

New Radical Allylation Reaction of Iodides

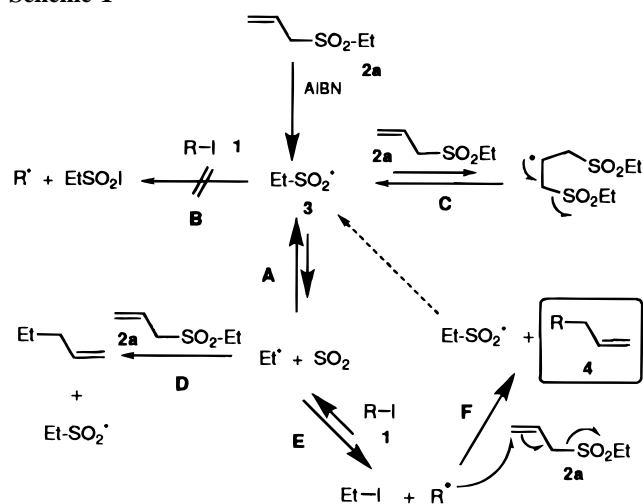
Frédéric Le Guyader,[†] Béatrice Quiclet-Sire,[†]
Stéphanie Seguin,[†] and Samir Z. Zard^{*,†,‡}Institut de Chimie des Substances Naturelles, CNRS
91198 Gif-sur-Yvette, France
Laboratoire de Synthèse Organique associé au CNRS
Ecole Polytechnique, 91128 Palaiseau, France

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Although iodine is very rarely present in natural products,¹ organoiodine compounds are extremely useful intermediates in organic synthesis in general. For instance, iodides are necessary starting materials for a large number of organometallic reagents and reactions.² In other transformations, the introduction of the iodine atom is concomitant with the creation of another bond, as in the powerful iodolactonization reaction and related procedures.³ Organoiodine derivatives are also excellent precursors for a wide variety of radical reactions, especially when used in connection with stannane chemistry. One such process is the replacement of the iodine with an allyl group through a radical reaction involving an allylstannane.^{4,5} Other allylating agents such as allyl sulfides or allyl sulfones can be used in combination with equimolar amounts of hexabutyliditin.^{5,6} This radical allylation is synthetically very useful since a new carbon–carbon bond is created and the allyl group (which may be substituted in the 2-position) can serve as a precursor to a host of other derivatives. The use of tin-based reagents is, however, not always convenient because of the inherent toxicity of organotin derivatives and the difficulty often encountered in removing tin residues from the product.^{4,7} These drawbacks become especially acute in large-scale work or in the preparation of active compounds for biological testing. We now describe a new process which does not involve tin chemistry and which hinges on the use of degenerate reactions as a means of controlling the selectivity.

The process relies on the reaction of an alkyl iodide **1** with an allyl ethyl sulfone **2**; the reaction manifold underlying our working hypothesis is outlined in Scheme 1 (for clarity, un-

Scheme 1



substituted allyl ethyl sulfone **2a** is employed). Thus, in the presence of an initiator such as 2,2'-azobisisobutyronitrile (AIBN), an ethylsulfonyl radical (**3**) may be generated by an addition–fragmentation process. This radical is in equilibrium with sulfur dioxide and an ethyl radical, the equilibrium lying to the top, i.e., toward the more stable sulfonyl radical (step **A**).⁸ However, even though equilibrium **A** is unfavorable, the system can only evolve if the ethyl radical exchanges iodine with iodide **1** as in **E**, since sulfonyl radicals do not abstract iodides from alkyl iodides (path **B**)⁹ and, in this case, the reaction of ethylsulfonyl radicals with the starting allylsulfone **2a** is degenerate (path **C**). The iodine exchange (path **E**) is fast and reversible,¹⁰ but in most cases involving aliphatic or alicyclic substrates, the equilibrium will be tilted in the desired direction since an ethyl radical is an unstabilized primary radical.¹¹ Radical **R•** produced in this step now adds irreversibly to allyl sulfone **2a** (step **F**); its reaction with starting iodide **1** (i.e., **R•** + **R-I**), even though fast, is degenerate and therefore does not compete. In step **F**, an ethylsulfonyl radical is liberated to propagate the chain. In fact, the main irreversible and potentially competing side reaction is the addition of ethyl radicals to allyl sulfone **2a** (path **D**), but this is much slower than iodine atom transfer. If these considerations are valid, then upon initiation an alkyl iodide **1** should react with ethyl allyl sulfone **2a** to give an allyl derivative **4**, along with sulfur dioxide and ethyl iodide (both volatile) as co-products.¹² This productive pathway is indicated by the heavier arrows in Scheme 1.

