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[14] Due to hindered rotation, the (*S*,*R*)-diastereomer is unsymmetrical and gives twin peaks of equal height. (*S*,*R*)-diastereomer of **3a**: ^{13}C NMR ($CDCl_3$) δ = 23.9, 25.6, 32.3, 58.9, 59.0, 59.4, 59.9, 73.8, 74.2, 79.5, 81.7, 119.9, 124.9, 125.0, 125.1, 125.2, 126.7, 131.5, 131.8, 142.8, 151.3, 175.2, 175.3.

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[16] Empirical formula $C_{56}H_{64}N_2O_6Si_2$: M_r = 917.27, C_2 (no. 5), a = 18.828(5), b = 10.4438(16), c = 13.293(4) Å, β = 100.26(2)°, V = 2572.0(10) Å^3, Z = 2, ρ_{calcd} = 1.184 g cm^{-3}, $\lambda Mo_{K\alpha}$ = 0.71073 Å, μ = 0.120 mm^{-1}, $F(000)$ = 284, T = 293(2) K, $R1$ = 0.0458, $wR2$ = 0.1309, absolute structure parameter = 0.07(16). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-137887. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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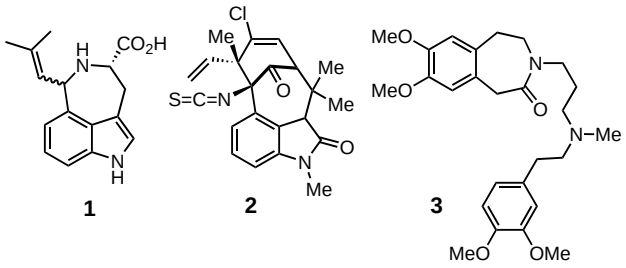
[19] In order to compare the relative diastereoselectivities a coupling reaction was carried out with the similar chiral auxiliary (*S*)-*N*-pyruvoyl-2-(*tert*-butyldiphenylsilyloxy)proline under the same reaction conditions to give low diastereoselectivity (*S*,*S*:*R*,*R*:*S*,*R* = 73:16:10).

An Expedient Construction of Seven-Membered Rings Adjoining Aromatic Systems**

Talbi Kaoudi, Béatrice Quiclet-Sire, Stéphanie Seguin, and Samir Z. Zard*

Dedicated to Professor Pierre Potier on the occasion of his 65th birthday

In contrast to the closure of five- and six-membered rings, the direct formation of a seven-membered ring by radical addition to an olefin is a relatively uncommon transformation.[1, 2] Examples of the even more difficult corresponding cyclization onto an aromatic ring are very rare.[3] Yet, seven-membered rings adjoining aromatic systems can be found in a variety of biologically active compounds, for example, clavicipitic acid (**1**), a metabolite related to lysergic acid,[4] the more complex, recently isolated welwitindolinones (e.g. *N*-methylwelwitindolinone C isothiocyanate (**2**)),[5] and the benzazepine family of drugs[6] such as Zatebradine (**3**), an antianginal and one of a new group of specific bradycardic agents.[6c,d]



1 **2** **3**

Construction of such seven-membered rings has relied almost exclusively on ionic chemistry.[7] Methods based on radicals have been very rarely applied, mainly because the desired cyclization is too slow to compete with other pathways open to the radical intermediate. Premature reduction, for example, is what is usually observed when organotin hydride based procedures are applied.[1, 2, 8] Indeed, the very few examples involving stannanes are generally low yielding and concern invariably pyrrole- or imidazole-type heteroaromatic structures activated by electron-withdrawing groups.[3a–d] Compounds with seven-membered (and even larger) rings fused to an aromatic nucleus have been obtained in modest yield by photolysis of suitable chloroamides.[3e–j] The mechanism here is not clear; formation of exciplexes and electron

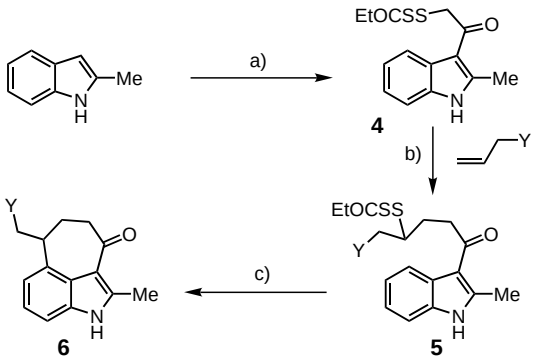
[*] Dr. S. Z. Zard,[+] T. Kaoudi, Dr. B. Quiclet-Sire, S. Seguin
Institut de Chimie des Substances Naturelles
91198 Gif-Sur-Yvette (France)
Fax: (+33) 1-69-07-72-47
E-mail: sam.zard@icsn.cnrs-gif.fr
[+] Additional Address:
Laboratoire de Synthèse Organique associé au CNRS
Ecole Polytechnique, 91128 Palaiseau Cedex (France)
Fax: (+33) 1-69-33-30-10

[**] We wish to thank the Ligue Contre le Cancer for generous financial support for S.S. and Michel Levart for recording numerous GC mass spectra.

transfers have been invoked but free radicals may also be involved.[3f,g] The other instances of the annelation of seven-membered rings to aromatic systems all start by the generation of the radical on the aromatic ring, thereby avoiding the extra activation energy arising from the temporary destruction of aromaticity.[2]

We have shown that radicals generated from xanthates through either a chain or nonchain process, under tin-free conditions, have a comparatively long effective lifetime and can add to unactivated olefinic traps.[9] In particular, we could annelate five- or six-membered rings to an aromatic nucleus, providing access to a number of useful structures such as oxindoles, indolines, indanes, and tetralones.[10] We have now found that the much more difficult formation of seven-membered rings is also feasible through this approach.

