Organic LETTERS

Letter

pubs.acs.org/OrgLett

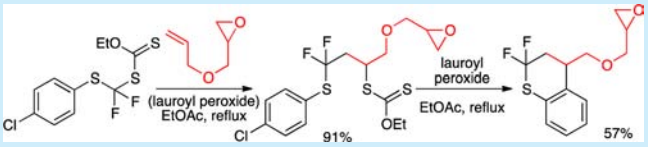
A Convergent Route to Geminal Difluorosulfides and to Functionalized Difluorothiochromans, a New Family of Organofluorine Compounds

Pierre Salomon and Samir Z. Zard*

Laboratoire de Synthèse Organique, CNRS UMR 7652 Ecole Polytechnique, 91128 Palaiseau, Cedex, France

Supporting Information

ABSTRACT: The synthesis of the novel *O*-ethyl-*S*-(4-chlorophenylthio)difluoromethyl xanthate and its radical addition to various terminal alkenes are described. The geminal difluorosulfide adducts undergo closure onto the aromatic ring by further treatment with peroxide to furnish difluorothiochromans, a new family of organofluorine compounds.



Fluorine containing molecules, and especially aromatics, heteroaormatics, and heterocycles, are of major importance to the pharmaceutical and agrochemical industries and to material sciences.[1] The presence of fluorine atoms deeply modifies the physical and chemical properties of molecules and increases the metabolic stability in the case of biologically active substances.[2] Since organofluorine compounds have never been found in animals[3] and remain very rare in plants,[4] they must be obtained by synthesis. It is therefore not surprising that the search for methods allowing the efficient introduction of fluorine or fluorine containing groups has remained unabated over many decades.

Essentially every type of reaction has been used to synthesize organofluorine derivatives, and the literature on the subject is indeed very extensive.[5] However, while sulfur based fluorinated synthons and reagents have become more popular in recent times, in particular fluoroalkylsulfinate salts and fluoroalkylsulfones,[6] the use of fluorinated sulfides has remained relatively limited so far.[7]

We and others have in the past applied the xanthate reversible addition−transfer process[8] to generate and capture the various fluorine containing radicals **1**−**7** displayed in Figure 1.[9] In order to expand the scope of this approach, we considered preparing xanthate **8** as a possible convenient source of arylthiodifluoromethyl radicals **9** (Figure 1). Such radicals have been produced from the corresponding halides, but their use in synthesis has remained limited.[10]

In a first approach, we attempted a direct substitution of the bromide in **10** by a xanthate (Scheme 1). The substitution by

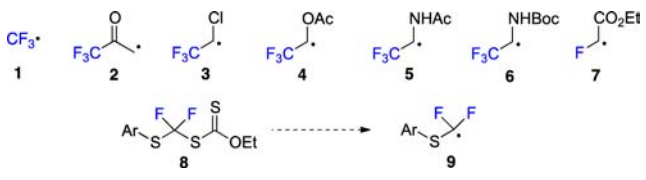
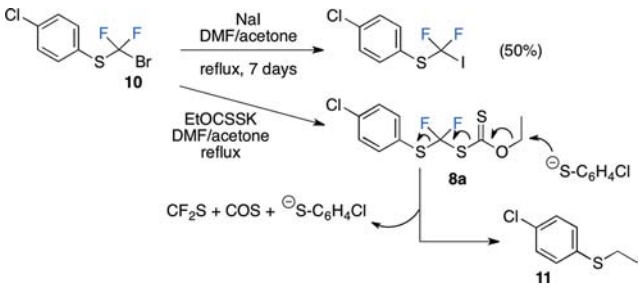


Figure 1. Fluorinated radicals generated from xanthates.

