Pergamon

Tetrahedron Letters, Vol. 35, No. 46, pp. 8573-8576, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01898-7

A NEW CYCLOPENTENONE ANNULATION METHOD

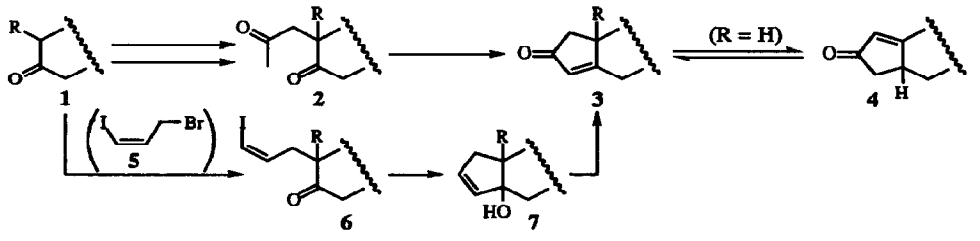
Edward Piers,* Katherine L. Cook, and Christine Rogers

Department of Chemistry, University of British Columbia
2036 Main Mall, Vancouver, British Columbia, Canada V6T 1Z1

Abstract: *Alkylation of the substrates **8-12** with (Z)-3-bromo-1-iodopropene (**5**), followed by n-BuLi-mediated cyclization of the resultant products **15-19**, provides the tertiary allylic alcohols **22-26**, which, upon oxidation with a Cr(VI) reagent, afford the cyclopentenones **29-33**. The α-methylcyclopentenones **34** and **35** are similarly derived from the keto esters **13** and **14**.*

Functionalized five-membered carbocycles are common structural features of many novel, biologically active compounds derived from living systems. It is not surprising, therefore, that the construction of substituted cyclopentanoid systems continues to be of wide interest to researchers involved in developing new methods and reagents for organic synthesis. Indeed, over the past couple of decades, an impressive number of effective protocols for the synthesis of cyclopentanoids has been developed[1-11] and many of these have proven to be of value in work directed toward the total synthesis of natural products.[2, 3b-7, 8b, 9]

Annulations represented in general terms by the conversion of **1** into **3** have played an important role in the synthesis of five-membered carbocycles.[8, 9, 11] However, the second step of this method, involving base-promoted intramolecular condensation-dehydration of diketones of general structure **2**, is often problematic. This is particularly true if the ring carbonyl group in **2** is in a sterically encumbered environment. Under these circumstances, the equilibrium between **2** and the corresponding ketol intermediate (the precursor of **3**) usually favors **2** and, therefore, "forcing" conditions are required to effect the overall conversion of **2** into **3**. Unfortunately, these conditions often cause the initially formed products **3** (R = H) to undergo at least partial base-catalyzed isomerization to the isomeric substances **4**. We report in this Letter a new cyclopentenone



annulation method that involves the following operations: alkylation of ketones (or suitable derivatives thereof) with (*Z*)-3-bromo-1-iodopropene (**5**),[12] *n*-BuLi-mediated ring closure of the resultant products **6** to give the tertiary allylic alcohols **7**, and oxidative conversion of **7** into the corresponding enones **3** by use of a Cr(VI) reagent. The second transformation of this method (conversion of **6** into **7**) is carried out under very mild conditions and, importantly, is a kinetically controlled process. Furthermore, under the conditions employed for the transformation of **7** into **3**, isomerization of the latter substances (R = H) into **4** does not occur.

