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Synthesis of benzo-fused five- and six-membered heterocycles by palladium-catalyzed cyclocarbonylation

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ABSTRACT

A novel and simple synthetic methodology, based on palladium-catalyzed cyclocarbonylation reaction, is presented for preparing five- and six-membered benzo-fused heterocycles. A mechanism for the process is also proposed and discussed.

Benzimidazol-, benzoxazol-, benzothiazol-, benzoxathiol-, benzodioxol-2-ones and their derivatives are important pharmacophores which occur in both pharmaceutical and agrochemical products.[1] Due to their ability to act as a metabolically stable mimic of phenol, catechol, coumarin, phenylurethane, phenylthiouretane groups, and related compounds have a broad spectrum of biological activities. For example, the analgesic Paraflex **I**,[2] the OP2 agonist **II**,[3] the insecticide and acaricide Phosalone **III**,[4] all possess a benzoxazolone scaffold (Fig. 1). 6-Arylbenzothiazolones **IV** were examined and found to be effective for progesterone receptor (PR) antagonist activities,[5] while Benazolin **V** and Chlobenthiazone **VI** are widely used in agriculture as herbicides and fungicides, respectively.[6] A series of 2-benzoxazolones **VII** and 2-benzothiazolone **VIII**[7] derivatives were evaluated for anticonvulsant activity. A series of monoalkylated benzimidazolones **IX** were shown to stimulate chloride secretion and thus useful for the treatment of cystic fibrosis and chronic obstructive pulmonary disease,[8] (Fig. 1).

All these compounds were usually produced by the reaction of phosgene with *o*-aminophenols, or *o*-phenylenediamines, or *o*-aminothiophenols or analogous *ortho*-disubstituted compounds.[9] However, because phosgene is highly toxic and corrosive, developing a non-phosgene method is highly desirable. Then, several alternative synthetic methodologies have been reported: the reactions of *o*-aminophenols, or *o*-phenylenediamines, or catechols with dimethyl carbonate have been used for the preparation of 2-benzoxazolones, or 2-benzimidazolones or 2-benzodioxolone.[10]

Cu-catalyzed reaction of 2-haloaryl isocyanates with O or S nucleophiles leads to 2-benzothiazolones in a cascade process,[11] while 2-benzoxazolones and 2-benzimidazolones have been also synthesized, in moderate to good yields, under a high pressure of CO by one-pot reductive carbonylation of 2-nitrophenols or 2-nitroanilines, respectively, in the presence of selenium as the catalyst.[12] 2-Benzoxazolidinones[13] and 2-benzimidazolones[14] were reported to be prepared by PdI_2/KI catalyzed oxidative cyclocarbonylation starting from *o*-aminophenols or *o*-phenylenediamines, respectively. 2-Benzimidazolones[15] have been also obtained using urea derivatives for carbonylation of *o*-phenylenediamines. 2-Benzoxathiolones were synthesized by cyclization of the corresponding *S*-(2-methoxyphenyl) *N*,*N*-dimethylthiocarbamates in HI.[16] It was also reported that a short heating in formamide converts anthranylohydroxamic acids into 2-benzimidazolones almost quantitatively.[17] A novel one-pot method was found for the synthesis of 2-benzimidazolones, 2-benzoxazolone and 2-benzothiazolone via in situ generation and cyclization of *ortho*-substituted benzoic acid azides.[18] More recently, the partial reduction of a nitrobenzene in the presence of a chloroformate followed by a microwave-assisted rearrangement/ring closure sequence was also reported as a procedure to prepare 2-benzoxazolones.[19]

The growing importance of these pharmacophores drove us to develop a new and simple synthetic methodology based on our knowledge on palladium-catalyzed cyclocarbonylation reactions. This report discusses the preparation of benzo-fused five- and six-membered heterocycles through a palladium-catalyzed cyclocarbonylation of phenols, thiophenols and anilines *ortho*-substituted by OH, SH and NH groups. This novel and easy protocol of synthesis consists in a cyclocarbonylation in THF of one of

