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A FACILE SYNTHESIS OF SPIRO-CYCLOPENTENONES FROM VARIOUS 1-ALKYNES AND CYCLIC *EXO*-METHYLENE COMPOUNDS BY INTERMOLECULAR PAUSON-KHAND REACTION

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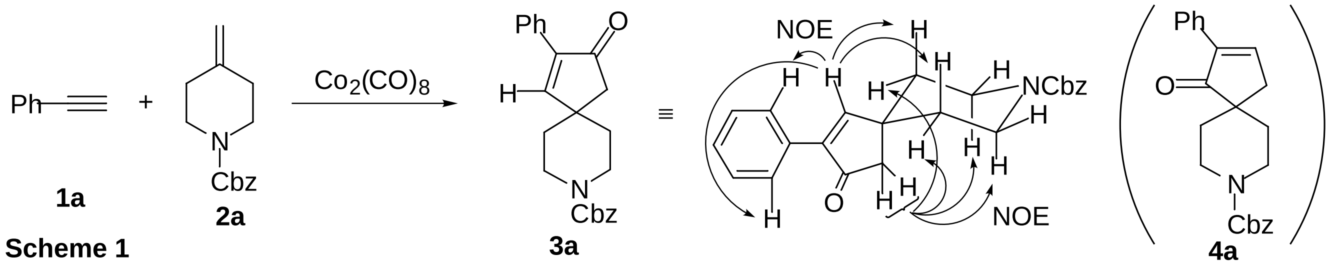
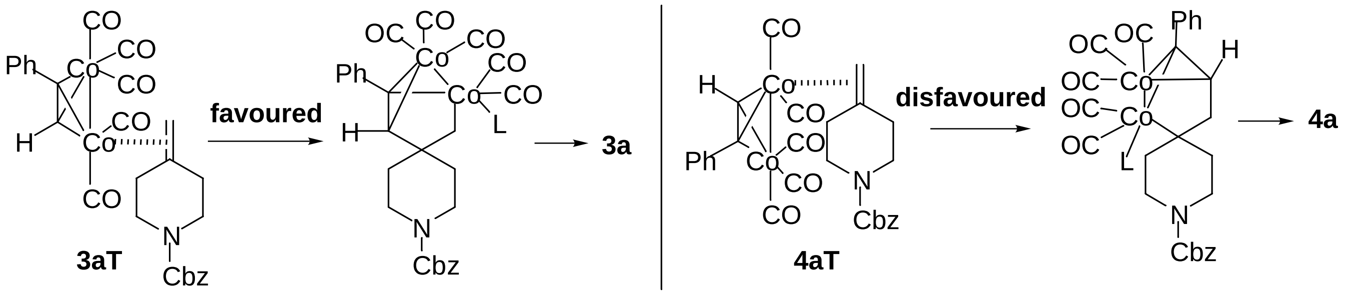
Abstract - Intermolecular Pauson-Khand reaction of various 1-alkynes with *exo*-methylene-piperidine and -cyclohexane derivatives was examined to give the title compounds in moderate to good yields.

Spirocyclic compounds are one of important key intermediates in the total synthesis of natural products[1] and several methodology to access them has been developed.[2] In connection with our recent work[3] on intramolecular Pauson-Khand reaction of *exo*-cyclic olefins, we envisaged that intermolecular Pauson-Khand reaction of *exo*-cyclic olefins could be convenient synthetic method of spirocycles. Since first report of Pauson-Khand reaction,[4] a few works have appeared on the reaction of *exo*-methylene cycles constituted by only small ring substrates such as cyclo-propanes[5a,b] and -butanes.[5b] Here, we wish to describe the Pauson-Khand reaction of various 1-alkynes with 6-membered cyclic *exo*-methylene compounds to furnish 6-5 spirobicyclic compounds.

At first, intermolecular Pauson-Khand reaction of phenylacetylene (**1a**) was examined with 2 eq. of *N*-benzyloxycarbonyl-4-methylenepiperidine (**2a**)[6] (Scheme 1). Among experiments, the reaction in boiling toluene gave stereoselectively spiro-cyclic compound (**3a**)[7,8](30%) and no improvement (29%) was observed in the reaction under CO atmosphere. Furthermore, the reaction in the presence of BuSMe[9] formed intractable mixture to give **3a** in only 9% yield. Also, the reaction with NMO[10] did not result in



