JOC*Article*

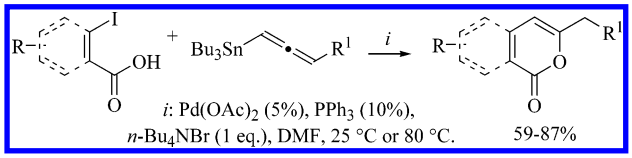
Synthesis of Isocoumarins and α-Pyrones via Tandem Stille Reaction/Heterocyclization

Khalil Cherry,[†] Jean-Luc Parrain,[‡] Jérôme Thibonnet,[†,‡] Alain Duchêne,[†] and Mohamed Abarbri*,[†]

Laboratoire de Synthèse et Physico-Chimie Organique et Thérapeutique, Faculté des Sciences de Tours, Parc de Grandmont, EA 3857, 37200 Tours, France, and Laboratoire Symbio, Equipe Synthèse par voie Organométallique associé au CNRS (UMR 6178), Université Paul Cézanne, Aix Marseille III, Campus Scientifique de Saint Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France

mohamed.abarbri@univ-tours.fr

Received April 1, 2005



A general route to α-pyrones and 3-substituted isocoumarins from (*Z*)-iodovinylic acids **1a**−**f** or 2-iodobenzoic acids **4a**−**c** is described, including compounds bearing a substituent on the aromatic ring. Treatment of (*Z*)-*β*-iodovinylic acids **1a**−**f** or 2-iodobenzoic acids **4a**−**c** with various allenyltributyltin reagents in the presence of palladium acetate, triphenylphosphine, and tetrabutylammonium bromide in dimethylformamide provided good yields of the corresponding α-pyrones **3a**−**k** or 3-substituted isocoumarins **5a**−**g** via tandem Stille reaction and 6-*endo*-dig oxacyclization.

Isocoumarins and α-pyrones are valuable intermediates in the synthesis of several natural products[1,2] and important hetero- and carbocyclic molecules, including isocarbostyrils, isoquinolines, isochromenes, and pyridones. These lactones also occur as structural subunits in numerous natural products that exhibit a wide range of biological activities,[3] including anticancer and HIV-1-specific reverse transcriptase inhibitor properties,[4] and antiallergic and antimicrobial,[5] immunomodulatory,[6] cytotoxic,[7] antifungal,[8] and antiinflammatory activities.[9] The prominence of coumarins and α-pyrones in natural products and biologically active molecules[3,10] has prompted considerable interest in their synthesis.[11,12]

Much attention has been focused on the selective synthesis of these ring systems by transition metal-catalyzed heteroannulation reactions.[13] In the past de-

* To whom correspondence should be addressed. Fax: 33 (0) 2 47 36 70 73.

[†] Laboratoire de Synthèse et Physico-Chimie Organique et Thérapeutique.

[‡] Université Paul Cézanne.

(1) (a) Barry, R. D. *Chem. Rev*. **1964**, 229. (b) Dickinson, J. *Nat. Prod. Rep*. **1993**, *10*, 71. (c) Kiselyov, A. S. *Tetrahedron Lett*. **1995**, *36*, 493. (d) Sugimoto, A.; Shinba-Tanaka, H.; Ishikawa, M. *Synthesis* **1995**, 431. (e) Goff, D. A.; Zuckermann, R. N. *J. Org. Chem*. **1995**, *60*, 5748.

(2) (a) Chen, C.-H.; Liao, C.-C. *Org. Lett*. **2000**, *2*, 2049. (b) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. *J. Org. Chem*. **1999**, *64*, 690. (c) Danieli, B.; Lesma, G.; Martinelli, M.; Passarella, D.; Peretto, I.; Silvani, A. *Tetrahedron* **1998**, *54*, 14081. (d) Jram, V.; Goel, A. *J. Chem. Res., Synop.* **1997**, 460. (e) Liu, Z.; Meinwald, J. *J. Org. Chem*. **1996**, *61*, 6693. (f) Afarinkia, K.; Berna-Canovas, J. *Tetrahedron Lett*. **2000**, *41*, 4955. (g) Stigers, K. D.; Mar-Tang, R.; Bartlett, P. A. *J. Org. Chem*. **1999**, *64*, 8409. (h) Cobas, A.; Diaz, M. T.; Escudero, S.; Pérez, D.; Guitiàn, E.; Castedo, L. In *Current Trends in Organic Synthesis*; Scolastico, C., Nicotra, F., Eds.; Kluwer Academic/Plenum Publishers: New York, 1999; pp 307−314. (i) Ram, V. J.; Srivastava, P.; Saxena, A. S. *J. Org. Chem*. **2001**, *66*, 5333.

(3) (a) Livingstone, R. In *Rodd's Chemistry of carbon compounds*; Caffey, S., Ed.; Elsevier: New York, 1977; vol. IV, Part E, pp 290−297. (b) Hill, R. A. *Progress in the Chemistry of Organic Natural Products*; Springer−Verlag: Weinheim−New York, 1986; Vol. 49, pp 1−78.

(4) (a) Naser-Hijazi, B.; Stolze, B.; Zanker, K. S. *Second Proceedings of the International Society of the Coumarin Investigators*; Springer: Berlin, 1994. (b) Murray, R. D. H.; Méndez, J.; Brown, S. A. *The Natural Coumarins*: *Occurrence, Chemistry, and Biochemistry*; J. Wiley: New York, 1982.

(5) (a) Matsuda, H.; Shimoda, H.; Yoshikawa, M. *Bioorg. Med. Chem. Lett*. **1999**, *7*, 1445. (b) Yoshikawa, M.; Harada, E.; Naitoh, Y.; Inoue, K.; Matsuda, H.; Shimoda, H.; Yamahara, J.; Murakami, N. *Chem. Pharm. Bull*. **1994**, *42*, 2225.

(6) (a) Matsuda, H.; Shimoda, H.; Yamahara, J.; Yoshikawa, M. *Bioorg. Med. Chem. Lett*. **1998**, *8*, 215. (b) Shimoda, H.; Matsuda, H.; Yamahara, J.; Yoshikawa, M. *Biol. Pharm. Bull*. **1988**, *21*, 809.