Indeed, when a refluxing solution of iodolactone **1a** and allyl ethyl sulfone **2a** (3 equiv) in heptane was treated portionwise

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(8) (a) Chatgililoglu, C. In *The Chemistry of Sulfoxides and Sulfonamides*; Patai, S.; Rappoport, Z.; Stirling, C. J. M., Eds.; Wiley: Chichester, 1988; pp 1089–1113. (b) Bertrand, M. *Org. Prep. Proc. Int.* **1994**, *26*, 257–290.

(9) The reverse process, i.e., abstraction of iodine from a sulfonyl iodide, is very efficient: (a) Serra, A. C.; da Silva Corrêa, C. M. M.; Vieira, M. A. M. S. A.; Gomes, M. A. *Tetrahedron* **1990**, *46*, 3061–3070. (b) Serra, A. C.; da Silva Corrêa, C. M. M.; do Vale, M. L. C. *Tetrahedron* **1991**, *47*, 9463–9488 and references cited therein.

(10) The rate for iodine exchange has been measured for some systems and found to be in the range of 10^7 – 10^8 M⁻¹s⁻¹, see: Curran, D. P.; Bosch, E.; Kaplan, J.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 1826–1831.

(11) Methyl radicals, generated stoichiometrically by iron-catalyzed decomposition of hydrogen peroxide in dimethyl sulfoxide, have been used to generate alkyl radicals from iodides, see: Fontana, F.; Minisci, F.; Vismara, E. *Tetrahedron Lett.* **1988**, *29*, 1975–1978.

[†] Institut de Chimie des Substances Naturelles.[‡] Laboratoire de Synthèse Organique associé au CNRS.(1) Gribble, G. W. *Prog. Chem. Org. Nat. Prod.* **1996**, *68*, 1–423.(2) Chambers, R. D.; James, S. R. In *Comprehensive Organic Chemistry*; Barton, D. H. R., Ollis, W. D., Eds; Pergamon Press: Oxford, 1979; Vol. 1, pp 493–575.(3) (a) Knapp, S. in *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI Press Inc.: Greenwich, CT, 1996, pp 57–98. (b) Harding, K. E.; Tiner, T. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 1.9, pp 363–421. (c) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321–3408. (d) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, 171–197.(4) (a) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987. (b) Neumann, W. P. *Synthesis* **1987**, 665. (c) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 715–831. (d) Curran, D. P. *Synthesis* **1988**, 417; 489. (e) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1991.(5) (a) Servens, C.; Pereyre, M. *J. Organomet. Chem.* **1971**, *26*, C4–C6. (b) Grignon, J.; Pereyre, M. *J. Organomet. Chem.* **1973**, *61*, C33–C35. (c) Grignon, J.; Servens, C.; Pereyre, M. *J. Organomet. Chem.* **1975**, *96*, 225–235. (d) Kosugi, M.; Kurino, K.; Takayama, K.; Migita, T. *J. Organomet. Chem.* **1973**, *56*, C11–C13. (e) Keck, G. E.; Yates, J. B. *J. Org. Chem.* **1982**, *47*, 3590–3591. (f) Keck, G. E.; Enholm, E. J. *Tetrahedron Lett.* **1985**, *26*, 3311–3314. (g) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079–4094. (h) Keck, G. E.; Byers, J. H. *J. Org. Chem.* **1985**, *50*, 5442–5444. (i) Baldwin, J. E.; Adlington, R. M.; Lowe, C.; O'Neil, I. A.; Sanders, G. L.; Schofield, C. J.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1988**, 1030–1031. (j) Baldwin, J. E.; Adlington, R. M.; Birch, D. J.; Crawford, J. A.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1986**, 1339–1340. (k) Baldwin, J. E.; Adlington, R. M.; Basak, A. *J. Chem. Soc., Chem. Commun.* **1984**, 1284–1285. (l) Hanessian, S.; Alpegianni, M. *Tetrahedron* **1989**, *45*, 941–950. (m) Russell, G. A.; Herold, L. L. *J. Org. Chem.* **1985**, *50*, 1037–1040. (n) Mizuno, K.; Ikeda, M.; Toda, S.; Otsuji, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1288–1290. (o) Boivin, J.; Camara, J.; Zard, S. Z. *J. Am. Chem. Soc.* **1992**, *114*, 7909–7910.