Heating a solution of the readily accessible xanthate **4** and allyl acetate (5 equiv) in 1,2-dichloroethane/chlorobenzene (1/1) at reflux in the presence of a small amount of the radical initiator lauroyl peroxide gave the expected adduct **5a** in 77% yield (Scheme 1). When a stoichiometric amount of lauroyl

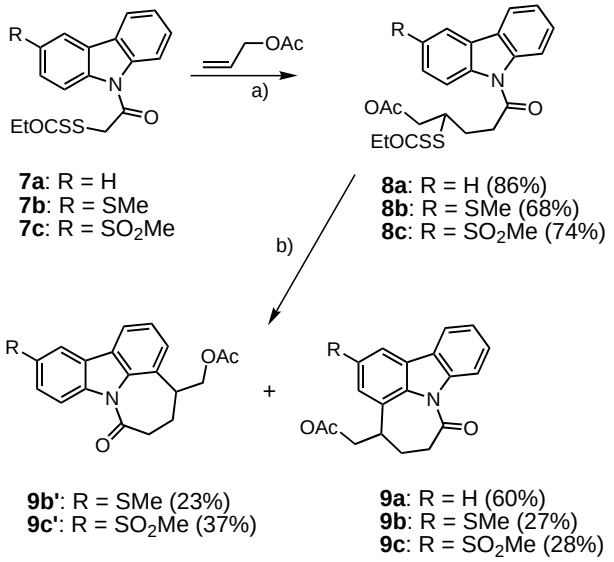


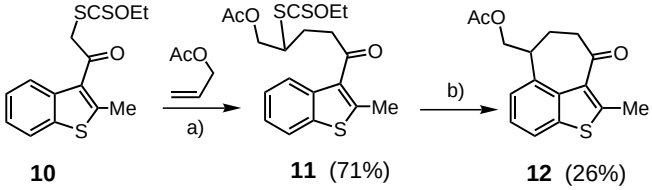
Y = OAc: **5a** (77%), **6a** (54%); Y = Phth: **5b** (88%), **6b** (47%); Y = CN **5c** (66%), **6c** (48%); Y = $(CH_2)_8OAc$: **5d** (88%), **6d** (32%); Y = CH_2CO_2Et: **5e** (76%), **6e** (35%)

Scheme 1. Xanthate-mediated radical annelation of a seven-membered ring to 2-methylindole. a) $ClCH_2COCl$, $AlCl_3$, CH_2Cl_2; EtOCSSK, acetone; b) lauroyl peroxide (0.1–0.2 equiv), $ClCH_2CH_2Cl$/PhCl (1/1), reflux; c) lauroyl peroxide (1.25 equiv), chlorobenzene, reflux. Phth = phthalimido.

peroxide was added in portions (over 1–2 h) to a boiling solution of **5a** in chlorobenzene, annelation to position 4 of the indole ring took place to furnish **6a** in 54% yield along with a small amount (18%) of a reduced side product (in which the xanthate group in **5a** is replaced with a hydrogen). The same sequence was applied with other olefins to give the tricyclic derivatives **6b**–**e** in comparable overall yields.

The seven-membered ring may be fused at the nitrogen atom in these heteroarenes. This is illustrated by the synthesis of **9a** (60%), **9b** (27%) and **9b′**(23%), and **9c** (28%) and **9c′**(37%) from precursors **8a**–**c**, respectively, which were efficiently obtained by addition of the appropriate xanthates **7a**–**c** to allyl acetate (Scheme 2). The combined yield of the two isomeric products in the case of **9b**,**b′** and **9c**,**c′** is acceptable, but there is essentially no regioselectivity. The sulfide and sulfone groups are in a *meta* disposition with respect to site of cyclization and therefore have little influence