(7) Whyte, A. C.; Gloer, J. B.; Scott, J. A.; Mallock, D. *J. Nat. Prod*. **1996**, *59*, 765.

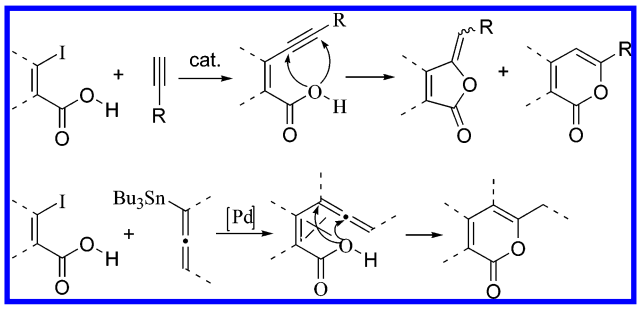
(8) Nozawa, K.; Yamada, M.; Tsuda, Y.; Kawai, K.; Nakajima, S. *Chem. Pharm. Bull*. **1981**, *29*, 2689.

(9) Furuta, T.; Fukuyama, Y.; Asakawa, Y. *Phytochemistry* **1986**, *25*, 517.

(10) (a) Khalmuradov, M. A.; Said-Khodzhaev, A. I. *Chem. Nat. Compd*. **1999**, *35*, 364. (b) Murakami, A.; Gao, G.; Omura, M.; Yano, M.; Ito, C.; Furukawa, H.; Takahashi, D.; Koshimizu, K.; Ohigashi, H. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 59. (c) Maier, W.; Schmidt, J.; Nimtz, M.; Wray, V.; Strack, D. *Phytochemistry* **2000**, *54*, 473. (d) Garcia-Argaez, A. N.; Ramirez-Apan, T. O.; Delgado, H. P.; Velazquez, G.; Martinez-Vazquez, M. *Planta Med*. **2000**, *66*, 279. (e) Wu, J.; Wang, L.; Fathi, R.; Yang, Z. *Tetrahedron Lett*. **2002**, *43*, 4395.

10.1021/jo050638z CCC: $30.25
Published on Web 07/27/2005

SCHEME 1



cade, numerous methods reported for the synthesis of α-pyrones have utilized halolactonization or transition metals (Ag, Hg, Rh, Pd) to promote intramolecular addition of carboxylic acid to alkynes.[14] In general, these reactions of 4-alkynoic acids occur with poor regioselectivity, and in many cases mixtures of γ-alkylidenebutenolides and α-pyrones are obtained (Scheme 1). The problem of regioselectivity was recently solved by Larock et al., who demonstrated that substituted isocoumarins or α-pyrones could be prepared by treating β-halogeno α,β-unsaturated esters with internal alkynes in the presence of a palladium catalyst.[15] Nevertheless, in the case of nonsymmetric alkynes, two α-pyrone regioisomers were obtained. More recently, Negishi et al. proposed the selective conversion of (*Z*)-2-en-4-ynoic acids into α-pyrones in the presence of a catalytic amount of $ZnBr_2$ (10%) or to furanone in the presence of silver salts.[16] On the other hand, we have previously described the synthesis of dienoic acids and enynes bearing a carboxylic acid function from β-iodovinylic acids and vinyltin or alkynylzinc reagents.[17] This methodology was then applied to the synthesis of γ-tributyltin methylidenebutenolides.[18] We have also described our first results of the synthesis of the α-pyrones by approaches involving intramolecular addition of carboxylic acids to allenylstannanes.[19] We now present our full results in this field and their extension to regioselective synthesis of isocoumarins, and our investigation of the scope and limitation of the reaction.

To broaden our synthesis strategy and to design a system suitable for 6-*exo* lactonization, we planned the preparation of allenyl-substituted alkenoic acids, which we believed would exclusively undergo 6-*endo* mode cyclization mediated by a palladium complex (Scheme 1).

Results and Discussion

Synthesis of α-Pyrones. Our investigation began with the coupling of tributylstannylallene[20] with (*Z*)-3-iodoprop-2-enoic acid[17] under conditions identical to those used for the synthesis of γ-tributyltin methylidenebutenolides [$Pd(PPh_3)_4$ (1%), DMF, 25 °C].[18,21] Unfortunately, neither allenyl-substituted propenoic acid nor cyclized products (five- or six-membered ring lactones) were detected. Only a large amount of tin byproducts were recovered, among them the tributylstannyl ester of the starting iodovinylic acid. To avoid the proteolysis of allenylstannane and to promote the cross-coupling reaction, we examined the reaction under various conditions (solvent, catalyst, presence of additives, ...). The influence of the nature of the carboxylic acid derivative on conversion rates was examined first. In DMF and in the presence of 1% of tetrakis(triphenylphosphine)palladium, the ethyl ester of **1a** yielded exclusively ethyl hex-2-en-4-ynoate in 75% yield. The use of tributyltin carboxylate under conditions identical to those used for the synthesis of tributyltin methylidenebutenolides provided 52% yield of 6-methylpyran-2-one **3a**, without any trace of hexa-2,4,5-trienoic acid or hex-2-en-4-ynoic acid.