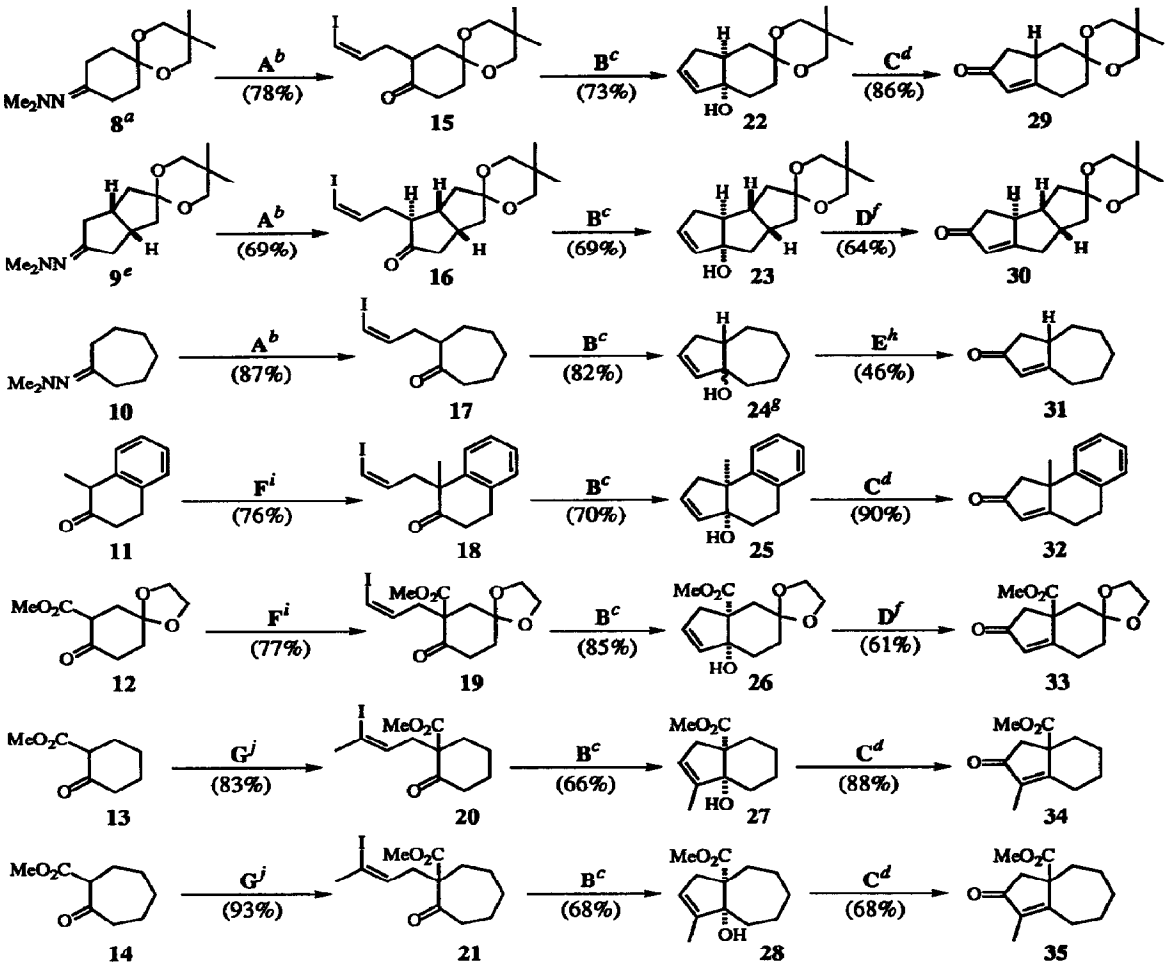
Representative examples of the new annulation protocol are given in **Scheme 1**. Alkylation[14] of the dimethylhydrazones **8-10** with (*Z*)-3-bromo-1-iodopropene (**5**)[12] provided, efficiently, the corresponding monoalkylated products. Although hydrolysis of the dimethylhydrazone function of the latter materials was attempted via a number of known methods,[14] the use of buffered aqueous acetic acid in THF[15] proved to be the most satisfactory and produced the keto iodides **15-17** in very good to excellent yields. Direct alkylation of substrates **11** and **12** with **5** provided **18** and **19**, while similar transformations involving the reaction of keto esters **13** and **14** with (*Z*)-1-bromo-3-iodo-2-butene (**36**)[16] gave substances **20** and **21**.

