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$Co_2(CO)_8$-Catalyzed Intramolecular Hetero-Pauson–Khand Reaction of Alkynecarbodiimide: Synthesis of (±)-Physostigmine

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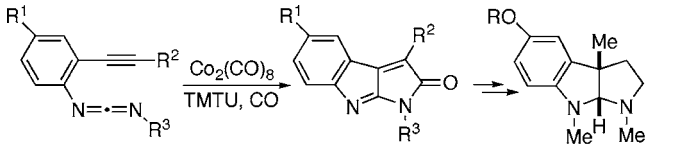
ABSTRACT



Herein we describe a novel $Co_2(CO)_8$-catalyzed intramolecular aza-Pauson–Khand-type reaction of alkynecarbodiimide derivatives affords pyrrolo[2,3-*b*]indol-2-one ring systems in reasonable yields. This is the first reported $Co_2(CO)_8$ successfully applied in the hetero-Pauson–Khand reaction. Significantly, the transformation of one of our pyrrolo[2,3-*b*]indol-2-one derivatives into the indole alkaloid, (±)-physostigmine, was completed in a highly stereoselective manner.

The intramolecular Pauson−Khand reaction[1] is well recognized as one of the most straightforward and powerful methodologies for the construction of bicyclic carbon frameworks. This intriguing reaction is a formal metal-mediated (or catalyzed) [2 + 2 + 1]-cycloaddition reaction of the alkyne π-bond, the alkene π-bond, and carbon monoxide. The reaction would generally be referred to as the "hetero-Pauson−Khand reaction" if more than one carbon atom of the newly generated cyclopentenone framework was replaced by an oxygen atom and/or nitrogen functionalities. Thus, the hetero-Pauson−Khand reaction would be realized for the oxa(aza)alkyne and/or an oxa(aza)alkene counterpart that could take part in the [2 + 2 + 1]-cycloaddition reaction. The first hetero-Pauson−Khand-type reactions were independently achieved by Buchwald's[2] and Crowe's groups[3] in 1996, via the intramolecular titanium-mediated [2 + 2 + 1]-cycloaddition of δ-unsaturated ketones and aldehydes (between the alkene π-bond and the oxa-alkene π-bond) with carbon monoxide, which resulted in the formation of bicyclic

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(2) (a) Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 5818−5819. (b) Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4424−4431.

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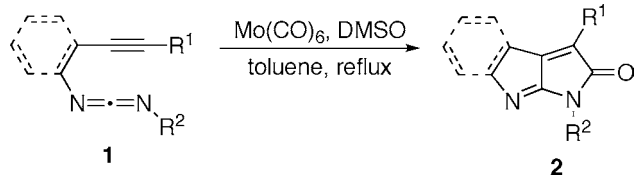
γ-lactone species (oxa-Pauson−Khand-type reaction). Several years later, Chatani and Murai[4] discovered that $Ru_3(CO)_{12}$ could efficiently catalyze not only the intramolecular oxa-Pauson−Khand reaction but also the aza-Pauson−Khand reaction to provide α,β-unsaturated γ-butenolides[4a] from the ynealdehydes (between alkyne π-bond and oxa-alkene π-bond), and the α,β-unsaturated lactams[4b] from the yneimines (between alkyne π-bond and aza-alkene π-bond), respectively. To the best of our knowledge, this $Ru_3(CO)_{12}$-catalyzed reaction is the first example of the metal-catalyzed hetero-Pauson−Khand reaction. $Ru_3(CO)_{12}$ was also found by Kang[5] to be effective for the intramolecular oxa-Pauson−Khand-type reaction of the δ-allenyl carbonyl congeners (instead of the ynealdehydes) to afford the corresponding α-methylene-γ-butyrolactones. Kang's group[5] also reported that the δ-allenyl moiety participated in the intramolecular aza-Pauson−Khand-type reaction with *N*-benzoylhydrazones (between allene π-bond and aza-alkene π-bond). A similar transformation of the δ-allenylcarbonyl compounds into the α-methylene-γ-butyrolactones under the $Mo(CO)_6$-mediated conditions was developed by Yu's group.[6] In addition, Saito[7] recently reported a new type of aza-Pauson−Khand reaction, involving the cyclocarbonylation of the alkyne carbodiimide substrates **1** (between alkyne π-bond and carbodiimide π-bond) to provide the diazabicyclic compounds **2** under the $Mo(CO)_6$-mediated conditions (stoichiometric version) (Scheme 1).