Next, the natures of the solvent and palladium complexes were examined. THF was found to be ineffective, whereas acetonitrile afforded a very poor yield (<25%)

(11) (a) Mishra, A.; Dash, B. L.; Behera, R. K. *Ind. J. Heterocycl. Chem*. **1996**, *6*, 149. (b) Nicolaides, D. N.; Fylaktakidou, K.; Litinas, E. K.; Papageorgiou, G.; Hadjipavlou-Litina, D. J. *J. Heterocycl. Chem*. **1998**, *35*, 619. (c) Fall, Y.; Teran, C.; Teijeira, M.; Santana, L.; Uriarte, E. *Synthesis* **2000**, 643. (d) Larock, R. C.; Varaprath, S.; Lau, H. H.; Fellows, C. A. *J. Am. Chem. Soc*. **1984**, *106*, 5274. (e) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. *J. Org. Chem*. **1995**, *60*, 3270. (f) Izumi, T.; Morishita, N. *J. Heteroycl. Chem*. **1994**, *31*, 145. (g) Ohta, S.; Kamata, Y.; Inagaki, T.; Masuda, Y.; Yamamoto, S.; Yamashita, M.; Kawasaki, I. *Chem. Pharm. Bull*. **1993**, *41*, 1188. (h) Yoshikawa, M.; Harada, E.; Yagi, N.; Okuno, Y.; Muraoka, O.; Aoyama, H.; Murakami, N. *Chem. Pharm. Bull*. **1994**, *42*, 721. (i) Yoshikawa, M.; Shimada, H.; Yagi, N.; Murakami, N.; Shimoda, H.; Yamahara, J.; Matsuda, H. *Chem. Pharm. Bull*. **1996**, *44*, 1890. (j) Mali, R. S.; Babu, K. N. *J. Org. Chem*. **1988**, *53*, 4676. (k) Rama, N. H.; Iqbal, R.; Zamani, K.; Saeed, A.; Iqbaql, M. Z.; Choudhary, M. I. *Indian J. Chem., Sect. B* **1998**, *37*, 365. (l) Bovicelli, P.; Lupattelli, P.; Crescenzi, B.; Sanetti, A.; Bernini, R. *Tetrahedron* **1999**, *55*, 14719. (m) Mal, D.; Bandyopadhyay, M.; Ghorai, S. K.; Datta, K. *Tetrahedron Lett*. **2000**, *41*, 3677. (n) Hussain, M. T.; Rama, N. H.; Malik, A. *Indian J. Chem., Sect. B* **2001**, *40*, 372. (o) Natsugari, H.; Ikeura, Y.; Kiyota, Y.; Ishichi, Y.; Ishimaru, T.; Saga, O.; Shirafuji, H.; Tanaka, T.; Kamo, T.; Doi, T.; Otsuka, M. *J. Med. Chem*. **1995**, *38*, 3106. (p) Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P.; Mannina, L. *Tetrahedron* **2003**, *59*, 2067. (q) An, Z.; Catellani, M.; Chiusoli, G. P. *Gazz. Chim. Ital*. **1990**, *120*, 383. (r) Catellani, M.; Chiusoli, G. P.; Solari, G. *Tetrahedron Lett*. **1994**, *35*, 5919. (s) Catellani, M.; Chiusoli, G. P.; Fagnola, M. C.; Solari, G. *Tetrahedron Lett*. **1994**, *35*, 5923. (t) Johnson, J. R. *Org. React*. **1942**, *1*, 210. (u) Sethna, S.; Phadke, R. *Org. React*. **1953**, *7*, 1.

(12) (a) Vara Prasad, J. V. N.; Para, K. S.; Lunney, E. A.; Ortwine, D. F.; Dunbar, J. B., Jr.; Fergunson, D.; Tummino, P. J.; Hupe, D.; Tait, B. D.; Domagala, J. M.; Humblet, C.; Bhat, T. N.; Liu, B.; Guerin, D. A. M.; Baldwin, E. T.; Erickson, J. W.; Sawyer, T. K. *J. Am. Chem. Soc.* **1994**, *116*, 6989. (b) Tuanli, Y.; Larock, R. C. *J. Org. Chem*. **2003**, *68*, 5936.

(13) (a) Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Heterocycles* **1995**, *41*, 2587. (b) Bellina, F.; Ciucci, D.; Vergamini, P.; Rossi, R. *Tetrahedron* **2000**, *56*, 2533. (c) Rossi, R.; Bellina, F.; Biagetti, M.; Catanese, A.; Mannina, L. *Tetrahedron Lett*. **2000**, *41*, 5281. (d) Minami, T.; Nishimoto, A.; Nakamura, M. *Chem. Pharm. Bull*. **1994**, *42*, 170. (e) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron Lett*. **2001**, *42*, 2852. (f) Kvita, V.; Fischer, W. *Chimica* **1992**, *45*, 457. (g) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem*. **2003**, *68*, 9423.

(14) For a recent synthesis using Pd or Ag catalysts, see: (a) Xu, C.; Negishi, E. *Tetrahedron Lett*. **1999**, *40*, 431. (b) Ma, S.; Shi, Z. *J. Org. Chem*. **1998**, *63*, 6387. (c) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron Lett*. **1998**, *39*, 7799. (d) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron Lett*. **1998**, *39*, 7599. (e) Rossi, R.; Bellina, F.; Mannina, L. *Tetrahedron Lett*. **1998**, *39*, 3017. (f) Rossi, R.; Bellina, F.; Bechini, C.; Mannina, L.; Vergamini, P. *Tetrahedron* **1998**, *54*, 135. (g) Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem*. **1997**, *62*, 367. (h) Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem*. **1995**, *60*, 796. (i) Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem*. **1996**, *61*, 3238. (j) Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Synlett* **1995**, 871.

(15) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.

(16) Anastasia, L.; Xu, C.; Negishi, E. *Tetrahedron Lett*. **2002**, *43*, 5673.

(17) (a) Duchêne, A.; Abarbri, M.; Parrain, J.-L.; Kitamura, M.; Noyori, R. *Synlett* **1994**, 524. (b) Abarbri, M.; Parrain, J.-L.; Cintrat, J. C.; Duchêne, A. *Synthesis* **1996**, 82.

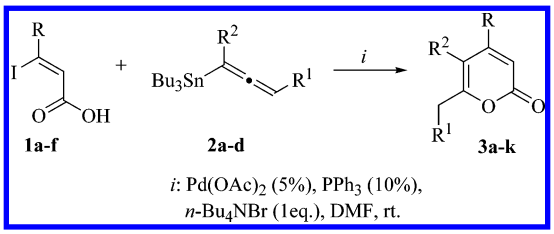
(18) Rousset, S.; Abarbri, M.; Thibonnet, J.; Duchêne, A.; Parrain, J.-L. *Org. Lett.* **1999**, *1*, 701.

