

AN UNUSUAL CASE OF KHAND-PAUSON CYCLIZATION INVOLVING THE
PARTICIPATION OF A CONJUGATED DOUBLE BOND. A PROMISING SEQUENCE
FOR THE ASSEMBLAGE OF POLYCYCLIC FRAMEWORK

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Summary. A short and convergent route for the synthesis of polycyclic linearly and/or angularly fused compounds is proposed based on the intramolecular alkyne-alkene-carbonyl cycloaddition with participation of the double bond bearing an electron withdrawing group.

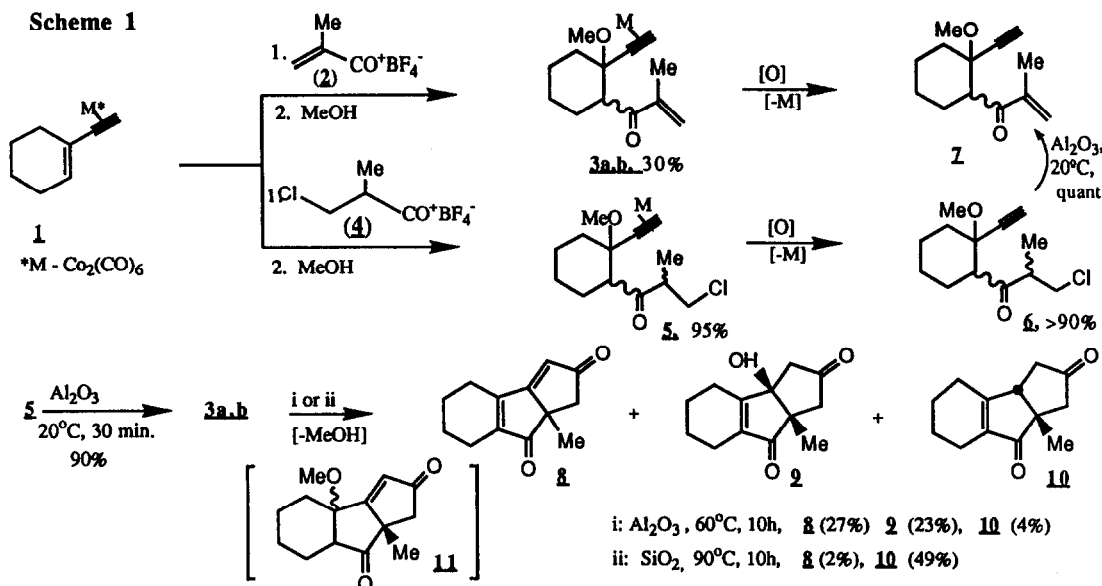
Intramolecular Khand-Pauson (IMKP) cyclization of dicobalthexacarbonyl complexes (DCHCC) of 1,6-enynes represents an extremely useful approach for the synthesis of various polycyclics containing a bicyclo[3.3.0]octenone fragment [1]. We have shown previously that the stepwise Ad_E reaction across the double bond of DCHCC of conjugated enynes with the use of α,β -unsaturated acylium tetrafluoroborates as electrophiles can be employed as a very efficient protocol for the assemblage of 1,6-enynes [2]. However, DCHCC of 1,6-enyn-3-ones thus formed were found to be unable to undergo the Khand Pauson reaction due to the presence of the deactivating EWG [3,4]. Hence the tandem sequence Ad_E plus IMKP reaction suggested earlier as a novel method for the synthesis of polycyclic compounds [5] necessarily involved an additional and non-constructive step, namely, transformation of the carbonyl functionality [3,6,7].

Here we present results showing that for some model systems the presence of the carbonyl group at the double bond does not interfere with the IMKP reaction and the latter could be carried out directly with the DCHCC of the 1,6-enyne-3-ones prepared by Ad_E route.

In the course of studies aimed at the utilization of the aforementioned approach for the synthesis of linearly fused tricyclic compounds [5], an acylation of the DCHCC of 1-cyclohexenylacetylene (**1**) was attempted with methacryloyl tetrafluoroborate (**2**), in order to prepare **3**. Contrary to expectations, the desired product **3** was formed in a frustratingly low yield (Scheme 1). This problem was circumvented by the use of an acylating agent equivalent to **2**, namely 2-methyl-3-chloropropionyl tetrafluoroborate (**4**). Reaction of the latter with **1** led to the formation of **5** as a mixture of four stereoisomers in the ratio 3:2:1:1 in an excellent total yield [8]. Adduct **5** was converted into respective decomplexed product **6**. Dehydrochlorination of the latter was achieved over the surface of Al_2O_3 [6] and gave the target product **7** in a nearly quantitative yield (mixture of two isomers in ratio 3:1). Application of this procedure for the Co-complexed adduct **5** led to results that turned out to be both unexpected and most rewarding. In fact, it was noticed that dehydrochlorination of DCHCC **5** on alumina at 20°C leading to **3** is accompanied by the formation of polar metal-free products with R_f values close to those observed earlier for Khand-Pauson cycloadducts (e.g., in ref. [6,7]). Under a slightly more forcing treatment (Al_2O_3 , 60°C, 10h) adduct **5** undergoes a complete conversion into these polar products which were separated by TLC and identified as the cycloadducts with a tricyclo[7.3.0.0^{2,7}] dodecane skeleton, **8**, **9** and **10** [8]. These results implied that under these dry state adsorption conditions (DSAC) a series of consecutive reactions occurred, namely, rapid dehydrochlorination of **5** into **3**, IMKP cyclization of **3** [9] accompanied by the elimination of methanol

leading to **8**, and Michael addition of water (from Al_2O_3) across the less hindered double bond of adduct **8**, which leads eventually to **9**. The same mixture of products **8**, **9**, and **10** was also obtained by the cyclization of preformed adduct **3** over Al_2O_3 . One might have expected that IMKP would initially produce the tricyclic methoxy enone **11**. In fact TLC data indicated the transient appearance of another polar product at the initial period of cyclization of **3**. However, in the course of its isolation by TLC on florasil this adduct underwent partial conversion into **8-10**, with only minor amounts of **11** left intact. The latter was tentatively identified by MS and the presence of a methoxy group signal in the PMR spectrum of this mixture. Formation of the adduct **10** indicates the occurrence of a hydrogenolysis side reaction in the course of the Khand-Pauson cyclization, a process not without precedents [9,10]. The cyclization of **3** on the surface of SiO_2 occurs under slightly more drastic conditions and results in the formation **10** as the major product (ratio **10:8** > 20:1).