Scheme 1. Failed Attempt at the Synthesis of Xanthate 8a

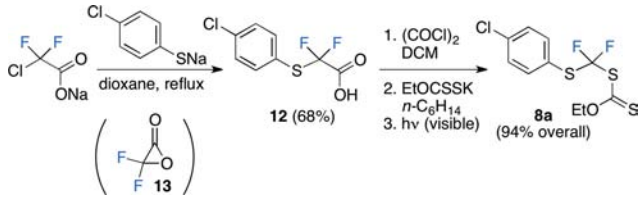


an iodide has been described.[10b] While this reaction, which is probably not a simple S_N2 process, is not very efficient, its expediency compensates for its sluggishness and the moderate yield. Unfortunately, the reaction of bromide **10** with commercial potassium *O*-ethyl xanthate was not only also sluggish, but further resulted in a complex mixture from which ethyl sulfide **11** could be isolated in poor yield. This undesired compound presumably arises through an ionic chain sequence, whereby attack by the *p*-chlorophenylthiolate on the ethyl group of xanthate **8a** regenerates the same thiolate, along with carbon oxysulfide and difluoromethanethione (difluorothiophosgene). Since the desired xanthate **8a** could not be made by direct substitution, we resorted to the indirect route depicted in Scheme 2. Thus, treatment of commercially available sodium chlorodifluoroacetate with the sodium salt of 4-chlorothiophenol in refluxing dioxane resulted in the replacement of the chlorine with the chlorothiophenyl group.[11] Acidification delivered the free carboxylic acid **12** in 68% yield. This unusual substitution possibly proceeds through the reactive α-lactone **13**. Exposure of carboxylic acid **12** to oxalyl chloride effected a clean conversion into the corresponding acid chloride, which was not purified but simply stirred with

Received: January 27, 2014
Published: February 14, 2014

   dx.doi.org/10.1021/ol5002939 | *Org. Lett.* 2014, 16, 1482−1485

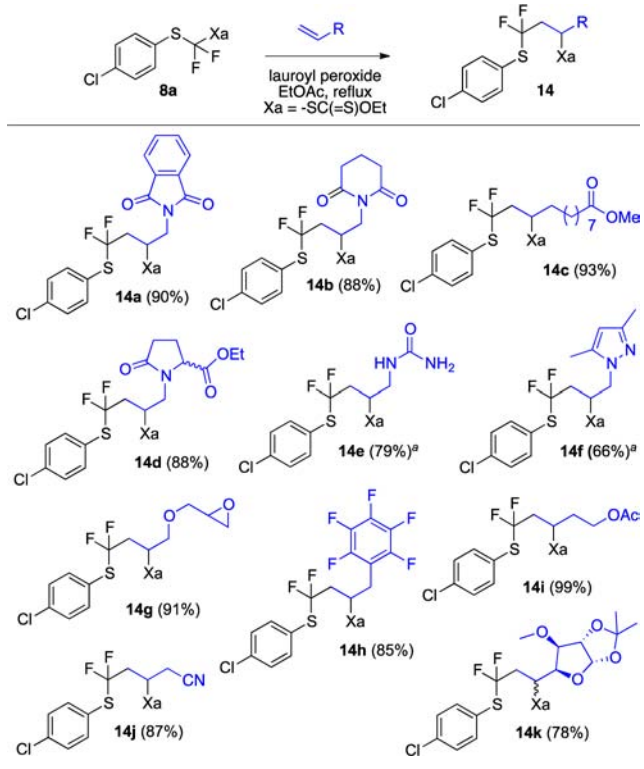
Scheme 2. An Efficient Route to Xanthate 8a



a suspension of potassium *O*-ethyl xanthate in hexane. Subsequent irradiation of the reaction mixture with a 250 W tungsten halogen lamp triggered a radical chain decarbonylation reaction to give xanthate **8a** as a beautifully crystalline solid in excellent overall yield (94%), without isolation of the intermediates (see Supporting Information).[12] This sequence was performed on a 15 g scale without significant loss in efficiency.