(19) Rousset, S.; Abarbri, M.; Thibonnet, J.; Duchêne, A.; Parrain, J.-L. *Chem. Commun*. **2000**, 1987.

(20) (a) Tanaka, H.; Hai, A. K.; Ogawa, A. H.; Torii, S. *Synlett* **1993**, 835. (b) Brandsma, L. *Synthesis of Acetylenes, Allenes, and Cumulenes: a laboratory manual*; Elsevier Scientific Pub. Co.: New York, 1981.

(21) Rousset, S.; Abarbri, M.; Thibonnet, J.; Parrain, J.-L.; Duchêne, A. *Tetrahedron Lett*. **2003**, *44*, 7633.

SCHEME 2



of cyclized product. We also observed that phosphine-ligated palladium appeared to be more efficient than other palladium salts such as palladium acetate (without additional triphenylphosphine) or bis(acetonitrile)palladium chloride. Tetrakis(triphenylphosphine)palladium gave approximately identical yields to the $Pd(OAc)_2/PPh_3$ couple. The use of an excess (1.5 equiv) of allenyltributyltin was essential to obtain good yields of these pyranones **3a**−**k**, and a stoichiometric quantity of allenyltributyltin provides the desired pyranones, but in poor yields (<40%). The use of sodium carbonate as base is not necessary in these heterocyclization reactions as we previously mentioned.[19] In the absence of a palladium complex, no reaction occurred between the (*Z*)-iodovinylic acids **1a**−**f** and the allenyltributyltins, the starting materials are recovered. After experimentation with a variety of conditions and methods, it was found that the best result for the final cyclization step was obtained using 5% palladium acetate, 10% triphenylphosphine, and tetrabutylammonium bromide in DMF at room temperature, providing an 83% yield of α-pyrone **3a** (Scheme 2). The results are summarized in Table 1.

The reaction of tributylstannylallene with a range of (*Z*)-3-substituted 3-iodoprop-2-enoic acids under regio- and stereocontrol gave good yields of 4-substituted-6-methyl-2-pyranones **3a**−**f** as the sole products (entries 1−6, Table 1). The scope and limitations of this annulation reaction were studied by allowing a wide variety of allenyltributyltins to react with various *β*-iodo propenoic acids under our optimized reaction conditions. High regioselectivity was observed in each case. The use of 3-alkylallenylstannanes (entries 7−10, Table 1) showed that the regioselective heteroannulation reaction occurred only on carbons 1 and 2 of the allenyltin reagent. The methodology also proved to be very convenient and general for the synthesis of various 4,6-disubstituted 2-pyranones. The reaction temperature does not have any effect on the regioselectivity. The annulation reactions performed at 80 °C afforded 2-pyranones with comparable results. The α-pyrones were obtained without any trace of 3-allenyl or 3-alkynyl propenoic acids. On the other hand, the *γ*-alkylidenepyranones previously obtained by Larock et al. from a reaction of allenes with (*Z*)-3-iodopropenoic acids were not observed. This almost certainly indicates a mechanism different from those proposed by Larock and Yamamoto, respectively.[22,23] In our case, the regioselectivity of this process would arise from the nucleophilic attack of the carboxylate function on the central carbon of the allenyl moiety.

In continuation of our studies on the synthesis of α-pyrones by approaches that involve intramolecular addition of carboxylic acids to allenylstannanes, we next examined the possibility of regioselectively preparing isocoumarins by this same methodology and report our results here.

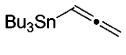
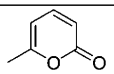
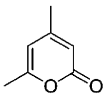
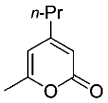
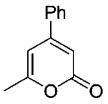
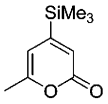
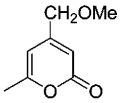
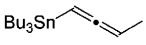
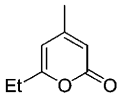
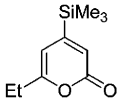
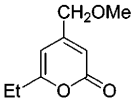
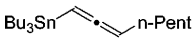
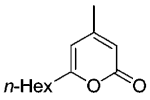
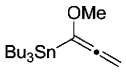
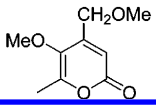
Synthesis of Isocoumarins. 3-Substituted isocoumarins are attractive synthesis targets because of their biological and pharmacological activities. These heterocycles have been prepared by the palladium-catalyzed coupling of 2-halobenzoate esters or 2-halobenzonitriles with alkenes,[24] vinylic stannanes,[25] or terminal alkynes,[26] with subsequent cyclization or *π*-allylnickel cross-coupling and palladium-catalyzed cyclization,[27] itself by coupling of 2-(2,2-dibromovinyl) benzoates and organostannanes,[28] or by palladium-catalyzed annulation of terminal alkynes and 2-iodophenols.[29] The cross-coupling of *o*-iodobenzoic acid and terminal alkynes produces either unsaturated phthalides[30,31] or 3-substituted isocoumarins[32] as major products. In our case, the reaction conditions chosen were those used for the synthesis of α-pyrones. Thus, the coupling of 2-iodo benzoic acids **4a**−**c** with tributylstannylallene at 80 °C under identical conditions provided a highly regioselective method for the synthesis of isocoumarins (Scheme 3). It should be noted that the reaction requires heating because no reaction occurred at room temperature. The results are summarized in Table 2.

Both 2-iodo benzoic acids **4a**−**c** and a variety of allenyltributyltins were successfully utilized. This process afforded reasonable yields of substituted isocoumarins **5a**−**g**, including compounds bearing a substituent group on the aromatic ring (**5c**−**g**). Thus, the cyclization of 2-iodo benzoic acid bearing an electron-withdrawing group ortho to the hydroxycarbonyl group proved to be nearly as successful as 2-iodobenzoic acid itself (entries 3, 5, and 7, Table 2). In addition, the yield was comparable to the yield obtained with the parent 2-iodo benzoic acid. These results are important, because isocoumarins possessing an electron-withdrawing group such as fluorine, and an electron-donating group such as methoxy group, have been synthesized.