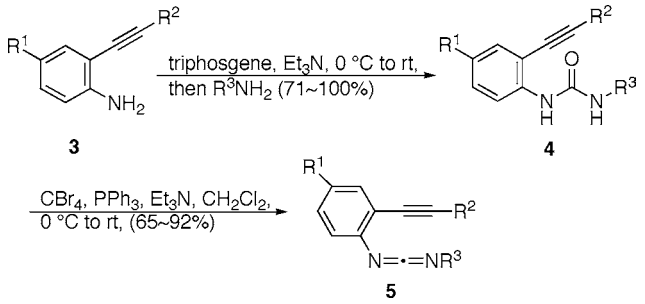
Scheme 1



Our recent interest[8] in the development of rhodium-catalyzed intramolecular Pauson−Khand-type reactions between the alkyne π-bond and the allene π-bond (instead of the olefin π-bond) led to an easy preparation of the bicyclo[4.3.0]nonadienone as well as bicyclo[5.3.0]decadienone frameworks. We have now become very interested in the *metal-catalyzed* cyclocarbonylation between the alkyne π-bond and the diaza-allene π-bond (carbodiimide functionality) because the carbodiimide group might be regarded as an isoelectronic alternative to the allenyl moiety in the Pauson−Khand-type reaction (aza-Pauson−Khand-type reaction), although Saito[7] already developed the stoichiometric procedure using $Mo(CO)_6$. Thus, we focused our efforts on the development of a new *metal-catalyzed* intramolecular aza-Pauson−Khand-type reaction of the *N*-[2-(1-alkynyl)-phenyl]-*N*′-phenylcarbodiimide derivatives.[9] This letter describes the preliminary results of (i) the novel $Co_2(CO)_8$-catalyzed intramolecular aza-Pauson−Khand-type reaction of *N*-[2-(1-alkynyl)phenyl]-*N*′-phenylcarbodiimide derivatives to obtain the pyrrolo[2,3-*b*]indol-2-one framework in onestep and (ii) a short and reasonably rapid synthesis of (±)-physostigmine[10] based on the thus-developed catalytic aza-Pauson−Khand-type product. We note, in advance, that this is the first example of the $Co_2(CO)_8$-catalyzed aza-[2 + 2 + 1] cycloaddition process ever reported.

The required alkynecarbodiimide substrates **5** for the cyclocarbonylation were prepared in a straightforward manner from the known 2-alkynylaniline derivatives **3**. Treatment of **3** with triphosgene and Et_3N was followed by exposure to primary amines[11] afforded the urea derivatives **4** in high yield. Exposure of **4** to carbon tetrabromide and triphenylphosphine[12] effected dehydration to provide the carbodiimides **5** as shown in Scheme 2.

Scheme 2



Our initial evaluation of the metal-catalyzed cyclocarbonylation of an alkynecarbodiimide was carried out using compound **5a** (Table 1). Chatani and Murai's conditions (catalytic amounts of $Ru_3(CO)_{12}$ in toluene at 120 °C under 10 atm of CO)[4] were first applied to compound **5a** to afford the desired pyrrolo[2,3-*b*]indol-2-one **6a** in 35% yield along with the urea **4a** in 27% yield[13] (entry 1).