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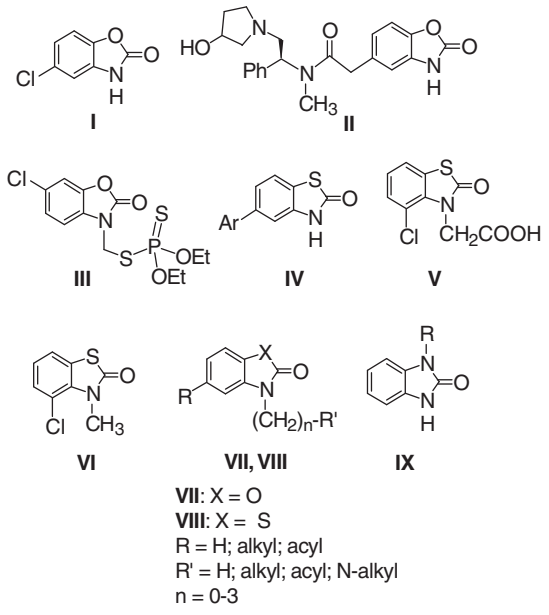
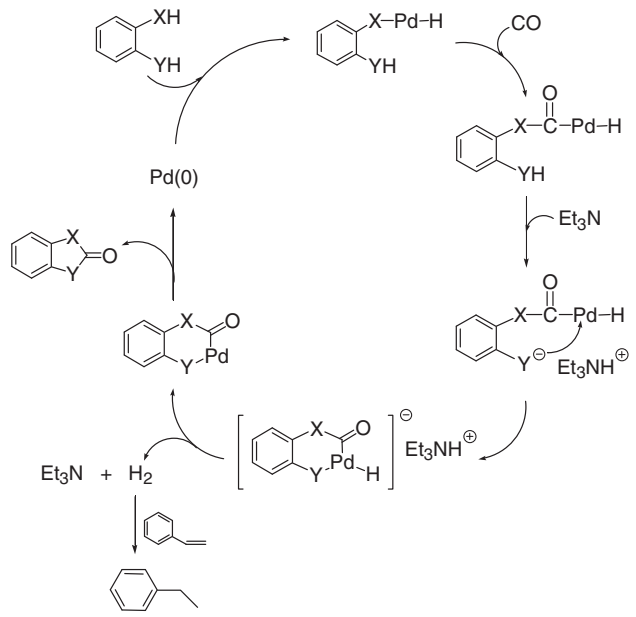
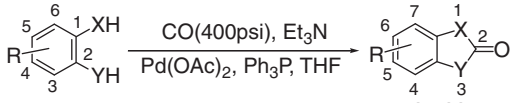


Figure 1. Biologically active benzo-fused heterocycles.



Scheme 1. Suggested mechanism for the palladium-catalyzed cyclocarbonylation reaction.

Table 1
Palladium-catalyzed cyclocarbonylation of *ortho*-substituted phenols, thiophenols and anilines



1-12 1a-11a

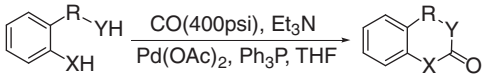
Entry	X	Y	R	Reaction time (h)	Product	Yield[a] (%)
1	O	O	H	15	**1a**[b]	89
2	O	O	4-CH_3	15	**2a**[b]	93
3	O	NH	H	60	**3a**[c]	95
4	O	S	H	15	**4a**[d]	90
5	O	S	4-OCH_3	15	**5a**[d]	92
6	O	S	6-CH_3	15	**6a**[d]	94
7	NH	NH	H	72	**7a**[e]	45
8	NH	NCH_3	H	72	**8a**[e]	60
9	S	NH	H	60	**9a**[c]	62
10	S	NH	6-CH_3	60	**10a**[f]	73
11	S	NCH_3	H	60	**11a**[c]	63
12	S	S	H	72	—	—

[a] Yield measured by GC analysis on the basis of the converted starting material.
[b] Product commercially available.
[c] Data from Ref. 7.
[d] Data from Ref. 16.
[e] Data from Ref. 19.
[f] Data from Ref. 11.

substrates **1–12** performed in autoclave under CO pressure and in the presence of Et_3N, $Pd(AcO)_2$, and Ph_3P. The reaction was carried out at 100–110 °C under magnetic stirring.[20] The optimum reaction time for a good transformation yield was obtained monitoring the starting material by gas chromatography. Compounds **1a–11a** were isolated and characterized; the spectroscopic data were consistent with assigned structures reported in the literature.[20]

Table 1 shows 12 examples of this easy cyclocarbonylation that proceeded in moderate to good yields. All reactions were completed over-night, and the lowest yields even at longer reaction times were observed using *o*-phenylenediamines as substrates.

Table 2
Synthesis of benzo-fused six-membered heterocycles by palladium-catalyzed cyclocarbonylation



13-16 13a-16a

Entry	R	Y	X	Reaction time (h)	Product	Yield[a] (%)
1	SO_2	NH	NH	72	**13a**[b]	35
2	SO_2	NCH_3	NH	72	**14a**[b]	27
3	CH_2	O	O	6	**15a**[c]	60
4	CH_2	O	NH	10	**16a**[b]	45

[a] Yield measured by GC analysis on the basis of the converted starting material.
[b] Product commercially available.
[c] Data from Ref. 21.

In order to better understand the mechanism of the cyclocarbonylation process we performed a few more experiments. Firstly, we verified that the triethylamine presence is essential for the catalytic cycle. In the absence of Et_3N the reaction times became much longer and the transformation yield very poor: after 90 h only 10% of the product was recovered. In a second instance, the generation of H_2 during the cycle has been proved by performing the reaction described in Table 1, entry 1 adding styrene (1 mmol): a partial reduction to ethylbenzene was observed at the end of the reaction. On the basis of these results we suggest the mechanism reported on Scheme 1 for the cyclocarbonylation reaction.