When 2-iodo-4-methoxybenzoic acid was allowed to react with allenylstannane (entries 4 and 6, Table 2), the desired isocoumarins **5d** and **5f** were produced at 65% and 61% yield, respectively. The starting materials for our synthesis of isocoumarins, 2-iodo benzoic acid **4a** and 2-fluoro-6-iodo benzoic acid **4b**, were commercially available. 2-Iodo-4-methoxybenzoic acid **4c** was synthesized from 4-methoxybenzoic acid by a known procedure.[33]

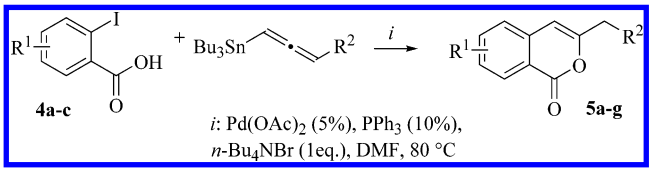
(22) Larock, R. C.; He, Y.; Leon, W. W.; Han, X.; Refvik, M. D.; Zenner, M. J. *J. Org. Chem*. **1998**, *63*, 2154.
(23) Yamamoto, Y.; Al-Masum, M.; Fujiwara, N. *J. Chem. Soc., Chem. Commun*. **1996**, 381.
(24) (a) Izumi, T.; Nishimoto, Y.; Kohei, K.; Kasahara, A. *J. Heterocycl. Chem.* **1990**, *27*, 1419. (b) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1988**, *27*, 453.
(25) Sakamoto, T.; Kondo, Y.; Yasuhara, A.; Yamanaka, H. *Tetrahedron* **1991**, *47*, 1877.
(26) (a) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1988**, *27*, 2225. (b) Sakamoto, T.; An-naka, M.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull*. **1986**, *34*, 2754. (c) Sakamoto, T.; An-naka, M.; Kondo, Y.; Araki, T.; Yamanaka, H. *Chem. Pharm. Bull*. **1988**, *36*, 1890.
(27) Korte, D. E.; Hegedus, L. S.; Wirth, R. K. *J. Org. Chem*. **1977**, *42*, 1329.
(28) Wang, L.; Shen, W. *Tetrahedron Lett*. **1998**, *39*, 7625.
(29) Kadnikov, D. V.; Larock, R. C. *J. Organomet. Chem*. **2003**, *687*, 425.
(30) Kundu, N. G.; Pal, M.; Nandi, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 561.
(31) Kundu, N. G.; Pal, M. *J. Chem. Soc., Chem. Commun*. **1993**, 86.
(32) (a) Liao, H.-Y.; Cheng, C.-H. *J. Org. Chem*. **1995**, *60*, 3711. (b) Sashida, H.; Kawamukai, A. *Synthesis* **1999**, 1145.

TABLE 1. Synthesis of Substituted α-Pyrones 3a−k

Entry	R (**1**)	Allenylstannane	α-pyrone		Yield (%)[a]
1	H (**1a**)			**3a**	**83**
2	Me (**1b**)	"		**3b**	**85**
3	*n*-Pr (**1c**)	"		**3c**	**81**
4	Ph (**1d**)	"		**3d**	**87**
5	Me_3Si (**1e**)	"		**3e**	**79**
6	CH_2OMe (**1f**)	"		**3f**	**84**
7	Me (**1b**)			**3g**	**85**
8	Me_3Si (**1e**)	"		**3h**	**86**
9	CH_2OMe (**1f**)	"		**3i**	**84**
10	Me (**1b**)			**3j**	**84**
11	CH_2OMe (**1f**)			**3k**	**82**

[a] Isolated yield of analytically pure products.

SCHEME 3



Isocoumarins **5a−g** were obtained without any trace of 2-allenyl benzoic acids, and without any trace of five-membered ring products, giving a regioselective character to the cyclization process where only 6-*endo* mode cyclization was observed (Scheme 3 and Table 2). As illustrated in Tables 1 and 2, better yields were obtained in the case of α-pyrones as compared to the isocoumarins. On the basis of the above results, we believe that this isocoumarin synthesis proceeds by the same mechanism as that proposed for the synthesis of α-pyrones.

All of the isocoumarins **5a−g** and α-pyrones **3a−k** were well characterized by satisfactory spectroscopic (MS, IR, ^{1}H NMR, and ^{13}C NMR) and analytical data.

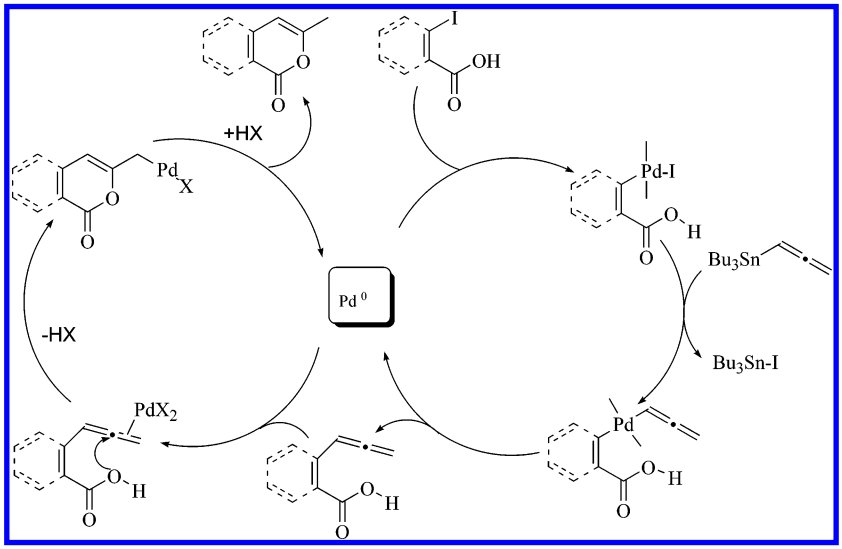
(33) (a) Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787. (b) Meyers, A. I.; Mihelich, E. D. *J. Org. Chem.* **1975**, *40*, 3158. (c) Liang, P.-H.; Hsin, L.-W.; Pong, S.-L.; Hsu, C.-H.; Cheng, C.-Y. *J. Chin. Chem. Soc.* **2003**, *50*, 449.

