Thiocarbonyl induced heterocumulenic Pauson–Khand type reaction: expedient synthetic method for thieno[2,3-*b*]indol-2-ones†

Takao Saito,* Hiroshi Nihei, Takashi Otani, Toshiyuki Suyama, Naoki Furukawa and Masatoshi Saito

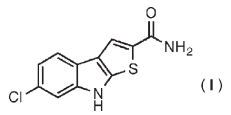
Received (in Cambridge, UK) 17th August 2007, Accepted 28th September 2007
First published as an Advance Article on the web 16th October 2007
DOI: 10.1039/b712739a

The first examples of C=S induced Pauson–Khand type reactions are described; 2-alkynylphenyl isothiocyanates were converted to 3-substituted-2*H*-thieno[2,3-*b*]indol-2-ones in the presence of a stoichiometric amount of $Mo(CO)_6$ or $Co_2(CO)_8$, or a catalytic amount of Rh catalyst under an atmospheric pressure of carbon monoxide.

The Pauson–Khand (PK) reaction (including the Pauson–Khand type reaction) is a metal-promoted three-component reaction, formulated as a formal [2 + 2 + 1] cocycloaddition of an alkyne, an alkene and carbon monoxide leading to a cyclopentenone.[1,2] Allenes instead of alkenes have also been utilized successfully in the PK reaction to give 4- and/or 5-alkylidenecyclopentenones.[3] The hetero PK reaction using a heteroalkene counterpart such as an aldehyde, ketone or imine, leading to, *e.g.*, δ-butyrolactones or lactams, has been reported.[4] Extensive efforts have been made to develop transition metal-catalyzed transformations in carbo- and heterocyclic synthesis.[5] Nevertheless, the known PK (type) reagents (metal carbonyl complexes, promoters) which are applicable to the hetero PK (type) reaction seem to be still very limited compared to those for the carbo PK reaction.

Very recently, we succeeded in performing the stoichiometric and catalytic heterocumulenic PK cyclocarbonylation that incorporates a carbodiimide function together with an internal alkyne and carbon monoxide to give 1*H*-pyrrolo[2,3-*b*]indol-2-ones and 4,5-dihydro-1*H*-pyrrolo[2,3-*b*]pyrrolin-2-ones.[6] Mukai *et al.* reported a $Co_2(CO)_8$-catalyzed version of the method for construction of the pyrrolo[2,3-*b*]indol-2-one ring system and applied the method to the synthesis of the indole alkaloid, (±)-physostigmine.[7] To develop the heterocumulenic PK method,[8] we next focused on a thiacumulenic PK reaction using an isothiocyanate system.[8a] Despite the expectation that a thiocarbonyl bond-involved PK reaction would be a convenient method for the synthesis of thiolactones, no successful thia-PK reactions have been reported so far.

We report here an isothiocyanate PK reaction, which represents the first example of a hetero PK reaction involving a thiocarbonyl functionality. Furthermore, the present PK reaction also offers a novel and efficient synthetic method for 2*H*-thieno[2,3-*b*]indol-2-ones. Thieno[2,3-*b*]indole derivatives are also target compounds because they have potentially biological activities.[9] For example, thienodolin (**I**), which was isolated from the fermentation broth of a streptomycete strain identified as *Streptomyces albogriseolus* MJ286-76F6, has both growth promoting and inhibiting activities in rice seedlings.[10]

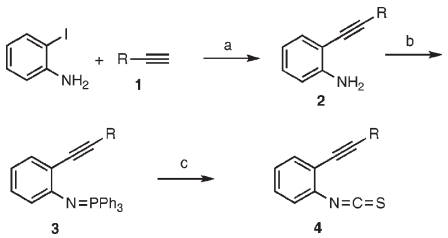


(I)

To explore the feasibility of an isothiocyanate-PK reaction and to develop a new synthetic method for the target thienoindole derivatives, we took advantage of an intramolecular variant by choosing alkynyl-isothiocyanate **4**, in which an isothiocyanate function and an alkynyl group are present as *ortho* substituents on a benzene ring. Scheme 1 illustrates our preparative method for *o*-alkynylphenyl isothiocyanates[11] **4** from commercially available *o*-iodoaniline *via* (a) Sonogashira coupling, (b) conversion to the iminophosphorane and (c) aza-Wittig reaction with CS_2. The substrates **4a**–**4h** were obtained in high yields (Table 1).