With a convenient access to xanthate **8a** in hand, we could explore its addition to alkenes. As indicated by the examples in Scheme 3, this fluorinated xanthate proved to be particularly

Scheme 3. Radical Addition of Xanthate 8a to Alkenes[a]

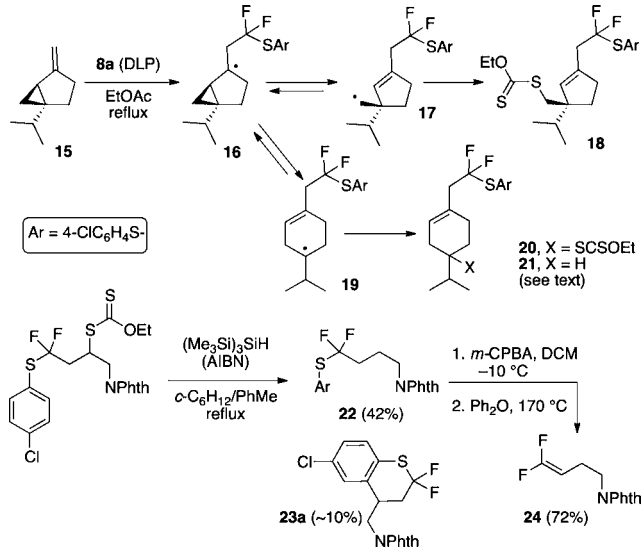


[a]Reaction in the presence of 1.2 equiv of camphorsulfonic acid.

effective, providing a generally high yield of the expected adducts **14**. Numerous groups are tolerated, including epoxide, carbohydrate, urea, and pyrazole. In the case of addition to *N*-allyl urea and to *N*-allyl-2,4-dimethylpyrazole, addition of camphorsulfonic acid (CSA) neutralized the nucleophilic nitrogens and prevented interference by unwanted ionic reactions with the xanthate group.[13] In its absence, the reactions gave complex mixtures. We found it advantageous in most examples to use the xanthate in slight excess (generally 1.5 equiv). The excess xanthate is easily recovered at the end.

The case of addition to (+)-sabinene **15** is interesting. As depicted in Scheme 4, the addition is followed as expected by

Scheme 4. Further Transformations of the Radical Adducts



fragmentation to give the two inseparable isomeric adducts **18** and **20** in a 2:1 ratio and in 80% combined isolated yield. However, reduction of the mixture with the triethylammonium salt of hypophosphorus acid[14] furnished only the dexanthylated derivative **21** in 60% yield. No trace of the product of direct reduction of **18** was observed. Presumably, the slow reducing hypophosphorus salt allows the corresponding carbon radical **17** time to rearrange into the most stable tertiary radical **19** via common intermediate radical **16** before hydrogen atom abstraction actually takes place.[15]

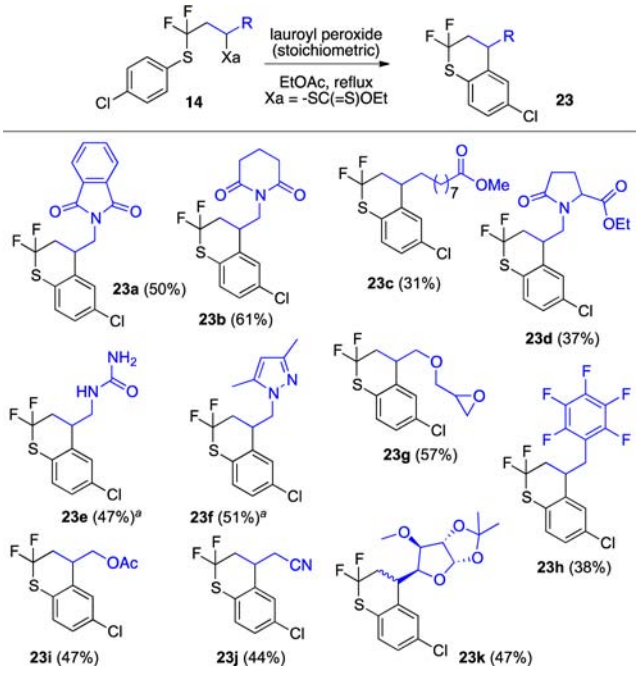
One obvious synthetic modification of the difluorosulfide motif in the adducts is the thermal elimination of the corresponding sulfoxide to introduce an alkene. Indeed, reductive removal of the xanthate group in **14a**, oxidation of the resulting sulfide **22** to the sulfoxide, and thermolysis furnished the expected *N*-(4,4-difluoro-3-butenyl)phthalimide **24**. In line with earlier observations,[10] the elimination of the sulfoxide required a much higher temperature than that for ordinary sulfoxides, but proceeded nevertheless in good yield. What was surprising to us was the relatively low yield of the reduction step. Reductive dexanthylations with tris(trimethylsilyl)silane (TTMSS) are usually nearly quantitative. In the present case, a main side product was formed which turned out to be difluorothiochroman **23** (~10%).