TABLE 2. Synthesis of 3-Substituted Isocoumarins 5a–g

Entry	R^1 (4)	Allenylstannane	Isocoumarin		Yield (%)[a]
1	H (**4a**)	Bu_3Sn		**5a**	65
2	"	Bu_3Sn		**5b**	59
3	F (**4b**)	Bu_3Sn		**5c**	62
4	MeO (**4c**)	"		**5d**	65
5	F (**4b**)	Bu_3Sn		**5e**	60
6	MeO (**4c**)	"		**5f**	61
7	F (**4b**)	Bu_3Sn *n*-Bu		**5g**	63

[a] Isolated yield of analytically pure product.

SCHEME 4. Proposed Mechanism of the Formation of Isocoumarin and α-Pyrone



Mechanism. Based on the above observations and the known palladium chemistry, a possible mechanism for the formation of α-pyrones and isocoumarins by a single-step palladium-catalyzed reaction of (*Z*)-3-iodopropenoic acid or 2-iodobenzoic acid derivatives with allenylstannanes is shown in Scheme 4. First, $Pd(OAc)_2$ is reduced to a Pd(0) complex, which is the actual catalyst in the process, followed by an oxidative addition of the vinylic (or aromatic) iodide to palladium (0). A Stille mechanism[34] would yield 3-allenylpropenoic acid (or 2-allenylbenzoic acid) by transmetalation and reductive elimination. After activation by complexation with palladium, the allene undergoes intramolecular 6-*exo*-dig nucleophilic attack by the carboxylate function, the catalytic cycle being completed by protonolysis, and affords α-pyrone or isocoumarin as the final product.

An alternative pathway involving the vinylic palladium addition to the central carbon atom of the stannylallene could be excluded on the basis of the experiments conducted with 1- or 3-substituted allenylstannanes because other regioisomers should have been obtained rather than **3a**−**k** or **5a**−**g**.[22]

On the other hand, an isomerization of allene to alkyne prior to nucleophilic attack of the carboxylate function is also excluded, because, in this case, a probable mixture of five- and six-membered ring products will be formed.[30−32]

Conclusion

In summary, we have developed a general and convenient regioselective method for the preparation of 3-substituted isocoumarins and substituted α-pyrones via the palladium-catalyzed coupling of 2-iodobenzoic acid derivatives or vinylic acids and allenyltributyltins. The heteroannulation reaction proceeded selectively and provided good isolated yields of a variety of 3-substituted isocoumarins and substituted α-pyrones.

Experimental Section

General Procedure for the Preparation of α-Pyrones 3a−k. Palladium acetate (112 mg, 0.5 mmol), triphenylphosphine (262 mg, 1 mmol), and tetrabutylammonium bromide (3.2 g, 10 mmol) were progressively added to a degassed solution of 3-substituted-3-iodopropenoic acids **1a**−**f** (10 mmol) in anhydrous DMF (40 mL). The mixture was stirred at room temperature for 10 min, and allenylstannane (15 mmol) was then added. The reaction mixture was stirred for 4h after conversion was complete (checked by TLC), and the reaction was quenched with aqueous NH_4Cl solution. After ether extraction (3 × 20 mL) and usual treatments, the crude products were chromatographed on silica gel (hexane/ether = 80/20) to obtain compounds **3a**−**k**.

6-Methyl-2*H*-pyran-2-one (3a).[35] IR (neat) 2960, 2926, 2856, 1732, 1713, 1636, 1559, 1341, 1099; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.24 (s, 3H), 5.96 (dd, J = 6.5 Hz, J = 0.7 Hz, 1H), 6.1 (dd, J = 9.4 Hz, J = 0.7 Hz, 1H), 7.23 (dd, J = 9.4 Hz, J = 6.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.5, 103.8, 113.5, 144.3, 163.3, 163.5; MS (EI) *m/z* (%) 110 (M•$^+$, 40), 95 (39), 82 (50), 43 (50), 39 (100). Anal. Calcd for $C_6H_6O_2$: C, 65.45; H, 5.49. Found: C, 65.40; H, 5.42.

4,6-Dimethyl-2*H*-pyran-2-one (3b).[36] IR (neat) 2959, 2926, 1736, 1704, 1651; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.24 (s, 3H), 5.87 (s, 1H), 5.97 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.6, 21.2, 106.2, 110.3, 156, 161, 163; MS (EI) *m/z* (%) 124 (M•$^+$, 42), 96 (70), 95 (21), 53 (100), 43 (61). Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.68; H, 6.45.

6-Methyl-4-propyl-2*H*-pyran-2-one (3c). IR (neat) 3071, 2963, 2875, 1770, 1731, 1644, 1562, 1463, 1231; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (t, J = 7.3 Hz, 3H), 1.17 (sext, J = 7.3 Hz, 2H), 2.21 (s, 3H), 2.33 (t, J = 7.3 Hz, 2H), 5.87 (s, 1H), 5.92 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.5, 19.7, 21.3, 37.8, 105.6, 109.6, 161.0, 161.9, 164.1; MS (EI) *m/z* (%) 152 (M•$^+$, 36), 124 (24), 96 (100), 95 (43), 43 (83). Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.09; H, 8.0.

6-Methyl-4-phenyl-2*H*-pyran-2-one (3d).[37] IR (neat) 2960, 2926, 2855, 1741, 1725, 1642, 1552; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.35 (bs, 3H), 6.35 (bs, 1H), 6.38 (s, 1H), 7.31−7.62 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.7, 104, 108.8, 127.3, 129.7, 131, 137, 157, 162.7, 163; MS (EI) *m/z* (%) 186 (M•$^+$, 53), 158 (100), 129 (40), 115 (69), 51 (15), 43 (39). Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.36; H, 5.36.