with AIBN (0.12 equiv), a smooth reaction occurred to give the expected allyl derivative **4a** in 75% yield as an 85:15 mixture of the *exo* and *endo* epimers. Under similar conditions, a number of other iodides were easily allylated. When the starting iodide was not very soluble in heptane, a mixture of heptane/chlorobenzene was used.¹³ The results are collected in Table 1. As with radical reactions in general, a wide variety of functional groups are tolerated, and the stereochemistry of the end product is governed by steric factors inherent in the intermediate carbon radical. For example, whereas tricyclic iodolactone **1e** gave only one isomer of the corresponding allyl derivative **4e**, the carbohydrate iodide **1f**, prepared from methyl 2,3-dibenzoyl- α -L-arabinopyranoside through the Garregg iodination procedure,¹⁴ produced **4f** as a 1:1 mixture of epimers.¹⁵

Primary, secondary, and tertiary iodides could be used in the process, even though, for primary iodides, the yield was lower than average and a larger amount of AIBN (0.6 equiv) had to be used, reflecting perhaps the less favorable equilibrium depicted in step **E**. The allyl group can be substituted in the 2-position, leading to substituted allyl derivatives. This is exemplified by the conversion of iodide **1c** into the corresponding 2-chloroallyl epimers **4c'** by use of **2b** instead of **2a**, and iodide **1e** into methallyl derivative **4e'** by employment of **2c**.

By designing the present system such that most of the side reactions are redundant, we have succeeded in developing a new and general method for performing the radical allylation of aliphatic and alicyclic iodides that does not suffer from the drawbacks associated with tin (or other heavy metal)-based reagents. Yields are generally good and the purification is much simpler: many of the co-products are volatile (EtI, SO₂), and it is possible to remove excess allylating reagent by heating the mixture to 50–60 °C while passing a stream of nitrogen or dry air for a few hours. It is perhaps worth emphasizing the fact that the various allyl ethyl sulfones are cheap, easily stored, and trivial to make.¹⁶ Moreover, it is almost certain that many other substituents can be placed on the allyl group and that groups other than allyl could be transferred¹⁷ by analogy with the more extensively studied organotin derivatives.

(12) Alkyl allyl sulfone can be made to extrude sulfur dioxide under certain conditions to give allylated derivatives: (a) Quiclet-Sire, B.; Zard, S. Z. *J. Am. Chem. Soc.* **1996**, *118*, 1209–1210. For other radical reactions involving allyl sulfones, see: (b) Phillips, E. D.; Whitham, G. H. *Tetrahedron Lett.* **1993**, *34*, 2537–2540; 2541–2544. (c) Smith, T. A. K.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 313–317; 319–325. (d) Knight, D. J.; Lin, P.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2707–2713. (e) Padwa, A.; Kline, D. N.; Murphree, S. S.; Yeske, P. E. *J. Org. Chem.* **1992**, *57*, 298–306. (f) Padwa, A.; Bullock, W. H.; Dyszlewski, A. D. *Tetrahedron Lett.* **1987**, *28*, 3193–3196; *J. Org. Chem.* **1990**, *55*, 955–964. (g) Padwa, A.; Bullock, W. H.; Dyszlewski, A. D.; McCombie, S. W.; Shankar, B. B.; Ganguly, A. K. *J. Org. Chem.* **1991**, *56*, 3556–3564. (h) Barre, V.; Uguen, D. *Tetrahedron Lett.* **1987**, *28*, 6045–6048. (i) Baechler, R. D.; Bentley, P.; Deuring, L.; Fisk, S. *Tetrahedron Lett.* **1982**, *23*, 2269–2272. (j) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, 3609–3610.