The starting material is first complexed by the catalyst Pd(0), then CO insertion occurs between X and Pd. The base Et_3N removes the proton from YH forming the anion that closes the ring at the Pd–H moiety affording an anionic hydropalladacycle. This latter undergoes a reductive elimination to give the benzo-fused heterocycle.

The successful cyclocarbonylation procedure described above was also applied to the preparation of benzo-fused six-membered heterocycles.

Sulfonamides **13** and **14**, *o*-hydroxybenzyl alcohol **15** and *o*-aminobenzyl alcohol **16** were reacted under the same aforementioned conditions affording compounds **13a–16a**, respectively. Yields and reaction times are summarized in Table 2. The lower yields and the longer reaction times observed for compounds **13a** and **14a** are probably due to the lowered nucleophilicity of the anionic sulfamidic NH group, responsible of the ring closure.

In summary, we have developed an efficient and simple synthetic procedure for preparing benzo-fused five- and six-membered heterocycles in good yields. Such an easy procedure can be applied to the synthesis of substrates having great pharmaceutical and agrochemical interest. Furthermore, this new protocol can be extended to the synthesis of several other heterocycles structurally comparable.

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References and notes

1. Poupaert, J.; Carato, P.; Colacino, E.; Yous, S. *Curr. Med. Chem.* **2005**, *12*, 877–885.
2. Conney, A. H.; Burns, J. J. *J. Pharmacol. Exp. Ther.* **1960**, *128*, 340–343.
3. Barber, A.; Bender, H. M.; Gottschlich, R.; Greiner, H. E.; Harting, J.; Mauler, F.; Seyfried, C. A. *Methods Find. Exp. Clin. Pharmacol.* **1999**, *21*, 105.
4. (a) Venugopal, V.; Naidu, V. G.; Prasad, P. R. *Pestology* **2003**, *27*, 29; (b) Ahmad, R.; Kookana, R. S.; Alston, A. M.; Skjemstad, J. O. *Environ. Sci. Technol.* **2001**, *35*, 878–884; (c) Sanusi, A.; Millet, M.; Mirabel, P.; Wortham, H. *Sci. Total Environ.* **2000**, *263*, 263–277.
5. Zhang, P.; Terefenko, E. A.; Wrobel, J.; Zhang, Z.; Zhu, Y.; Cohen, J.; Marschke, K. B.; Mais, D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2747–2750.
6. (a) Inoue, S.; Kato, T. *J. Pesticide Sci.* **1983**, *8*, 333; (b) Inoue, S.; Uematsu, T.; Kato, T. *J. Pesticide Sci.* **1984**, *9*, 689; (c) Wei, H.; Yang, G.-F. *Bioorg. Med. Chem.* **2006**, *14*, 8280–8285; (d) Kato-Noguchi, H.; Macias, F. A.; Molinillo, J. M. G. *J. Plant Physiol.* **2010**, *167*, 1221–1225.
7. Ucar, H.; Van Derpoorten, K.; Cacciaguerra, S.; Spampinato, S.; Stables, J. P.; Depovere, P.; Isa, M.; Masereel, B.; Delarge, J.; Poupaert, J. H. *J. Med. Chem.* **1998**, *41*, 1138–1145.
8. Singh, S.; Syme, C. A.; Singh, A. K.; Devor, D. C.; Bridges, R. J. *J. Pharmacol. Exp. Ther.* **2001**, *296*, 600–611.
9. Boyd, G. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; 8, p 178.
10. (a) Yue, F.; Toshihide, B.; Yoshio, O. *J. Catal.* **2001**, *197*, 91–97; (b) Munusamy, V.; Gopinath, C. S. *J. Catal.* **2006**, *243*, 376–388.
11. Murru, S.; Mondal, P.; Yella, R.; Patel, B. K. *Eur. J. Org. Chem.* **2009**, 5406–5413.
12. Wang, X.; Ling, G.; Xue, Y.; Lu, S. *Eur. J. Org. Chem.* **2005**, 1675–1679.
13. Gabriele, B.; Mancuso, R.; Salerno, G.; Costa, M. *J. Org. Chem.* **2003**, *68*, 601–604.
14. Gabriele, B.; Salerno, G.; Mancuso, R.; Costa, M. *J. Org. Chem.* **2004**, *69*, 4741–4750.
15. Trownsend, L. B.; Devivar, R. V.; Turk, S. R.; Nassiri, M. R.; Drach, J. C. *J. Med. Chem.* **1995**, *38*, 4098–4105.
16. Traxler, J. T. *J. Org. Chem.* **1979**, *44*, 4971–4973.
17. Porzelle, A.; Woodrow, M. D.; Tomkinson, N. C. O. *Org. Lett.* **2010**, *12*, 812–815.
18. Sridhar, R.; Perumal, P. T. *Synth. Commun.* **2004**, *34*, 735–742.
19. (a) Eckstein, Z.; Jadach, T.; Lipczynska-Kochany, E. *J. Chem. