**. Further work and theoretical calculations are in progress to ascertain the mechanism pathway. For a stable iodonium ion, see: Brown, R. S.; Nagorski, R. W.; Bennet, A. J.; McClung, R. E: D.; Aarts, G. H. M.; Klobukowski, M.; McDonald, R.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1994**, *116*, 2448.

(14) The different availability of the lone pair of electrons onto the oxygen atom in ethers **1** compared to that onto nitrogen in sulfonamides **5** could argue in favor of differences observed between this two series.

(15) When **1g** was treated with 10 mol % of IPy_2BF_4/HBF_4, after reaction for 1 h at −85 °C, 32% of its isomer **1f** was isolated from the crude reaction mixture.

(16) A related observation has been recently noticed in the cyclization of geranyl phenyl ether **1f** using a chiral Brønsted acid as promoter, that led to a tricyclic compound similar to **4**, with a proton in place of the iodine. However, this rearrangement seems to follow an abnormal Claisen rearrangement to ortho-substituted phenol at −78 °C previous to the cyclization. See: Nakamura, S.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8131.

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