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LETTERS

The molybdenum-mediated tandem Pauson–Khand reaction. High yield entry into [5.5.5.5]tetracyclic systems

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Abstract

The [5.5.5.5]tetracyclic ring systems **1** and **2** were synthesized in high yield via a molybdenum carbonyl-mediated Pauson–Khand (type) reaction which is much easier to execute than the previous cobalt carbonyl mediated process. © 2000 Elsevier Science Ltd. All rights reserved.

The cobalt carbonyl-mediated cycloaddition of alkenes, alkynes and carbon monoxide (Pauson–Khand reaction) was discovered in the early 1970s, and has received much attention during the past three decades.[1–5] It has become a powerful tool for the preparation of cyclopentanones. In 1993, Jeong and coworkers reported molybdenum hexacarbonyl was also able to mediate the same process in the presence of 5–10 equivalents of DMSO at 100°C.[6] Recently, Brummond et al. reported that intramolecular alkynylallenes could be cyclized under the same conditions,[7] and employed this as a key reaction to synthesize the potent antitumor agent (±)-hydroxymethylacylfulvene.[8]

Compared to other transition metal complexes used to mediate this type of cyclization, molybdenum hexacarbonyl presents many advantages. Firstly, it is stable to air and moisture, therefore dry and oxygen free reaction conditions are not required. Secondly, when the reaction is completed the molybdenum byproducts will precipitate from the reaction solution and can be easily removed by filtration through a pad of silica gel. Finally, the affordable price, availability and low toxicity render it an important reagent even when employed in a stoichiometric sense; it is simply cheaper and easier to employ than $Co_2(CO)_8$.

The cobalt-mediated tandem Pauson–Khand reaction has provided a new regiospecific entry into the parent ring systems **1** and **2** of dicyclopenta[*a*,*e*]pentalene **3**[9,10] and dicyclopenta[*a*,*f*]-pentalene **4**.[10,11] The interest in these two 14π annulenes stems from the controversy in regard to their resonance energy and aromaticity determined from computational studies. These two molecules depicted in Fig. 1 have attracted much attention during the past three decades.[12–17]

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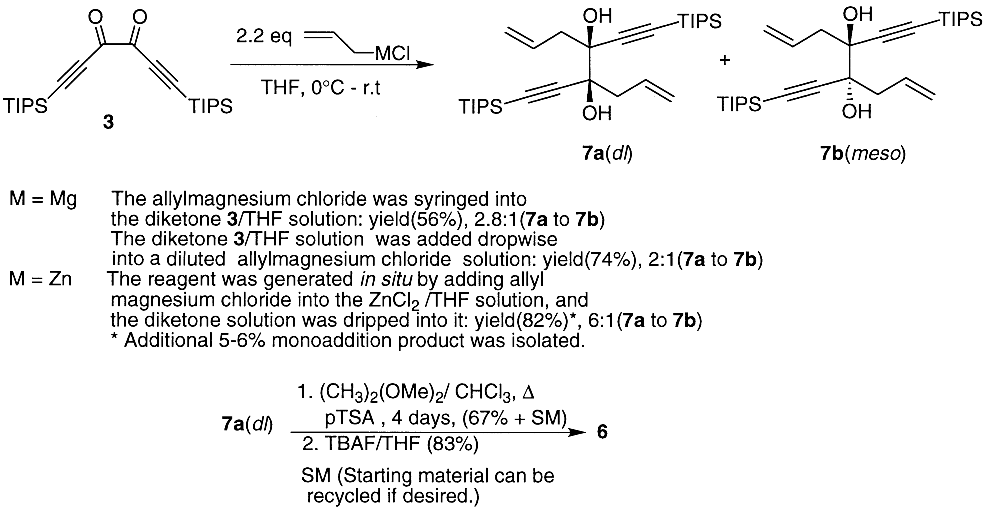
3 **4**

Figure 1. Potential target annulenes

In this letter we wish to report the scope of the tandem Pauson–Khand reaction has been extended to the molybdenum-mediated process and, in fact, takes place even more conveniently than the catalytic process. The yields are higher in most cases, and the workup procedure is more facile than even the catalytic cobalt-mediated sequence.[10] The diyne-diene **5** required for construction of **1** was synthesized analogous to the previous route. However,[10,11] a new and shorter route to the second framework constrained diyne-diene **6**(dl) has been developed (Scheme 1) to improve the stereoselectivity. In the pinacol coupling approach to the desired diyne-diene **7a**, the ratio of desired **7a** (TMS analogue) to undesired **7b** (TMS analogue) was only 1:3.



M = Mg The allylmagnesium chloride was syringed into the diketone **3**/THF solution: yield(56%), 2.8:1(**7a** to **7b**)
The diketone **3**/THF solution was added dropwise into a diluted allylmagnesium chloride solution: yield(74%), 2:1(**7a** to **7b**)
M = Zn The reagent was generated *in situ* by adding allyl magnesium chloride into the $ZnCl_2$/THF solution, and the diketone solution was dripped into it: yield(82%)*, 6:1(**7a** to **7b**)
* Additional 5-6% monoaddition product was isolated.