6-Methyl-4-trimethylsilyl-2*H*-pyran-2-one (3e). IR (neat) 2960, 1764, 1730, 1624, 1523, 1253; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.23 (s, 9H), 2.23 (bs, 3H), 5.97−6.0 (m, 1H), 6.28 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ −0.8, 14, 105.7, 118, 160.3, 160.4, 161.6; MS (EI) *m/z* (%) 182 (M•$^+$, 19), 154 (27), 139 (100), 73 (49), 43 (60). Anal. Calcd for $C_9H_{14}O_2Si$: C, 59.30; H, 7.74. Found: C, 59.35; H, 7.80.

4-Methoxymethyl-6-methyl-2*H*-pyran-2-one (3f). IR (neat) 2995, 2928, 2824, 1738, 1715, 1645, 1568, 1449, 1308, 1199; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.2 (s, 3H), 3.38 (s, 3H), 4.18 (bs, 2H), 5.92 (bs, 1H), 6.08 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.5, 59.4, 72.5, 103, 109, 156.7, 162.7, 163.5; MS (EI) *m/z* (%) 154 (M•$^+$, 22), 122 (21), 95 (28), 45 (19), 43 (100). Anal. Calcd for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found: C, 62.28; H, 6.48.

6-Ethyl-4-methyl-2*H*-pyran-2-one (3g).[38] IR (neat) 2981, 2977, 2968, 1713, 1644; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.05 (t, J = 7.5 Hz, 3H), 1.97 (s, 3H), 2.33 (t, J = 7.5 Hz, 2H), 5.73 (bs, 1H), 5.77 (bs, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.3, 22.9, 27.1, 105.2, 110.7, 156.9, 163.6, 166.3; MS (EI) *m/z* (%) 138 (M•$^+$, 53), 111 (51), 109 (100), 95 (63), 53 (92). Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.49; H, 7.27.

6-Ethyl-4-trimethylsilyl-2*H*-pyran-2-one (3h). IR (neat) 2960, 1745, 1727, 1622, 1523, 1255; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.17 (s, 9H), 1.15 (t, J = 7.5 Hz, 3H), 2.41 (q, J = 7.5 Hz, 2H), 5.90 (s, 1H), 6.19 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −2.1, 11.7, 27.3, 104.6, 118.6, 162.2, 163.1, 165.5; MS (EI) *m/z* (%) 196 (M•$^+$, 22), 168 (30), 153 (100), 75 (15), 57 (17). Anal. Calcd for $C_{10}H_{16}O_2Si$: C, 61.18; H, 8.21. Found: C, 61.13; H, 8.13.

6-Ethyl-4-methoxymethyl-2*H*-pyran-2-one (3i). IR (neat) 3084, 2995, 2928, 2844, 1738, 1714, 1645, 1568, 1199; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (t, J = 7.5 Hz, 3H), 2.46 (q, J = 7.5 Hz, 2H), 3.33 (s, 3H), 4.14 (s, 2H), 5.87 (s, 1H), 6.04 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.4, 27.3, 59.3, 72.4, 101.1, 108.9, 156.7, 163.5, 167.4; MS (EI) *m/z* (%) 168 (M•$^+$, 71), 139 (100), 111 (54), 57 (71), 45 (35). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.20; H, 7.14.

6-Hexyl-4-methyl-2*H*-pyran-2-one (3j).[21,39] IR (neat) 2958, 2930, 2860, 1736, 1647, 1564; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.76 (t, J = 6.3 Hz, 3H), 1.15−1.18 (m, 6H), 1.53 (m, 2H), 2.0 (s, 3H), 2.33 (t, J = 7.3 Hz, 2H), 5.75 (s, 1H), 5.82 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 21.8, 22.8, 27.2, 29.0, 31.8, 33.9, 106.1, 110.8, 156.8, 163.8, 165.3; MS (EI) *m/z* (%) 194 (M•$^+$, 26), 124 (33), 109 (100), 96 (48), 95 (76). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.13; H, 9.29.

5-Methoxy-4-methoxymehyl-6-methyl-2*H*-pyran-2-one (3k). IR (neat) 2994, 2938, 2826, 1738, 1642, 1558, 1230, 1122; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.18 (s, 3H), 3.40 (s, 3H), 3.59 (s, 3H), 4.27 (s, 2H), 6.15 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.3, 59.7, 62.5, 68.9, 109.7, 138.5, 154.2, 154.6, 162.4; MS (EI) *m/z* (%) 184 (M•$^+$, 23), 169 (22), 141 (22), 43 (100), 39 (14). Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.66; H, 6.49.

(34) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813. (c) Mitchell, T. N. *Synthesis* **1992**, 803. (d) Farina, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G., Wilkinson, G., Eds.; Elsevier: Oxford, 1995; Vol. 12, Chapter 3.4, pp 161−241. (e) Farina, V.; Roth, G. P. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: New York, 1996; Vol. 5, pp 1−53. (f) Farina, V.; Krishnamurthy, V.; Scott, W. J. In *Org. React.*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 50, Chapter 1, pp 1−652. (g) Farina, V.; Krishnamurthy, V. *The Stille Reaction*; Wiley: New York, 1999.

(35) (a) Kotretsou, S. I.; Georgiadis, M. P. *Org. Prep. Proced. Int.* **2000**, *32*, 161. (b) Izumi, T.; Kasahara, A. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1673.

(36) (a) Zhou, M.; Yoshida, Y.; Ishii, S.; Noguchi, H. *Synth. Commun.* **1999**, *29*, 2241. (b) Dieter, R. K.; Fishpaugh, J. R. *J. Org. Chem.* **1988**, *53*, 2031.

(37) (a) Kalinin, V. N.; Shilova, O. S.; Okladnoi, D. S.; Schmidhammer, H. *Dokl. Akad. Nauk* **1996**, *351*, 67. (b) Fairlamb, I. J. S.; Marrison, L. R.; Dickinson, J. M.; Lu, F. J.; Schmidt, J. P. *Bioorg. Med. Chem.* **2004**, *12*, 4285.