Scheme 1



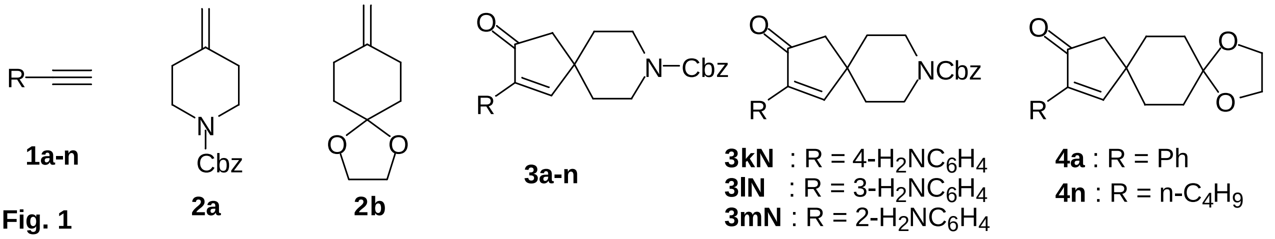
Scheme 2

formation of **3a** and only decomplexation was observed on TLC. Structure of **3a** was determined by NOE experiment. In all cases, regioisomer (**4a**) of **3a** was not formed. It should be due to severe steric interaction between alkyne-cobalt complex and piperidine ring as depicted in Scheme 2 (**3aT** vs **4aT**).

It is well known that strained cyclic alkenes such as norbornene and 2,5-norbornadiene are good substrates in intermolecular Pauson-Khand reaction, in which when excess amounts (3-10 eq.) of them are used, the cyclized products are formed in good yield.[11] Based on the findings, secondly, the reaction with increased amounts of **2a** was examined. Gratifyingly, when five and ten equivalents of **2a** were employed, **3a** was produced in 55 and 78% yields, respectively. Thus, excess of **2a** (10 eq)[11] was required to obtain good yield of Pauson-Khand adduct. Unchanged **2a** could be recovered in 75% yield and reused [**3a** (76%); **2a** (77%)].

From these results, the reaction of various 1-alkynes (**1a**-**n**) was conducted with ten equivalents of *exo*-cyclic olefins (**2a**,**b**).[6] The results are summarized in Table 1. The reaction of arylacetylenes having acetoxy (**1b**,**c**), methoxycarbonyl (**1e**,**f**), and methoxy (**1g**,**h**) groups in 4- and 3-positions on benzene ring with **2a** gave the corresponding spiro-cyclopentenones (**3b**,**c**,**e**,**f**,**h**,**i**)[7] in good yield (68-80%) along with unchanged **2a** (75-79%). On the other hand, similar reaction of 2-substituted arylacetylenes (**1d**,**g**,**j**) afforded corresponding adducts (**3d**,**g**,**j**)[7] in moderate yield (40-44%). In these cases, many by-products were detected on TLC, which could not be isolated. These results would be rationalized by considering that sterically hindered 2-substituents on benzene ring interfered to approach the alkyne-cobalt complex to olefin moiety. Also another possibility that intramolecular coordination of 2-substituted oxygen or nitrogen atom to cobalt one in alkyne-cobalt complex accelerates decomplexation[12] to give the corresponding starting alkynes might be not excluded.

Interestingly, the reaction of arylacetylenes (**1k**-**m**) bearing benzyloxycarbonylamino group with **2a** afforded corresponding spiro-cyclopentenones (**3k**-**m**)[7] in moderate yield (43-44%) along with free anilino products (**3kN**-**3mN**).[7,13] The latter products would be formed by debenzyloxycarbonylation, which might be accelerated by coordination of nitrogen atom to cobalt complex during the reaction. The reaction of 1-hexyne (**1n**) with **2a** required long reaction time to afford **3n** in 43% yield. In a similar manner, the reaction of **1a** and **1n** with 8-methylene-1,4-dioxaspiro[4.5]decane (**2b**) proceeded to give spiro-cyclopentenones (**4a**,**n**)[7] in 63% and 42% yield.



3kN : R = 4-$H_2NC_6H_4$
3lN : R = 3-$H_2NC_6H_4$
3mN : R = 2-$H_2NC_6H_4$

4a : R = Ph
4n : R = n-C_4H_9

Fig. 1

Table 1. Intermolecular Pauson-Khand Reaction of Various 1-Alkynes and Olefins.[a]

Run	1-Alkynes	R	Olefin	Time (h)	Product	Yield (%)	mp (˚C)	Recovered olefin (%)
1	**1a**	C_6H_5	**2a**	3	**3a**	78	131-132	75
2	**1b**[b]	4-$AcOC_6H_4$	**2a**	3	**3b**	77	109-110	78
3	**1c**[c]	3-$AcOC_6H_4$	**2a**	4	**3c**	68	oil	77
4	**1d**[d]	2-$AcOC_6H_4$	**2a**	4	**3d**	44	oil	78
5	**1e**[e]	4-$MeO_2CC_6H_4$	**2a**	3	**3e**	78	96-97	75
6	**1f**[e]	3-$MeO_2CC_6H_4$	**2a**	3	**3f**	80	oil	79
7	**1g**[e]	2-$MeO_2CC_6H_4$	**2a**	3	**3g**	42	oil	76
8	**1h**[f]	4-$MeOC_6H_4$	**2a**	4	**3h**	70	100-101	79
9	**1i**[f]	3-$MeOC_6H_4$	**2a**	3	**3i**	68	oil	78
10	**1j**[f]	2-$MeOC_6H_4$	**2a**	4	**3j**	40	oil	79
11	**1k**[g]	4-$CbzNHC_6H_4$	**2a**	4	**3k+3kN**	44+9	69-70, 62-63	81
12	**1l**[g]	3-$CbzNHC_6H_4$	**2a**	4	**3l+3lN**	43+11	65-66, 47-48	83
13	**1m**[h]	2-$CbzNHC_6H_4$	**2a**	3	**3m+3mN**	44+1	57-58, 150-151	85
14	**1n**	n-C_4H_9	**2a**	9	**3n**	43	oil	77
17	**1a**	C_6H_5	**2b**	4	**4a**	63	88-89	77
18	**1n**	n-C_4H_9	**2b**	10	**4n**	42	oil	71

a) All reactions were carried out in boiling toluene with 10 eq. of olefin. b) M. Kotora and E. Negishi, *Synthesis*, 1997, 121. c) P. T. W. Cheng, P. Devasthale, Y. T. Jeon, S. Chen, and H. Zhang, PCT Int. Appl. WO 0121602, 2001. d) M. C. Pirrung and Y. R. Lee, *J. Org. Chem.*, 1993, **58**, 6961. e) S. J. Havens and P. M. Hergenrother, *J. Org. Chem.*, 1985, **50**, 1763. f) U. Appelberg, N. Mohell, and U. Hacksell, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 415. g) Obtained by benzyloxycarbonylation of 4- or 3-ethynylaniline (T. Takeichi and J. K. Stille, *Macromolecules*, 1986, **19**, 2093). h) Obtained by benzyloxycarbonylation of 2-ethynylaniline (S. Cacchi, G. Fabrizi, and P. Pace, *J. Org. Chem.*, 1998, **63**, 1001).

In summary, we have investigated intermolecular Pauson-Khand reaction of various arylacetylenes (**1a-m**) and 1-hexyne (**1n**) with 6-membered cyclic *exo*-methylene compounds (**2a**,**b**) to give spiro-cyclopentenones. The reaction of arylacetylenes bearing substituents (except for benzyloxycarbonylamino group) in 3- and 4-positions on benzene ring gave the corresponding adducts in good yields, whereas that of 2-substituted and nitrogen-containing arylacetylenes, and aliphatic 1-alkyne furnished the corresponding spiro-cyclopentenones in moderate yields.

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6. S Olefins (**2a**,**b**) were synthesized from corresponding commercially available ketones by Wittig methylenation (PPh_3•MeBr, *t*-BuOK, THF, rt) in 98 and 83% yield, respectively.
7. All new compounds gave satisfactory ^{1}H- and ^{13}C-NMR, IR, and MS spectral data.
8. Representative procedure of Pauson-Khand reaction (Table 1, Run 1): A mixture of **1a** (0.020 g, 0.2 mmol), **2a** (0.462 g, 2.0 mmol), and $Co_2(CO)_8$ (0.083 g, 0.23 mmol) in toluene (2 mL) was stirred at rt for 1 h and at reflux for 4 h. The mixture was diluted with Et_2O. The precipitate was filtered through Celite 545 short pad. The filtrate was evaporated *in vacuo* to afford a residue, which was purified by preparative TLC on silica gel (AcOEt : hexane = 1 : 2) to give **3a** (0.057 g, 78%) and **2a** (0.344 g, 75%). **3a** : mp 131-132 ˚C; ^{1}H NMR δ 7.70 (2H, dd, J = 1.7, 7.9 Hz), 7.57 (1H, s), 7.32-7.42 (8H, m), 5.16 (2H, s), 4.05 (2H, br d, J = 13 Hz), 3.11 (2H, br t, J = 11.5 Hz), 2.51 (2H, s), 1.77 (2H, br t, J = 11.5 Hz), 1.52 (2H, br d, J = 13 Hz); ^{13}C NMR δ 205.3, 164.4, 155.2, 141.6, 136.2, 130.9, 128.7, 128.5, 128.4, 128.1, 127.9, 127.2, 67.2, 47.1, 41.4, 41.0, 35.9; IR 1698, 1681, 1497 cm^{-1}; MS *m/z* 361 (M^+); HRMS *m/z* calcd for $C_{23}H_{23}NO_3$ (M^+) 361.1678, found: 361.1676.
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13. The reaction of 4-aminophenylacetylene with **2a** gave the corresponding adduct (**3kN**) in only 16% yield.