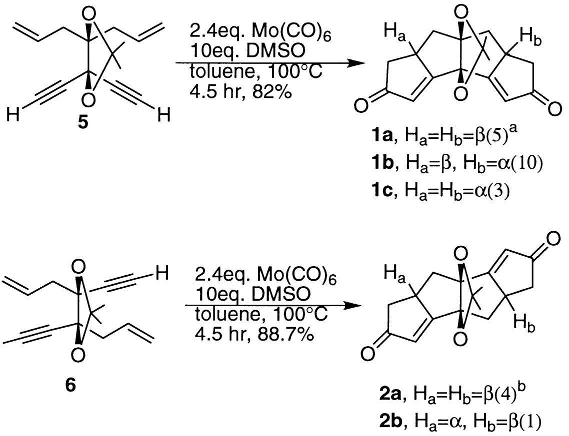
1. $(CH_3)_2(OMe)_2$/ $CHCl_3$, Δ pTSA , 4 days, (67% + SM)
2. TBAF/THF (83%)

SM (Starting material can be recycled if desired.)

Scheme 1.

The dialkynyl-1,2-diketone **3** required for this new approach was synthesized analogous to the literature procedure[18] in one pot in 82% yield. Treatment of **3** with an allylmetal chloride in THF from 0°C to room temperature provided the diyne-diene with the desired isomer **7a**[19] predominating. The choice of metal played an important role with respect to the stereoselectivity and yield of **7a**. As shown in Scheme 1, when magnesium was employed, the yields varied from 55 to 75% and the ratios (dl-isomer **7a** to *meso*-isomer **7b**[20]) ranged from 2:1 to 3:1. However, when allylzinc chloride was used [generated in situ by treating the zinc chloride/THF solution with the allylmagnesium chloride solution (a large amount of white precipitate appeared immediately when they were mixed at 0°C)], the yield increased to over 80% accompanied by 5–6% of the monoaddition product. This could be recycled to make more of the desired diol **7a**. More significantly, the ratio of the desired dl isomer **7a** to *meso*-isomer **7b** improved to 6:1. This chelation-controlled process has provided the desired isomer **7a** in a 6:1 ratio, whereas the previous approach furnished **7a** as the minor isomer (1:3).[10] The required acetonide **6** was obtained by heating **7a** with 2,2′-dimethoxypropane under the same conditions employed previously[10](67%); prolonged reaction times did not affect the conversion. The TIPS groups were removed with TBAF in THF (Scheme 1).

Analogous to the procedure reported by Jeong[6] and Brummond[7] (Scheme 2), the diyne-diene acetonides **5** and **6**, individually, were heated with 2.4 equivalents of $Mo(CO)_6$ and 10 equivalents of DMSO in toluene at 100°C. After 4.5 h, a large amount of blue precipitate had accumulated in the reaction flask and the mixture was allowed to cool. This was filtered through a pad of silica gel to remove the precipitate and the solution was washed with water to remove the DMSO. The concentrated organic phase was further purified by flash column chromatography. This furnished **1** and **2** (individually) in regiospecific fashion in 82 and 89% yields, respectively. Compared with the cobalt-mediated processes (60–70% yields in most cases)[10], the Mo-mediated yields were significantly higher. This sequence avoids the laborious process required to remove the NMO, $Co_2(CO)_8$ and their byproducts during the purification. The molybdenum-mediated process was simply much cleaner. Moreover, the molybdenum-mediated approach took less time (4.5 h) to complete than the cobalt-mediated sequence (12 h when the NMO facilitated process was carried out and over 1 day when the photochemical reaction was executed.)[10] Finally, the ratios of the stereoisomers were 5:10:3 (**1a**:**1b**:**1c**) and 4:1 (**2a**:**2b**) which are different from the $Co_2(CO)_8$-mediated processes facilitated photochemically or with *N*-methylmorpholine *N*-oxide.[10] However, these ratios are unimportant in regard to planar annulenes **3** and **4**.



Scheme 2. (a) Ratio by isolation; (b) ratio by ^1H NMR (integration)

In conclusion, a chelation-controlled approach to the key diyne-diene **7a** with much higher stereoselectivity and in higher yield has been achieved. Furthermore, the molybdenum carbonyl-mediated tandem Pauson–Khand (type) reaction has been shown to provide a facile entry into the two [5.5.5.5]tetracyclic ring systems **1** and **2**. Importantly, six carbon–carbon bonds have been generated in each system in greater than 96% (**1**) and 98% (**2**) yields, respectively, by a process that is cheap, less toxic and much easier to execute than the corresponding cobalt-mediated sequence.[10]

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19. Compound **7a**: ^{1}HNMR (300 MHz, $CDCl_3$) δ 6.16–6.02 (m, 2H), 5.22 (s, 2H), 5.18 (d, J = 9 Hz, 2H), 2.83–2.66 (m, 4H), 2.62 (s, 2H), 1.07 (s, 42H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 133.51, 119.10, 106.51, 87.78, 75.47, 41.77, 18.50, 11.42; IR (neat) 3454, 2864, 2166, 1640, 1462, 1017 cm^{-1}. LRMS (EI$^+$, 15eV) *m*/*z* 252 (6%), 210 (42%), 167 (100%).
20. Compound **7b**: ^{1}HNMR (300 MHz, $CDCl_3$) δ 6.16–6.02 (m, 2H), 5.21 (s, 2H), 5.16 (d, J = 6 Hz, 2H), 2.70–2.57 (m, 6H), 1.07 (s,42H); ^{13}CNMR (75 MHz, $CDCl_3$), δ 133.55, 118.70, 106.88, 88.65, 76.33, 40.41, 18.61, 11.12; IR (neat) 3454, 2864, 2164, 1641, 1458, 1026 cm^{-1}. LRMS (EI$^+$, 15eV) *m*/*z* 252 (11%), 210 (55%), 167 (100%).