While we have observed (and exploited) the radical closure onto aromatic and heteroaromatic rings,[16] it is very unusual that a normally sluggish radical cyclization[17] would be able to compete with a relatively fast reducing agent such as TTMSS.[18] Indeed, exposure of adduct **14a** to a stoichiometric amount of peroxide in the absence of an added hydrogen atom source furnished difluorothiochroman **23a** in 50% yield. It is interesting that no significant side products resulting from an *ipso* substitution via a radical Smiles rearrangement of the sulfide were observed. Such rearrangements are well-known with arylsulfonamides and can be exploited to accomplish useful aryl transfer reactions.[19]

In the same manner, various other difluorothiochromans were prepared starting with all the adducts **14** collected in Scheme 3. The corresponding difluorothiochromans are displayed in Scheme 5, and not unexpectedly, the same broad tolerance to functional groups is exhibted in this second

dx.doi.org/10.1021/ol5002939 | *Org. Lett.* 2014, 16, 1482–1485

Scheme 5. Synthesis of Difluorothiochromanes[a]

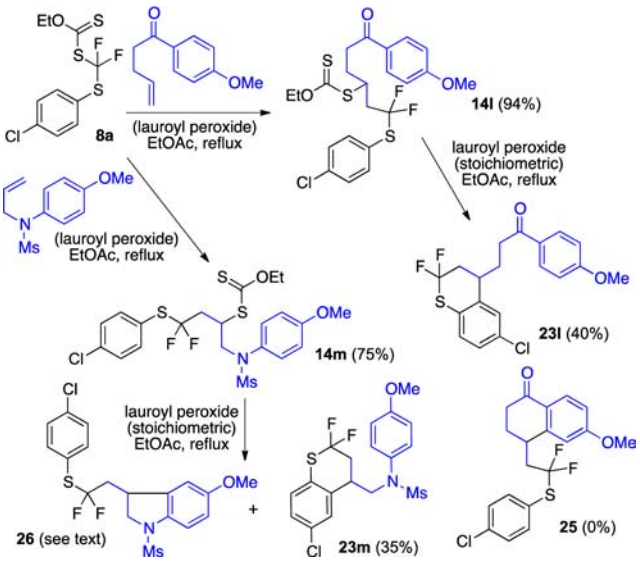


[a]Reaction in the presence of 1.2 equiv of camphorsulfonic acid.

transformation. The moderate yields are in part due to difficulties encountered during purification, especially with nonpolar examples which tended to be contaminated with coproducts derived from lauroyl peroxide.

In order to gauge the relative rate of cyclization onto the aromatic ring, we performed two competition experiments. The first involved examining the behavior of adduct **14l**, obtained in high yield by addition of **8a** to 1-(4-methoxyphenyl)-pent-4-en-1-one (Scheme 6). In this case, the intermediate radical can cyclize on either of the two aromatic rings to give difluorothiochroman **23l** or tetralone **25**.[20] In the event, only the former was obtained, with no trace of tetralone **25** visible in the NMR of the crude reaction mixture.

Scheme 6. Two Competition Experiments



The second competition experiment was carried out on adduct **14m** derived by radical addition of **8a** to *N*-allyl-*N*-methanesulfonyl-4-methoxyaniline. The two competing pathways now are the formation of difluorothiochroman **23m** or indoline **26**.[21] Examination of the crude mixture from the cyclization reaction indicated an 85:15 ratio in favor of the former, which could be isolated in 35% yield. This is a surprising outcome, since cases where the formation of a six-membered ring is favored over a five-membered ring in a radical cyclization are relatively rare.[22] The underlying reasons in the present case are not clear, and a more detailed study is necessary to unravel the factors responsible for this preference.