Ring closure of the iodo ketones **15-21** to the corresponding tertiary alcohols **22-28** could be carried out efficiently by treatment of each of the former substances with *n*-BuLi in THF at low temperature.[17] For substrates **15-18** it was convenient to use 2.2-2.5 equivalents of *n*-BuLi. In these cases, it is apparent that the lithium-iodine exchange process and the cyclization step are both rapid and the possible competing intermolecular addition of *n*-BuLi to the carbonyl group is not observed to any appreciable extent. In the reactions involving the keto esters **19-21**, however, the amount of *n*-BuLi employed proved to be of importance. If too much (e.g. 2.5 equivalents) of the reagent was used, the desired product was accompanied by compounds derived from reaction of *n*-BuLi with the ester function. On the other hand, use of the quantities indicated in **Scheme 1** resulted in conversion of the substrates **19-21** into the required products **26-28** in good yields.

Each of the cyclization products **22**, **23**, and **25-28** consisted of a single isomer. That each of these substances possesses the expected *cis*-fused configuration was shown by a variety of ^{1}H NMR spectroscopic experiments.[18] The only cyclization process that produced a mixture of diastereomers involved the transformation of **17** into **24**.

The final step of each of the cyclopentenone annulation sequences entails oxidative rearrangement[19] of the requisite tertiary allylic alcohol with pyridinium chlorochromate (PCC).[20] The use of PCC on alumina[21] is particularly effective (substrates **22**, **25**, **27**, **28**), although PCC in the presence of Celite[22] (substrates **23**, **26**) and the more traditional PCC-NaOAc[20] can also be employed. The yields of the annulation products **29-35** are good to excellent and, significantly, the substances **29** and **30** showed no tendancy to rearrange to the isomeric cyclopentenones under the reaction conditions.

In summary, a new, synthetically useful cyclopentenone annulation method has been developed. Experimentally, the individual reactions involved are relatively straightforward and the overall yields are very



Scheme 1. [a] Ref. 13. [b] **A:** LDA, THF, 0°C; (*Z*)-3-bromo-1-iodopropene (**5**), r. t.; HOAc, NaOAc, THF, H_2O, r. t. [c] **B:** Commercial *n*-BuLi in hexanes [substrate (equiv of *n*-BuLi): **15** (2.2), **16** (2.5), **17** (2.5), **18** (2.2), **19** (1.6), **20** (1.2), **21** (1.9)], THF, -78°C, 20 min to 1 h; $NaHCO_3$, H_2O. [d] **C:** PCC (2.2-3 equiv) on alumina, CH_2Cl_2, r. t. [e] For the keto ketal corresponding to **9**, see Piers, E.; Karunaratne, V. *Can. J. Chem.* **1989**, *67*, 160-164. [f] **D:** PCC (2.5 equiv), Celite, CH_2Cl_2, r. t. [g] This material consists of a 2 : 1 mixture of diastereomers (analysis by ^1H NMR spectroscopy). [h] **E:** PCC (2.5 equiv), NaOAc (4 equiv), CH_2Cl_2, r. t. [i] **F:** NaH, 1,2-dimethoxyethane (DME), r. t.; (*Z*)-3-bromo-1-iodopropene (**5**), r. t. [j] **G:** NaH, DME, 40°C (substrate **13**) or r. t. (substrate **14**); (*Z*)-1-bromo-3-iodo-2-butene (**36**), r. t.

good. The presence of acid-sensitive ketal groups or electrophilic alkoxycarbonyl functions is not detrimental to the success of the method. It is also pertinent to mention that this new annulation protocol has played an important role in the total synthesis of the tetraquinane diterpenoid (±)-crinipellin B.[23]

Acknowledgements. We are grateful to NSERC of Canada for financial support, for a Postgraduate Scholarship (to K. L. C.), and for a Postdoctoral Fellowship (to C. R.).

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(*Received in USA* 18 *July* 1994; *revised* 16 *September* 1994; *accepted* 21 *September* 1994)