We first carried out the PK reaction of **4a** using $Co_2(CO)_8$ (Scheme 2).[1] The results are shown in Table 2. When **4a** was treated with $Co_2(CO)_8$ (1.1 equiv.) in the absence of a promoter in CH_2Cl_2 at room temperature for 40 h, the expected PK product **5a**, the 2*H*-thieno[2,3-*b*]indol-2-one, was obtained in 21% yield (entry 1). Heating in toluene or THF–dimethyl sulfoxide (DMSO)[12] was much less effective (0–8% yield of **5a**, entries 2 and 3). Remarkably, *N*-methylmorpholine-*N*-oxide (NMO, 6 equiv.)[13] promotes the reaction very well to give 2,3-dihydrothieno[2,3-*b*]indol-2-one **6a** in 46% yield together with a small amount of **5a** (2% yield, entry 4). The formation of **6a** can be regarded as a result of a reductive PK reaction.[2b,14] In fact, **6a** was formed in good yield from **5a** when isolated **5a** was treated with $Co_2(CO)_8$ (1.0 equiv.) in the presence of NMO (6 equiv.) in CH_2Cl_2.

Next, we used $Mo(CO)_6$[15] in the PK reaction of **4a** since this catalyst proved to be effective in the stoichiometric carbodiimide-PK reaction.[6a] Treatment of **4a** with $Mo(CO)_6$ in the absence of a



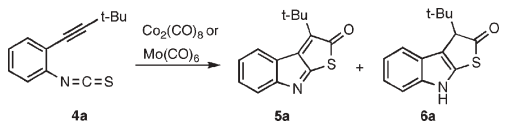
Scheme 1 Preparation of *o*-alkynyl isothiocyanates. *Reagents and conditions*: (a) $Pd(PPh_3)_2Cl_2$ (2 mol%), CuI (1 mol%), Et_3N, rt, 2 h; (b) PPh_3 (1.2 equiv.), C_2Cl_6 (1.2 equiv.), Et_3N (2.4 equiv.), benzene, rt, 4 h; (c) CS_2, rt, 12 h.

Department of Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo, 162-8601, Japan. E-mail: tsaito@rs.kagu.tus.ac.jp

† Electronic supplementary information (ESI) available: Detailed experimental procedures and characterization data for all new compounds. See DOI: 10.1039/b712739a

Table 1 Yields of isolated products **2**–**4**

Entry	R	1–4	Yield (%)		
			2	**3**	**4**
1	*t*-Bu	**a**	99	85	96
2	*i*-Pr	**b**	98	81	88
3	*n*-Bu	**c**	99	77	99
4	*n*-Pen	**d**	99	78	99
5	*n*-Hex	**e**	99	82	99
6	Bn	**f**	99	78	90
7	TMS	**g**	99	75	99
8	TBS	**h**	99	81	86



Scheme 2 Pauson–Khand reaction of **4a** with $Co_2(CO)_8$ or $Mo(CO)_6$.

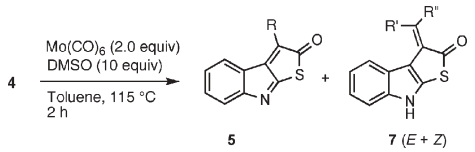
promoter in refluxing toluene resulted in a complex mixture containing only a trace amount of the expected 3-*tert*-butyl-2*H*-thieno[2,3-*b*]indol-2-one (**5a**) (entry 5). After screening promoters and reaction conditions, DMSO was found to give the best yield of **5a** (75%, entry 9).

Under the optimized reaction conditions (entry 9, Table 2), the $Mo(CO)_6$-mediated PK reactions of isothiocyanates **4b**–**4f** bearing a variety of substituents (R) on the acetylene carbon were performed (Scheme 3, Table 3). Surprisingly, the reaction of **4b** (R = *i*-Pr) afforded the H-migrated PK product **7b** in 22% yield and **5b** in 32% yield (entry 2). Compound **7b** must be formed by 1,5-H migration from **5b** rather than by the direct PK reaction of the allenylphenyl isothiocyanate generated from **4b** under the conditions, because separated **5b** was transformed into **7b** quantitatively under the same reaction conditions. The reactions of **4c**–**4f**, bearing a primary alkyl group or benzyl group at R, afforded **7c**–**7f** as *E*,*Z*-isomer mixtures (*ca.* 7 : 3) in relatively good

Table 2 Pauson–Khand reaction of **4a** with $Co_2(CO)_8$ or $Mo(CO)_6$

Entry	$M_x(CO)_y$ 1.1 equiv.	Solvent	Promoter (equiv.)	Conditions	Yield[a] (%)	
					5a	**6a**
1	$Co_2(CO)_8$	DCM	None	40 h, rt	21	0
2	$Co_2(CO)_8$	MePh	None	1 h, 115 °C	0	0
3	$Co_2(CO)_8$	THF	DMSO (5.0)	1 h, 50 °C	8	0
4	$Co_2(CO)_8$	DCM	NMO (6.0)	0.1 h, rt	2	46
5	$Mo(CO)_6$	MePh	None	3 h, 115 °C	Tr[c]	0
6	$Mo(CO)_6$	MePh	DMF (5.0)	3 h, 115 °C	0	0
7	$Mo(CO)_6$	MePh	DMF (5.0)	1 h, 115 °C	Tr[c]	0
8	$Mo(CO)_6$	MePh	DMSO (5.0)	2 h, 115 °C	60	0
9[b]	$Mo(CO)_6$	MePh	DMSO (10)	3 h, 115 °C	75	0

[a] Isolated yield. [b] 2.0 equiv. of $Mo(CO)_6$ was used. [c] Trace amount of **5a** was detected in a crude mixture.



Scheme 3 Pauson–Khand reaction of **4** with $Mo(CO)_6$.

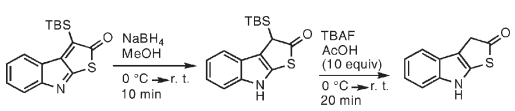
Table 3 Pauson–Khand reaction of **4** bearing a variety of substituents

Entry	**4**	R	R′	R″	Yield[a] (%)	
					5	**7** (*E* : *Z*)[b]
1	**4a**	*t*-Bu	—	—	75	—
2	**4b**	*i*-Pr	Me	Me	32	22
3	**4c**	*n*-Bu	*n*-Pr	H	0	50 (70 : 30)
4	**4d**	*n*-Pen	*n*-Bu	H	0	54 (69 : 31)
5	**4e**	*n*-Hex	*n*-Pen	H	0	59 (71 : 29)
6	**4f**	Bn	Ph	H	0	58 (>95 : 5)
7[c]	**4g**	TMS[d]	—	—	14	—
8[c]	**4h**	TBS[e]	—	—	64	—

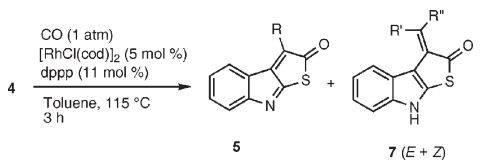
[a] Isolated yield. [b] Ratio in equilibrium. [c] Substrate **4g**,**4h** was slowly added during the reaction; time 2 h. [d] Trimethylsilyl. [e] *t*-Butyldimethylsilyl.

yields without the initial products **5c**–**5f** (entries 3–6). Isomers *E*-**7** and *Z*-**7** were separated by column chromatography on silica gel and their geometries were determined from NMR spectroscopy (NOE). It was found that they isomerized readily to reach equilibrium in $CDCl_3$. The *E* : *Z* ratios of isomers **7c**–**7f** depended upon the substituent R′. While the reaction of unsubstituted ethynylphenyl isothiocyanate **4** (R = H) failed to afford any cycloadduct **5** or **6**, the silyl substituted isothiocyanates **4g** (R = TMS) and **4h** (R = TBS) gave the corresponding PK products **5g** and **5h** in 14 and 64% yields, respectively (entries 7 and 8). Product **5h** is stable enough to allow its isolation in better yield, whereas **5g** gradually decomposes during the reaction and work-up. The TBS-substituted thienoindolone **5h** was readily converted to an analogue, **8**, of a thienodolin (**I**) precursor *via* the dihydro derivative **6h** (Scheme 4).

Since the early report of the catalytic PK reaction by Pauson and co-workers,[1b] catalytic PK reactions, including asymmetric variants, have also been extensively studied.[2] In these catalytic PK reactions, Co,[2,16] Ti,[17] Ru,[18] Rh,[19] and Ir[20] complexes were often used as transition metal catalysts. We recently succeeded with catalytic carbodiimide-PK reactions using *in situ* prepared $[RhCl(CO)dppp]_2$ under an atmospheric pressure of carbon monoxide, and therefore, we applied the catalytic system to the isothiocyanate-PK reaction (Scheme 5). Treatment of **4a** in the presence of $[RhCl(CO)dppp]_2$ (5 mol%), prepared from $[RhCl(cod)]_2$ (5 mol%) and dppp (11 mol%) under a carbon monoxide atmosphere in refluxing toluene, resulted in the formation of **5a** in only 5% yield (Table 4, entry 1). Gratifyingly, however, the isothiocyanates **4b**–**4f**, bearing various substituents



Scheme 4 Conversion of **5h** to dihydrothieno[2,3-*b*]indolone **8**.



Scheme 5 Rhodium catalyzed Pauson–Khand reaction of **4**.

Table 4 Rhodium-catalyzed Pauson–Khand reaction of **4**

					Yield[a] (%)	
Entry	**4**	R	R′	R″	**5**	**7**
1	**4a**	*t*-Bu	—	—	5	—
2	**4b**	*i*-Pr	Me	Me	Trace	52
3	**4c**	*n*-Bu	*n*-Pr	H	0	46
4	**4d**	*n*-Pen	*n*-Bu	H	0	45
5	**4e**	*n*-Hex	*n*-Pen	H	0	50
6	**4f**	Bn	Ph	H	0	50

[a] Isolated yield. *E* + *Z* mixture for **7**. dppp: diphenylphosphinopropane.

such as a secondary alkyl (*i*-Pr), primary alkyl (*n*-Bu, *n*-Pen, *n*-Hex) or arylalkyl (Bn) group on the acetylene carbon, reacted efficiently to afford the PK products **7b**–**7f** in fairly good yields.

In conclusion, we have developed stoichiometric and catalytic isothiocyanate PK reactions that are the first C=S bond-involved PK (type) cyclocarbonylations. Continued studies to extend this thia- and heterocumulenic PK method to provide thienodolin (**I**) and a variety of heterocycles are under way.

This work was partly supported by a Grant-in-Aid for Young Scientist (B) from JSPS (to T. O.).

Notes and references

1 (*a*) I. U. Khand, G. R. Knox, P. L. Pauson and W. E. Watts, *J. Chem. Soc. D*, 1971, 36; (*b*) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts and M. I. Foreman, *J. Chem. Soc., Perkin Trans. 1*, 1973, 977.

2 For reviews: (*a*) S. Laschat, A. Becheanu, T. Bell and A. Baro, *Synlett*, 2005, 2547; (*b*) L. V. R. Boñaga and M. E. Krafft, *Tetrahedron*, 2004, **60**, 9795; (*c*) J. Blanco-Urgoiti, L. Anorbe, L. Perez-Serrano, G. Dominguez and J. Perez-Castells, *Chem. Soc. Rev.*, 2004, **33**, 32.

3 (*a*) J. L. Kent, H. Wan and K. M. Brummond, *Tetrahedron Lett.*, 1995, **36**, 2407; (*b*) M. Ahmar, F. Antras and B. Cazes, *Tetrahedron Lett.*, 1995, **36**, 4417; (*c*) C. Mukai, I. Nomura, K. Yamanishi and M. Hanaoka, *Org. Lett.*, 2002, **4**, 1755.

4 For oxa-PK, Ti: (*a*) S. K. Mandal, R. Amin and W. E. Crowe, *J. Am. Chem. Soc.*, 2001, **123**, 6457; (*b*) W. E. Crowe and A. T. Vu, *J. Am. Chem. Soc.*, 1996, **118**, 1557; (*c*) N. M. Kablaoui, F. A. Hicks and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 5818; Ru: (*d*) S.-K. Kang, K.-J. Kim and Y.-T. Hong, *Angew. Chem., Int. Ed.*, 2002, **41**, 1584; (*e*) N. Chatani, T. Morimoto, Y. Fukumoto and S. Murai, *J. Am. Chem. Soc.*, 1998, **120**, 5335; Mo: (*f*) C.-M. Yu, Y.-T. Hong and J.-H. Lee, *J. Org. Chem.*, 2004, **69**, 8506; Ni: (*g*) S. Ogoshi, M. Oka and H. Kurosawa, *J. Am. Chem. Soc.*, 2004, **126**, 11802; (*h*) J. Adrio and J. C. Carretero, *J. Am. Chem. Soc.*, 2007, **129**, 778; For aza-PK, Ru: (*i*) A. Göbel and W. Imhof, *Chem. Commun.*, 2001, 593; (*j*) T. Morimoto, N. Chatani and S. Murai, *J. Am. Chem. Soc.*, 1999, **121**, 1758.

5 I. Nakamura and Y. Yamamoto, *Chem. Rev.*, 2004, **104**, 2127.

6 (*a*) T. Saito, M. Shiotani, T. Otani and T. Hasaba, *Heterocycles*, 2003, **60**, 1045 (stoichiometric); (*b*) T. Saito, K. Sugizaki, T. Otani and T. Suyama, *Org. Lett.*, 2007, **9**, 1239 (catalytic).

7 C. Mukai, T. Yoshida, M. Sorimachi and A. Odani, *Org. Lett.*, 2006, **8**, 83.

8 (*a*) This research was presented at: 85th Annual Meeting of the Chemical Society of Japan, Yokohama, March, 2005, Abstract 1B2-25; (*b*) Very recently, the Ru-catalyzed intermolecular PK type cocyclization of isocyanates has been reported. T. Kondo, M. Nomura, Y. Ura, K. Wada and T. Mitsudo, *J. Am. Chem. Soc.*, 2006, **128**, 14816; see also: (*c*) Y. Ohshiro, K. Kinugasa, T. Minami and T. Agawa, *J. Org. Chem.*, 1970, **35**, 2136; (*d*) H. Hoberg and B. W. Oster, *J. Organomet. Chem.*, 1982, **234**, C35.

9 (*a*) M. Soledade, C. Pedras and M. Suchy, *Bioorg. Med. Chem.*, 2006, **14**, 714. Despite the relative simplicity of the structure, there is only one report on the total synthesis of thienodolin (**I**): (*b*) R. Engqvist, A. Javaid and J. Bergman, *Eur. J. Org. Chem.*, 2004, 2589. For synthesis of thieno[2,3-*b*]indoles, see: (*c*) K. C. Majumdar and S. Alam, *J. Chem. Res.*, 2006, 289; (*d*) J. Levy, D. Royer, J. Guilhem, M. Cesario and C. Pascard, *Bull. Soc. Chim. Fr.*, 1987, 193; (*e*) P. Olesen, J. Hansen and M. Engelstoft, *J. Heterocycl. Chem.*, 1995, **32**, 1641.

10 (*a*) K. Kanbe, M. Okamura, S. Hattori, H. Nakagawa, K. M. Hamada, Y. Okami and T. Takeuchi, *Biosci., Biotechnol., Biochem.*, 1993, **57**, 632; (*b*) K. Kanbe, H. Nakagawa, K. T. Nakamura, Y. Okami and T. Takeuchi, *Biosci., Biotechnol., Biochem.*, 1993, **57**, 636.

11 There is a report of the preparation of isothiocyanate **4** (R = Ph) from the reaction of **2** (R = Ph) with thiophosgene: (*a*) L. Benati, G. Calestani, R. Leardini, M. Minozzi, D. Nanni, P. Spagnolo, S. Strazzari and G. Zanardi, *J. Org. Chem.*, 2003, **68**, 3454; (*b*) M. Minozzi, D. Nanni, G. Zanardi and G. Calestani, *ARKIVOC*, 2006(6), 6.

12 Y. K. Chung, B. Y. Lee, N. Jeong, M. Hudecek and P. L. Pauson, *Organometallics*, 1993, **12**, 220.

13 (*a*) S. Shambayani, W. E. Crowe and S. L. Schreiber, *Tetrahedron Lett.*, 1990, **31**, 5289; (*b*) N. Jeong, Y. K. Chung, B. Y. Lee, S. H. Lee and S.-E. Yoo, *Synlett*, 1991, 204.

14 (*a*) A.-M. Montaña, A. Moyano, M. A. Pericas and F. Serratosa, *Tetrahedron*, 1985, **41**, 5995; (*b*) C.-S. Li and E. Lacassew, *Tetrahedron Lett.*, 2002, **43**, 3565.

15 (*a*) N. Jeong, S. J. Lee, B. Y. Lee and Y. K. Chung, *Tetrahedron Lett.*, 1993, **34**, 4027; (*b*) J. L. Kent, H. Wan and K. M. Brummond, *Tetrahedron Lett.*, 1995, **36**, 2407.

16 (*a*) B. L. Pagenkopf and T. Livinghouse, *J. Am. Chem. Soc.*, 1996, **118**, 2285; (*b*) T. Sugihara and M. Yamaguchi, *Synlett*, 1998, 1384; (*c*) T. Sugihara and M. Yamaguchi, *J. Am. Chem. Soc.*, 1998, **120**, 10782; (*d*) N. Jeong, S. H. Hwang, Y. Lee and Y. K. Chung, *J. Am. Chem. Soc.*, 1994, **116**, 3159; (*e*) M. Hayashi, Y. Hashimoto, Y. Yamamoto, J. Usuki and K. Saigo, *Angew. Chem., Int. Ed.*, 2000, **39**, 631.

17 (*a*) S. C. Berk, R. B. Grossman and S. L. Buchwald, *J. Am. Chem. Soc.*, 1993, **115**, 4912; (*b*) F. A. Hicks, N. M. Kablaoui and S. L. Buchwald, *J. Am. Chem. Soc.*, 1996, **118**, 9450.

18 (*a*) T. Morimoto, N. Chatani, Y. Fukumoto and S. Murai, *J. Org. Chem.*, 1997, **62**, 3762; (*b*) T. Kondo, N. Suzuki, T. Okada and T. Mitsudo, *J. Am. Chem. Soc.*, 1997, **119**, 6187.

19 (*a*) Y. Koga, T. Kobayashi and K. Narasaka, *Chem. Lett.*, 1998, **27**, 249; (*b*) T. Kobayashi, Y. Koga and K. Narasaka, *J. Organomet. Chem.*, 2001, **624**, 73; (*c*) N. Jeong, S. Lee and B. K. Sung, *Organometallics*, 1998, **17**, 3642; (*d*) P. A. Wender, M. P. Croatt and N. M. Deschamps, *Angew. Chem., Int. Ed.*, 2006, **45**, 2459.

20 (*a*) T. Shibata and K. Takagi, *J. Am. Chem. Soc.*, 2000, **122**, 9852; (*b*) T. Shibata, S. Kadowaki, M. Hirase and K. Takagi, *Synlett*, 2003, 573; (*c*) T. Shibata, N. Toshida, M. Yamasaki, S. Maekawa and K. Takagi, *Tetrahedron*, 2005, **61**, 9974.