$[RhCl(CO)_2]_2$,[8] a suitable catalyst for the ring-closing reaction between the alkyne and allene groups, gave **6a** in a

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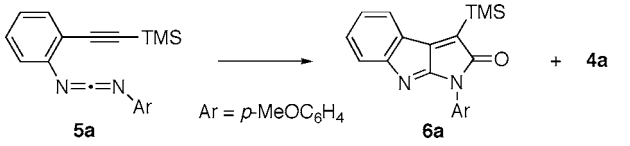
(9) The thermal transformation of the *N*-[2-(1-alkynyl)phenyl]-*N*′-phenylcarbodiimides into the 6*H*-indolo[2,3-*b*]qinolines via the biradical intermediates and its related reactions were reported; see: (a) Schmittel, M.; Steffen, J.-P.; Engels, B.; Lennartz, C.; Hanrath, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2371−2373. (b) Shi, C.; Zhang, Q.; Wang, K. K. *J. Org. Chem.* **1999**, *64*, 925−932. (c) Zhang, Q.; Shi, C.; Zhang, H.-R.; Wang, K. K. *J. Org. Chem.* **2000**, *65*, 7977−7983. (d) Schmittel, M.; Rodríguez, D.; Steffen, J.-P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2152−2155. (e) Lu, X.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2002**, *67*, 5412−5415. (f) Lu, X.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2002**, *67*, 7797−7801. (g) Li, H.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2003**, *68*, 5512−5518. (h) Li, H.; Yang, H.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2004**, *69*, 4500−4508.,

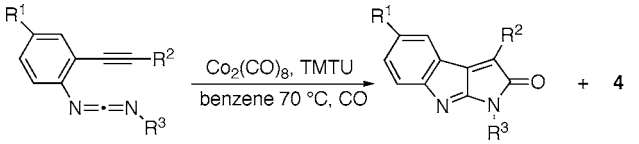
Table 1. Aza-Pauson−Khand Reaction of Carbodiimide **5a**



entry	metal	solvent	temp.	time	atmosphere	**6a** (%)	**4a** (%)
1	$Ru_3(CO)_{12}$ (5 mol %)	toluene	120 °C	1.5 h	CO (10 atm)	35	27
2	$[RhCl(CO)_2]_2$ (10 mol %)	DCE	80 °C	12 h	CO (1 atm)	8	-
3	$Co_2(CO)_8$ (1.2 equiv)	MeCN	70 °C	1 h	N_2	42	14
4	$Co_2(CO)_8$[a] (1.2 equiv)	THF	70 °C	1 h	N_2	36	-
5	$Co_2(CO)_8$[b] (1.2 equiv)	CH_2Cl_2	-78 °C[c]	4.5 h	O_2	66	20
6	$Co_2(CO)_8$[d] (10 mol %)	C_6H_6	70 °C	1 h	CO (1 atm)	69	7
7	$Mo(CO)_6$[e] (1.2 equiv)	toluene	80 °C	10 min	N_2	76	7

[a] DMSO (6.0 equiv) was used. [b] TMANO (4.0 equiv) was used. [c] Reaction temperature was warmed to rt. [d] TMTU (60 mol %) was used. [e] DMSO (10 equiv) was used.

Table 2. Aza-Pauson−Khand Reaction of Carbodiimide **5b−k** with $Co_2(CO)_8$[a]