(38) Dieter, R. K.; Fishpaugh, J. R. *J. Org. Chem.* **1987**, *52*, 923.

(39) Pittet, A. O.; Klaiber, E. M. *J. Agric. Food Chem.* **1975**, *23*, 1189.

General Procedure for the Preparation of Isocoumarins 5a−g. Palladium acetate (112 mg, 0.5 mmol), triphenylphosphine (262 mg, 1 mmol), and tetrabutylammonium bromide (3.2 g, 10 mmol) were progressively added to a degassed solution of 2-iodobenzoic acids **4a−c** (10 mmol) in anhydrous dimethylformamide (40 mL). The mixture was stirred at room temperature for 10 min, and allenylstannane (15 mmol) was then added. The reaction mixture was heated in an oil bath at 80 °C for the necessary period of time. After conversion was complete (checked by TLC, reaction time < 10 h), the reaction mixture was cooled, diluted with diethyl ether, and quenched with aqueous NH_4Cl solution. After ether extraction (3 × 20 mL) and usual treatments, the products **5a−g** were isolated by chromatography (hexane/ether: 70/30) on silica gel column or by crystallization in diethyl ether.

3-Methylisocoumarin (5a).[40] Isolated as colorless prisms with mp 71−73 °C (lit.[S6(b)] mp 71 °C).

3-Ethylisocoumarin (5b).[11j,41] Isolated as a pale yellow solid with mp 72−74 °C (lit.[S7(a)] mp 72−73 °C).

8-Fluoro-3-methylisocoumarin (5c). Mp 110−112 °C; IR (KBr) 3083, 2973, 1743, 1661, 1614; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.28 (d, J = 1.0 Hz, 3H), 6.26 (q, J = 1.0 Hz, 1H), 7.06−7.16 (m, 2H), 7.59−7.70 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20, 103.5, 109.4 (d, J_{C-F} = 7 Hz), 115 (d, J_{C-F} = 21 Hz), 121.3 (d, J_{C-F} = 4 Hz), 136.5 (d, J_{C-F} = 10 Hz), 140.6, 156, 159 (d, J_{C-F} = 5.5 Hz), 163 (d, J_{C-F} = 266 Hz); ^{19}F NMR (188 MHz, $CDCl_3$) δ −108.5; MS (EI) *m/z* (%)178 (M•$^+$, 100), 163 (38), 107 (65), 43 (79). Anal. Calcd for $C_{10}H_7FO_2$: C, 67.42; H, 3.96. Found: C, 67.38; H, 3.95.

6-Methoxy-3-methylisocoumarin (5d).[42] Mp 86−88 °C; IR (KBr) 3079, 2992, 1726, 1648, 1610, 1150; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.94 (s, 3H), 6.23 (s, 1H), 6.75 (d, J = 2.5 Hz, 1H), 7.02 (dd, J = 8.8 Hz, J = 2.5 Hz, 1H), 8.21 (d, J = 8.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.1, 56, 104, 107.3, 113.4, 116.3, 132.1, 140.4, 155.6, 163.2, 165.1; MS (EI) *m/z* (%) 190 (M•$^+$, 100), 175 (49), 148 (18), 119 (54), 43 (28). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.44; H, 5.25.

3-Ethyl-8-fluoro-isocoumarin (5e). IR (neat) 3083, 2973, 1743, 1661, 1614; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, J = 7.5 Hz, 3H), 2.58 (qd, J = 7.5 Hz, J = 1.2 Hz, 2H), 6.26 (t, J = 1.2 Hz, 1H), 7.07−7.18 (m, 2H), 7.60−7.70 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.5, 27, 102 (d, J_{C-F} = 3 Hz), 109.4 (d, J_{C-F} = 7 Hz), 115 (d, J_{C-F} = 21 Hz), 121.3 (d, J_{C-F} = 4 Hz), 136.5 (d, J_{C-F} = 10 Hz), 140.6, 159 (d, J_{C-F} = 5.5 Hz), 161, 163 (d, J_{C-F} = 265 Hz); ^{19}F NMR (188 MHz, $CDCl_3$,) δ −108; MS (EI) *m/z* (%) 192 (M•$^+$, 100), 163 (63), 136 (28), 107 (96), 57 (33). Anal. Calcd for $C_{11}H_9FO_2$: C, 68.74; H, 4.72. Found: C, 68.79; H, 4.76.

3-Ethyl-6-methoxyisocoumarin (5f). Mp 93−95 °C; IR (KBr) 3088, 2990, 1725, 1650, 1606, 1160; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31 (t, J = 7.5 Hz, 3H), 2.60 (q, J = 7.5 Hz, 2H), 3.94 (s, 3H), 6.23 (s, 1H), 6.78 (d, J = 2.4 Hz, 1H), 8.21 (d, J = 8.8 Hz, 1H), 7.02 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 8.21 (d, J = 8.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.6, 27.1, 56, 102.4, 107.6, 113.7, 116.3, 132.2, 140.4, 160.6, 163.2, 165.1; MS (EI) *m/z* (%) 204 (M•$^+$, 94), 175 (82), 148 (34), 119 (100), 65 (22). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.54; H, 5.94.

Acknowledgment. We thank MESR and CNRS for providing financial support and the "Service d'analyse chimique du vivant de Tours" for recording NMR and mass spectra.

Supporting Information Available: Lists of the ^{1}H and/or ^{13}C chemical shifts of the compounds **3c−f**, **3i**, **3k**, and **5c−f**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050638Z

(40) (a) Sashida, H.; Kawamukai, A. *Synthesis* **1999**, 1145. (b) Larock, R. C.; Varaprath, S.; Lau, H. H.; Fellows, C. A. *J. Am. Chem. Soc.* **1984**, *106*, 5274.

(41) Tirodkar, R. B.; Vsgaonkar, R. N. *Indian J. Chem*. **1970**, *8*, 123.

(42) Hauser, F. M.; Dorsch, W. A.; Mal, D. *Org. Lett*. **2002**, *4*, 2237.