Synthesis of cyclopentanoids—a never ending challenge

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Abstract: A novel four-step sequence has been developed for the direct conversion of acyclic and cyclic ketones to vicinally substituted cyclopentanones and spiro cyclopentanones respectively for entry into a wide range of cyclopentanoids. The key step involves a pinacol type rearrangement of alkoxy cyclobutane derivatives involving migration of the stereoelectronically disfavored cyclobutane bond.

A diverse range of cyclopentanoids bear cyclopentane rings of the general structure 1 having substituents on two or three contiguous centres as exemplified by the terpenoids 2-7 (1-5). The synthesis of cyclopentanoids remains a never ending formidable task (6) due to lack of availability of a general method for constructing appropriately substituted cyclopentane rings (7). Our preliminary work on the development and application of a novel strategy that allows synthesis of both substituted cyclopentanones and spiro cyclopentanones from acyclic and cyclic ketones respectively are presented here.

The strategy is illustrated by transformation (8) of diethyl ketone 8a to the substituted cyclopentanone 12a (Scheme-1). Reaction of diethyl ketone 8a with ethoxyvinyllithium afforded the carbinol 9a. The carbinol 9a was then converted to the diene 10a. Photoirradiation of the diene 10a in presence of CuOTf as catalyst afforded in very good yield the cyclobutane derivative 11a. Treatment of the adduct 11a with TfOH effected smooth rearrangement of the cyclobutane ring to produce the cyclopentanone derivative 12a arising by migration of the C1-C5 bond. Using this sequence
acetone 8b was transformed (9) to the known cyclopentanone derivative 12b, an advanced intermediate in the synthesis (10) of planococcyl acetate, the pheromone of citrus mealy bug. The four-step synthesis of the cyclopentanone derivative 12b compared to its reported eleven-step synthesis demonstrates the efficiency of the present synthetic protocol.

Scheme 1: Reagents and Conditions: i, BuLi, ethyl vinyl ether, THF, -70°C to rt; ii, NaH-THF, allyl bromide, HMPA, reflux; iii, hv, EtO, CuOTf; iv, TfOH, CH2Cl2, -78°C to rt; v, Jones reagent, acetone, 0°C to rt then CH2N2.

In case of unsymmetrical ketones, the size of the substituents had profound influence on the stereochemical outcome of the cycloaddition (11). This was reflected in the gradual increase in the ratio (3.8 to 5 to 19 to >99) of the photoadducts 11c-g and 14c-g with increasing size of the group from Et to CH2CH2Ph to CH2Ph to 4-methyl cyclohexyl. Rearrangement of the cyclobutanes 11c-g and 14c-g was found to be totally stereospecific to produce respectively the cyclopentanone derivatives 12c-g and 15c-g. The noteworthy feature in this strategy is the easy stereoselective synthesis of the otherwise difficultly accessible cyclopentanone derivatives 12f and 12g, the carbon skeleton of cuprenolide and trichodiene. However, this route failed to convert aldehydes eg. 8h to the cyclopentanone 12h as the photoadduct 11h was totally resistant to acids.

This protocol was found to be extremely efficient for stereoselective synthesis of cyclopentanones with three contiguous substituents (Scheme-2). The dienes 17a and 17b prepared from the carbinal 9b, afforded the photoadducts 18a and 18b along with their other diastereoisomers in 3:1 and 4:1 ratios respectively. Rearrangement of the photoadduct mixture obtained from 17a led to the substituted cyclopentanone derivative 19a along with its other diastereoisomer. The pho-adduct mixture obtained
from the diene 17b before rearrangement, was transformed to the thermodynamically more stable ester 18c (12). The cyclobutane ring in 18c underwent smooth rearrangement to produce exclusively the cyclopentanone derivative 19c in excellent yield.

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\begin{align*}
9b & \xrightarrow{i} 17 & \xrightarrow{ii} 18 & \xrightarrow{iii} 19 \\
& a, R=\text{Me}; b, R=\text{CH:CHMe}; c, R=\text{CO}_2\text{Me}
\end{align*}
\]

Scheme -2 Reagents and Conditions : i, NaH-THF, crotyl bromide (for a), MeCH:CHCH:CHCH\text{Br} (for b), HMPA, reflux; ii, hv, Et\text{2}O, CuOTf; iii, TfOH, CH\text{2}Cl\text{2} (for a), Os\text{O}_\text{3}-\text{NaIO}_4-Et\text{2}O, H\text{2}O then Jones reagent acetone and then CH\text{2}N\text{2}, Et\text{2}O (for b).

The greatest advantage of this protocol is its application in the synthesis of spiro cyclopentanones. A number of cyclic ketones 20a-c, 22, 24 was converted to the spiro cyclopentanones 21a-c, 23 and 25 respectively in overall good yield (13). Cyclic diones can also be used as demonstrated by transformation of the mono protected ketone 26 to the spiro cyclopentanone 25 through the photoadduct 27 after deketalisation, MeLi addition and rearrangement of the resulting cyclobutane 29. The spiro cyclopentanone 25 is suitably functionalised for elaboration to acoranes and cedranes. Using this strategy a formal synthesis of \(\alpha\)-cedrene has been accomplished (Scheme-3)(13).

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\begin{align*}
20 & n=1-3 \\
21 & \text{CH}_2\text{OH} \\
22 & \text{Me-}\text{CH}_2\text{OH} \\
23 & \text{Me-}\text{CH}(_2\text{OH})\text{Me} \\
24 & \text{Me-}\text{Me} & 25 & \text{Me-}\text{Me} & 27, R^1, R^2=O(\text{CH}_2)_4\text{O} & 28, R^1, R^2=O & 29, R^1, R^2=\text{Me, OH}
\end{align*}
\]

Scheme-3 : Reagents and Conditions : i, dihydropyran, PPTS, CH\text{2}Cl\text{2}; MeLi, THF, reflux; PPTS, MeOH; ii, DMSO, 165 C; iii, H\text{2}, PtO\text{2}, EtOH; iv, Swern oxidation; MeLi, Et\text{2}O; Jones reagent, acetone.

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The selectivity observed in the pinacol rearrangement of the cyclobutane derivatives 11 involving exclusive migration of the C1-C5 bond in contrast to the stereoelectronically favoured(15) C1-C7 bond is interesting. The origin of this unusual selectivity in bond migration is attributed as follows (Scheme-4). A concerted migration of the C1-C5 bond in the protonated species 34 leads to the formation of the cation 35 which is stabilised by the OH group through formation of the cyclic transition state 36. Rapid collapse of 36 leads to the products 12. In case of C1-C7 bond migration, the stabilisation of the cation by OH group requires unfavourable formation of the strained oxetane 37 and is thus inhibited.

REFERENCES