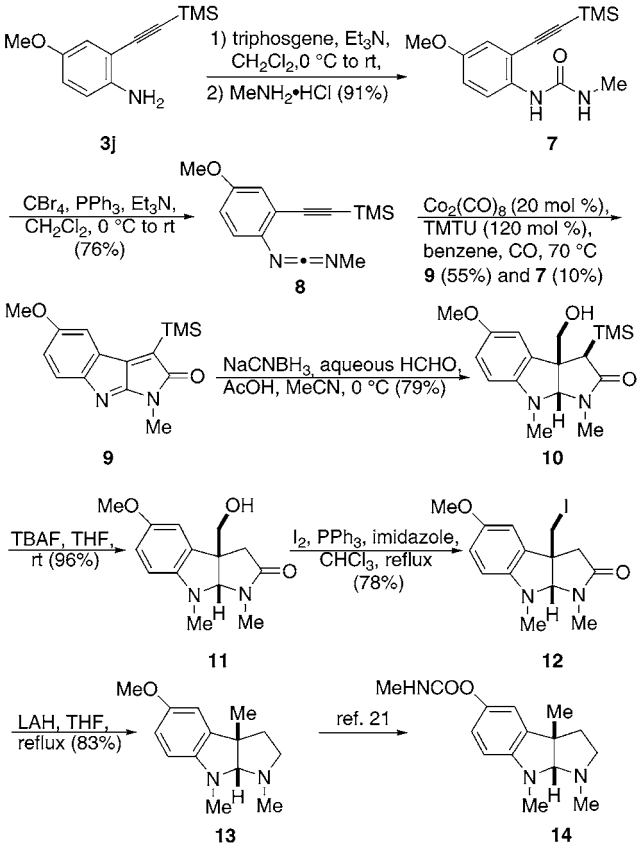


entry	**5**	R^1	R^2	R^3	**6** (%)	**4** (%)
1	**5b**	H	TMS	*p*-$PhOC_6H_4$	**6b** (57)	**4b** (6)
2	**5c**	H	TMS	*p*-$MeOC_6H_4CH_2$	**6c** (37)[b]	**4c** (6)
3	**5d**	H	TMS	Me	**6d** (41)[b]	**4d** (15)
4	**5e**	H	Pr	*p*-$MeOC_6H_4$	**6e** (66)	**4e** (10)
5	**5f**	H	$(CH_2)_2CHCMe_2$	*p*-$MeOC_6H_4$	**6f** (44)	**4f** (13)
6	**5g**	H	$(CH_2)_2OTBS$	*p*-$MeOC_6H_4$	**6g** (48)	**4g** (8)
7	**5h**	H	CH_2OTHP	*p*-$MeOC_6H_4$	**6h** (5)	**4h** (trace)
8	**5i**	Me	TMS	*p*-$MeOC_6H_4$	**6i** (54)	**4i** (19)
9	**5j**	MeO	TMS	*p*-$MeOC_6H_4$	**6j** (54)	**4j** (18)
10	**5k**	Cl	TMS	*p*-$MeOC_6H_4$	**6k** (52)	**4k** (7)

[a] A mixture of carbodiimide **5**, $Co_2(CO)_8$ (10 mol %), and TMTU (60 mol %) in benzene (0.1 M) was heated at 70 °C under an atmosphere of CO. [b] $Co_2(CO)_8$ (20 mol %) and TMTU (120 mol %) were used.

low yield (entry 2). $Co_2(CO)_8$[14] consistently provided **6a** as the major product (entries 3−6). In particular, **6a** was obtained in 69% yield when **5a** was exposed to 10 mol % $Co_2(CO)_8$ and tetramethylthiourea (TMTU)[14e] in benzene at 70 °C under an atmosphere of CO (entry 6). A control experiment using a combination of $Mo(CO)_6$ and DMSO at 80 °C in toluene[7,15] produced **6a** in 76% yield together with a small amount of **4a**[13] (entry 7). Thus, a catalytic amount of $Co_2(CO)_8$ was found to efficiently accelerate the intramolecular ring-closing step of **5a** to furnish the pyrrolo[2,3-*b*]-indol-2-one framework **6a**.

Scheme 3



(10) For recent total synthesis of physostigmine, see: (a) Node, M.; Hao, X.; Nishide, K.; Fuji, K. *Chem. Pharm. Bull.* **1996**, *44*, 715−719. (b) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500−6503. (c) Kawahara, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 675−678. (d) ElAzab, A, S.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 2757−2759. (e) Tanaka, K.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 1049−1052. (f) M.-Rios, M. S.; S.-Sanchez, N. F.; J.-Nathan, P. *J. Nat. Prod.* **2002**, *65*, 136−141. (g) Mekhael, M. K. G.; Heimgartner, H. *Helv. Chim. Acta* **2003**, *86*, 2805−2813. (h) Rage, P. D.; Johnson, F. *J. Org. Chem.* **2003**, *68*, 6133−6139. (i) Haung, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043−14053. (j) Santos, P. F.; Srinivasan, N.; Almeida, P. S.; Lobo, A. M.; Prabhakar, S. *Tetrahedron* **2005**, *61*, 9147−9156.