Difluorothiochromans were hitherto unknown compounds as far as we can tell, in contrast to thiochromans, which are fairly common.[23] Indeed, some members have some importance in medicinal chemistry as indicated by the couple of examples pictured in Figure 2. Tazarotene is a synthetic retinoid useful

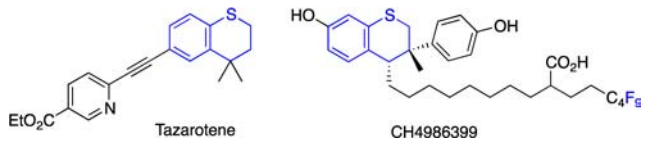


Figure 2. Examples of biologically active thiochromans.

for the topical treatment of acne, psoriasis, and photoaging (Tazorac/Zorac), and an orally effective formulation (Tazorac) has been developed.[24] Thiochroman CH4986399 is a non-steroidal estrogen receptor down-regulator developed by Kamakura Research Laboratories for the treatment of breast cancer.[25] Interestingly, the second compound contains a perfluorobutyl residue capping the long alkyl side chain.

The effect of the two fluorines on the pharmacological profile of biologically active thiochromans would be interesting to examine. The trifluoromethanethiyl group (CF_3S-) has one of the highest Hansch hydrophobicity parameter values (π_R = 1.44)[26] and is often introduced to enhance lipophilicity and other desirable properties in medicinal or agrochemical substances. The cyclic difluorothiyl motif could have a similar effect, in addition to increasing the metabolic stability because the fluorine atoms are now part of the ring structure.

The convergence, flexibilty, experimental simplicity, and tolerance for functional groups of the present approach should open access to a large number of such thiochromans, as well as to simpler structures such as difluorovinyl derivatives (e.g., **24**), which are also of much importance.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zard@poly.polytechnique.fr.

Notes

The authors declare no competing financial interest.

dx.doi.org/10.1021/ol5002939 | *Org. Lett.* 2014, 16, 1482−1485

■ ACKNOWLEDGMENTS

This paper is dedicated with respect to the memory of Professor Harry Wasserman (Yale University). We thank Ecole Polytechnique for a scholarship to P.S.

■ REFERENCES

(1) (a) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* (DOI: 10.1021/cr4002879). (b) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Blackwell: Oxford, 2009. (c) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley: New York, 2008. (d) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.

(2) (a) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679. (b) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Hiyama, T. *Organofluorine Compounds: Chemistry and Applications*; Springer: Berlin, 2000.

(3) (a) Gribble, G. W. Natural Production of Organohalogen Compounds. In *The Handbook of Environmental Chemistry*; Gribble, G. W., Ed.; Springer: Berlin, 2003; Vol. *3P*, pp 1−15. (b) Gribble, G. W. *Chemosphere* **2003**, *52*, 289.

(4) Murphy, C.; Schaffrath, C.; O'Hagan, D. *Chemosphere* **2003**, *52*, 455.

(5) (a) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, 2004. (b) Kirsch, P. *Modern Organofluorine Chemistry*; Blackwell: Oxford, 2004. (c) Uneyama, K. *Organofluorine Chemistry*; Blackwell: Oxford, 2006. (d) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214.

(6) For recent reviews covering sulfinates, see: (a) Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950. (b) Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 5048. (c) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494. For recent work on sulfones, see: (d) Zhu, L.; Li, Y.; Zhao, Y.; Hu, J. *Tetrahedron Lett.* **2010**, *51*, 6150. (e) Ni, C.; Liu, J.; Zhang, L.; Hu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 786.

(7) (a) Betterley, N. M.; Surawatanawong, P.; Prabpai, S.; Kongsaeree, P.; Kuhakarn, C.; Pohmakotr, M.; Reutrakul, V. *Org. Lett.* **2013**, *15*, 5666. (b) Pharikronburee, V.; Punirun, T.; Soorukram, D.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *Org. Biomol. Chem.* **2013**, *11*, 2022. (c) Bootwicha, T.; Panichakul, D.; Kuhakarn, C.; Prabpai, S.; Kongsaeree, P.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *J. Org. Chem.* **2009**, *74*, 3798. (d) Prakash, G.; Hu, J.; Wang, Y.; Olah, G. A. *J. Fluorine Chem.* **2005**, *126*, 527.