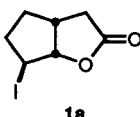
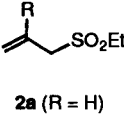
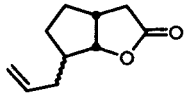
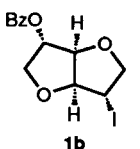
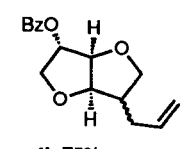
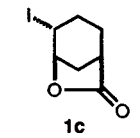
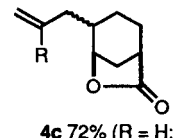
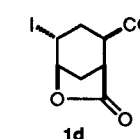
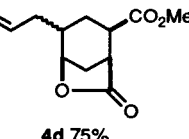
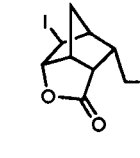
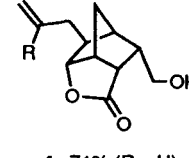
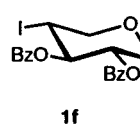
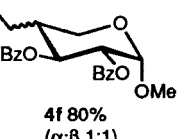
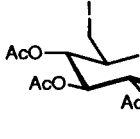
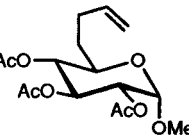
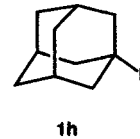
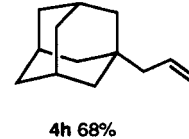
(13) A typical experimental procedure is as follows: A solution of iodide **1a–h** (1 mmol) and allyl ethyl sulfone **2a–c** (3 mmol) in degassed heptane (4 mL) or a 1:1 mixture of heptane and chlorobenzene (4 mL) was heated under reflux in the presence of AIBN (0.1 to 0.2 mmol), added portionwise over the course of the reaction which took 10–25 h as indicated by TLC monitoring. The solvents were evaporated under reduced pressure, and the residue was chromatographed on a silica gel column to afford the desired allyl derivatives **4a–h**. In some cases, the purification was greatly simplified by heating the crude residue in an oil bath at 50–60 °C under a stream of dry air (or nitrogen) for a few hours to remove excess allyl ethyl sulfone.

(14) (a) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866–2869. (b) Garegg, P. J.; Johansson, R.; Ortega, C.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 681–683.

(15) The relative stereochemistry, where applicable, was assigned by NMR and especially by comparison of the spectra with those of the starting iodides, whose stereochemistry is defined by the iodolactonization reaction. For **4a** and **4c**, the diastereomers could not be separated by preparative chromatography, in contrast to **4b**, **4c'**, and **4d**. In all cases, the diastereomeric ratio was confirmed by GC/MS. See the Supporting Information for details.

(16) Reagents **2a–c** are made by substituting the corresponding allyl bromide or chloride with ethanethiol followed by oxidation to the sulfone: (a) Svata, V.; Prochazka, M.; Bakos, V. *Coll. Czech. Chem. Commun.* **1978**, *43*, 2619–2634. (b) Böhme, H.; Bentler, H. *Chem. Ber.* **1956**, *89*, 1464–1468.

Table 1. Radical Allylation of Iodides

Iodide 1	Allyl sulfone 2	Product 4
	 2a (R = H)	 4a 75% (<i>exo:endo</i> 85:15)
	2a (R = H)	 4b 75% (<i>exo:endo</i> 10:1)
	2a (R = H) 2b (R = Cl)	 4c 72% (R = H; <i>exo:endo</i> 6:4) 4c' 64% (R = Cl; <i>exo:endo</i> 4.5:1)
	2a (R = H)	 4d 75% (<i>exo:endo</i> 5:1)
	2a (R = H) 2c (R = Me)	 4e 71% (R = H) 4e' 77% (R = Me)
	2a (R = H)	 4f 80% ($\alpha:\beta$ 1:1)
	2a (R = H)	 4g 50% (70% based on recovered 1g)
	2a (R = H)	 4h 68%

Acknowledgment. We thank Rhône-Poulenc for generous financial support.

Supporting Information Available: Experimental procedures for the preparation and allylation of the iodides, as well as a compilation of spectral and analytical data of all new compounds (8 pages). See any current masthead page for ordering and Internet access instructions.

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(17) See, for example: Kim, S.; Lee, I. Y.; Yoon, J.-Y.; Oh, D. H. *J. Am. Chem. Soc.* **1996**, *118*, 5138–5139.