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(12) Nishikawa, T.; Ohyabu, N.; Yamamoto, N.; Isobe, M. *Tetrahedron* **1999**, *55*, 4325−4340.

(13) The formation of the urea derivative **4** as a byproduct could tentatively be interpreted by hydrolysis with a small amount of water inevitably present in the reaction medium.

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We next investigated the scope of this ring-closing reaction using various substrates **5b**−**k** under the $Co_2(CO)_8$-catalyzed conditions (Table 2). The carbodiimides **5b**,**i**−**k**, having the phenyl substitutent on the nitrogen atom (R^3) as well as the TMS group at the alkyne terminus (R^2), consistently produced the corresponding pyrrolo[2,3-*b*]indol-2-one skeleta **6b**,**i**−**k** in reasonable yield (more than 50%) irrespective of the substituent (R^1) on the benzene ring (entries 1,8−10).The carbon appendages at the triple bond terminus, such as a propyl (entry 4), aklenyl (entry 5), and siloxyethyl (entry 6) were stable under the $CO_2(CO)_8$-catalyzed conditions and the corresponding cyclocarbonylated products **5e**−**g** were obtained in good yields. However, the benzyl and alkyl substituents on the nitrogen atom (R^3) **5c**,**d** provided the cyclized products **6c**,**d** in slightly lower yields (entries 2,3). The propargyl alcohol derivative **5h** was shown to be a poor substrate for this catalytic ring-closing reaction (entry 7).

Our application of the newly developed catalytic aza-Pauson-Khand-type reaction for the synthesis of natural products is the next subject. According to the $Co_2(CO)_8$-catalyzed cyclocarbonylation conditions, the pyrrolo[2,3-*b*]-indol-2-one **9** was prepared in 55% yield[16,17] yield from the carbodiimide **8**.[18] Reductive methylation of **9** with $NaCNBH_3$ in the presence of aq HCHO and AcOH effected the consecutive reduction, hydroxymethylation, and *N*-methylation to produce **10**[19] in 79% yield as a single stereoisomer.[20] Removal of a TMS group from **10** with TBAF gave **11** in 96% yield, conversion of which into (±)-esermethole (**13**)[10,21] was achieved by the conventional procedures via the iodo derivative **12** in high yields. The present synthesis of **13** amounts to the synthesis of (±)-physostigmine (**14**),[10,21] since the former has already been converted into the latter (Scheme 3).

In summary, we have developed the novel $Co_2(CO)_8$-catalyzed aza-Pauson−Khand-type reaction of alkynecarbodiimide derivatives to give a range of pyrrolo[2,3-*b*]indol-2-one skeleta. This is the first demonstration of the use of $Co_2(CO)_8$ in the hetero-Pauson−Khand reaction. In addition, a new synthesis of (±)-physostigmine, involving a one-step construction of the core framework, followed by a small number of chemical modifications, has been achieved.

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Supporting Information Available: General procedures for ring-closing reaction and preparation of ureas and carbodiimides, and characterization data for compounds **4a**−**k**, **5a**−**k**, **6a**−**k**, and **7**−**13**. ^1H and ^{13}C spectra for compounds **4b**,**d**, **5a**−**k**, **8**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) $Co_2(CO)_8$ (20 mol %) was used.

(17) A stoichiomeric amount of $Mo(CO)_6$ (1.2 equiv) and DMSO (10 equiv) afforded the desired **9** in 78% yield along with the urea **7** in 8% yield.

(18) Coumpound **8** was prepared from **3j** via **7**.

(19) A full mechanistic discussion is premature at this point, but the one-step transformation of **9** into **10** might be rationalized in terms of the initial attack of the hydride species at the C_3-position (1,4-reduction) of **9** resulting in the formation of the indole intermediate, which subsequently reacted with HCHO at the C_{3a}-position to give the corresponding indolenine derivative. The formed imine moiety (N_8−C_{8a}) would be susceptible to the hydride reduction, followed by *N*-methylation to produce **10**.

(20) The relative stereochemistry of **10** was determined by an NOE experiment.

(21) Yu, Q.-S.; Brossi, A. *Heterocycles* **1988**, *27*, 745−750.