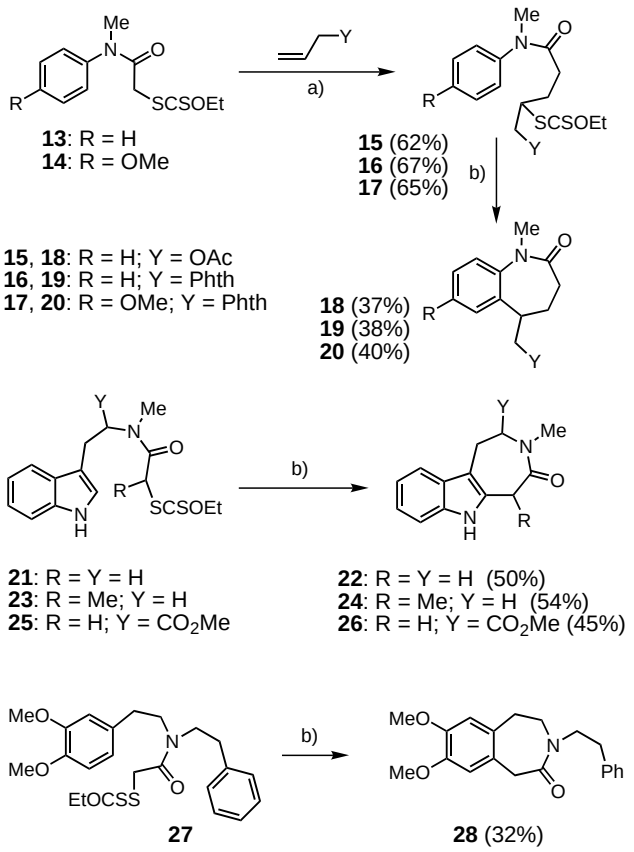
Scheme 2. Examples of xanthate-mediated annelations of seven-membered rings. a) Lauroyl peroxide (0.1–0.2 equiv), $ClCH_2CH_2Cl$, reflux; b) lauroyl peroxide (1.1–1.3 equiv), chlorobenzene, reflux.

on the reactivity of this site. In the last example in Scheme 2 (conversion **11** → **12**, 26%) the indole moiety was replaced by a benzothiophene ring.

Even simple anilines can be used as the starting substrates, as demonstrated by the examples collected in the top part of Scheme 3. Thus, xanthates **13** and **14** were transformed into benzazepinones **18**, **19**, and **20** with yields of 37, 38, and 40%, respectively, for the cyclization step. We had found in the past that treatment of xanthates **13** and **14** with a peroxide, in the absence of the external olefin, results in the formation of the corresponding oxindoles.[10a] Clearly, fusion of the five-membered ring to the aromatic nucleus is slower than intermolecular addition to an unactivated olefin. The fact that even a seven-membered ring can be made to close is indeed quite remarkable.

Somewhat simpler structures were obtained by starting from xanthate precursors derived from 2-arylethylamines by standard ionic chemistry (examples **22**, **24**, **26**, and **28** in Scheme 3). Cyclization of the tryptophan derivative **25** to give **26** (45%) is especially noteworthy. The influence of the substituents on the regiochemistry is highlighted by the last transformation (**27** → **28**), in which cyclization occurs preferentially on the more electron-rich aromatic nucleus. The initial radical derived from xanthate **27** is adjacent to the carbonyl group of the amide and therefore moderately electrophilic. Compound **28** is a close analogue of the antianginal drug **3**.

  0570-0833/00/3904-0732 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **2000**, *39*, No. 4



Scheme 3. Further examples of xanthate-mediated annelations of seven-membered rings. a) Lauroyl peroxide (0.2 equiv), $ClCH_2CH_2Cl$, reflux; b) lauroyl peroxide (1.2 equiv), $ClCH_2CH_2Cl$, reflux.

In this preliminary account, we have described a new, flexible, and convergent route to a variety of complex aromatic structures containing an adjoining seven-membered ring. No heavy or toxic metals are involved, and the starting materials are cheap and readily available. The generally modest (but unoptimized) yields must be considered in view of the fact that both the inter- and intramolecular radical additions in this sequence are difficult transformations beyond the reach of most other radical methods.

Experimental Section

Typical procedures:

Intermolecular radical addition: A solution of the xanthate (1 mmol) and olefin (3–5 mmol) in degassed 1,2-dichloroethane (1.2 mL; in the case of xanthate **4**, a 1:1 mixture of 1,2-dichloroethane and chlorobenzene was used for solubility reasons) was heated at reflux, and lauroyl peroxide (0.1–0.2 mmol) was added in portions. The reaction was monitored by TLC. The solvent was removed under reduced pressure and the crude residue purified by chromatography on a silica gel column to furnish the desired adducts.

Cyclization reactions: Procedure A: To a refluxing solution of the xanthate adduct (1 mmol) in degassed chlorobenzene (4.4 mL) was added dropwise a chlorobenzene solution of lauroyl peroxide (1.25 mmol in 11 mL) over 1–2 h. The solvent was removed under reduced pressure and the crude residue purified by chromatography on a silica gel column eluting with ethyl acetate/heptane mixtures.

Procedure B: Solid lauroyl peroxide was added portionwise every 1.5 h (0.1 mmol portions for a total of 1.2 mmol) to a solution of the xanthate adduct (1 mmol) in degassed 1,2-dichloroethane (5 mL) heated at reflux. The solvent was removed under reduced pressure and the crude residue purified by chromatography on a silica gel column eluting with ethyl acetate/heptane mixtures.

Received: August 2, 1999 [Z13817]

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