Scheme 1

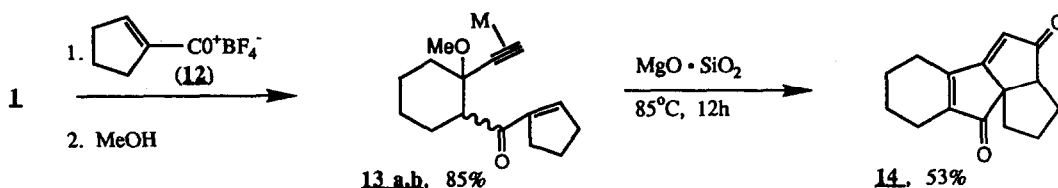


These results suggest a novel and promising opportunity for the utilization of 1,6-enynes containing a double bond bearing an EWG as substrates for the IMKP reaction. In fact, the synthesis of the tricyclic compound **8** from **3** outlined in Scheme 1 does not require such additional operations as: (a) the separation of isomers formed at the acylation step, and (b) carbonyl group transformations and hence represents a substantial improvement over the previously reported protocol [11].

To evaluate the scope of the described observation we also attempted this reaction with several related substrates. Acylation of **1** with 1-cyclopentenoyl tetrafluoroborate (**12**) under standard conditions of stepwise acylmethoxylation [2b] proceeded uneventfully and gave the expected DCHCC **13** (mixture of diastereomers in ratio 2:1) in an excellent yield [8] (Scheme 2). IMKP reaction of **13** under DSAC occurred sluggishly (compared to **3**) and in this case florasil turned out to be a better support than alumina. Heating of **13** applied to florasil at 85°C for 12h resulted in a formation of the expected tetracyclic product **14** in a good yield [8]. The structure of the latter was unequivocally proven by a single crystal X-ray analysis.

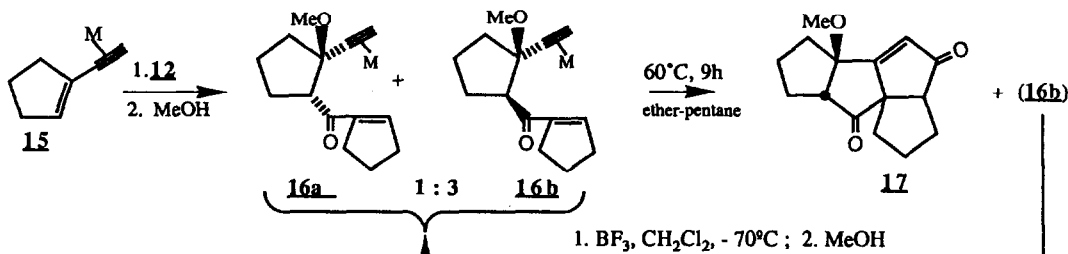
Control experiments have shown that the individual isomers **13a** and **13b** are converted into the same product **14** with a comparable rate.

Scheme 2



Similarly, the DCHCC **16** (formed in a nearly quantitative yield by acylation of DCHCC of 1-cyclopentenylacetylene (**15**) with **12**) was used as a substrate for IMKP reaction. In this case the cyclization proceeded effectively both under DSAC and upon the thermolysis of **16** in solution. Trial experiments with pure diastereomers **16a** and **16b** revealed that only the former (presumably with cis-orientation of ethynyl and acyl substituents, cf. data in ref.[2b]) undergoes the cyclization while the latter is left intact. In the preparative run with a 1:3 mixture of **16a** and **16b**, the respective tetracyclic product **17** [8] was obtained in a yield ca 73% (calculated for the content of **16a** in the initial mixture) (Scheme 3). The recovered **16b** could be equilibrated into the same 1:3 mixture **16a** and **16b** under the action of BF_3 in CH_2Cl_2 at -75°C (MeOH quench, yield ca. 85%) and hence the recycling of unreactive isomer **16b** could be easily achieved. It is noteworthy that the conversion of **16a** into **17** proceeded without the elimination of MeOH.

Scheme 3



The data given above clearly illustrate the potential of the utilized reaction sequence as a short and efficient [12] route for the assemblage of some tri- or tetracyclic compounds. It is worthwhile to mention that adducts **14** and **17** formed in two steps from readily available precursors contain the basic BCDE rings fragments which are present in the natural sesterterpene retigeranic acid [14] or diterpene crinimpellin-A **18** [15] respectively. The results shown in Schemes 2 and 3 suggest a novel approach to the convergent synthesis of these compounds based on the use of Ad_g and IMKP reactions as the key steps and we are currently exploring the viability of this route.

The increased propensity of **3**, **13** and **16** to undergo Khand-Pauson cyclization in contrast to other substrates (cf. the data in ref. [3,5-7, 11]) is difficult to account for. However, it is possible to speculate that the presence of an additional substituent at the α -atom of the double bond may serve as a factor restricting the conformational mobility of the side chain in such a way that the double bond becomes more proximate to the reacting Co-complexed alkyne moiety.

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