(8) For reviews on the xanthate radical transfer reaction, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed.* **1997**, *36*, 672. (b) Quiclet-Sire, B.; Zard, S. Z. *Chem.—Eur. J.* **2006**, *12*, 6002. (c) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (d) Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **2011**, *83*, 519. (e) For an account of the discovery of this process, see: Zard, S. Z. *Aust. J. Chem.* **2006**, *59*, 663.

(9) (a) Bertrand, F.; Pevere, V.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2001**, *3*, 1069. (b) Li, S.; Zard, S. Z. *Org. Lett.* **2013**, *15*, 5898. (c) Denieul, M.-P.; Quiclet-Sire, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1996**, 2511. (d) Gagosz, F.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 2655. (e) Gagosz, F.; Zard, S. Z *Org. Synth.* **2007**, *84*, 32. (f) Tournier, L.; Zard, S. Z. *Tetrahedron Lett.* **2005**, *46*, 455. (g) Jean-Baptiste, L.; Yemets, S.; Legay, R.; Lequeux, T. *J. Org. Chem.* **2006**, *71*, 2352.

(10) (a) Reutrakul, V.; Thongpaisanwong, T.; Tuchinda, P.; Kuhakarn, C.; Pohmakotr, M. *J. Org. Chem.* **2004**, *69*, 6913. (b) Yang, Y.; Fang, X.; Yang, X.; Zhao, M.; Han, Y.; Shen, Y.; Wu, F. *Tetrahedron* **2008**, *64*, 2259.

(11) Yagupol'skii, L. M.; Korin'ko, V. A. *J. Gen. Chem. USSR (Engl. Transl.)* **1967**, *37*, 1717.

(12) This reaction proceeds by way of the corresponding S-acyl xanthate, which undergoes a radical chain decarbonylation. See: (a) Barton, D. H. R.; George, M. V.; Tomoeda, M. *J. Chem. Soc.* **1962**, 1967. (b) Delduc, P.; Tailhan, C.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1988**, 308. See also refs 9a and 9b.

(13) Gagosz, F.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 4345.

(14) (a) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1992**, *33*, 5709. (b) Boivin, J.; Jrad, R.; Jugé, S.; Nguyen, V. T. *Org. Lett.* **2003**, *5*, 1645.

(15) For a related situation, see: Batey, R. A.; Grice, P.; Harling, J. D.; Motherwell, W. B.; Rzepa, H. S. *J. Chem. Soc., Chem. Commun.* **1992**, 942.

(16) For a review, see: El Qacemi, M.; Petit, L.; Quiclet-Sire, B.; Zard, S. Z. *Org. Biomol. Chem.* **2012**, *10*, 5707.

(17) Gansäuer, A.; Seddiqzai, M.; Dahmen, T.; Sure, R.; Grimme, S. *Beilstein J. Org. Chem.* **2013**, *9*, 1620.

(18) Chatgilialoglu, C. *Chem. Rev.* **1995**, *95*, 1229.

(19) For a review on radical Smiles reactions, see: Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649.

(20) For the synthesis of tetralones, see: Liard, A.; Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 1759.

(21) For the synthesis of indolines, see: Ly, T. M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2533.

(22) Liu, Z.; Qin, L.; Zard, S. Z. *Org. Lett.* **2012**, *14*, 5976.

(23) Rare examples of monofluorothiochromans have been described, made by electrophilic fluorination of the parent thiochroman: (a) Dawood, K. M.; Ishii, H.; Fuchigami, T. *J. Org. Chem.* **2001**, *66*, 7030. (b) Zupan, M.; Zajc, B. *J. Chem. Soc., Perkin Trans. 1* **1978**, 965.

(24) Frigoli, S.; Fuganti, C.; Malpezzi, L.; Serra, S. *Org. Process Res. Dev.* **2005**, *9*, 646.

(25) Yoneya, T.; Taniguchi, K.; Nakamura, R.; Tsunenari, T.; Ohizumi, I.; Kanbe, Y.; Morikawa, K.; Shin-Ichi Kaiho, S.-I.; Yamada-Okabe, H. *Anticancer Res.* **2010**, *30*, 873.

(26) (a) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *97*, 165. (b) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207.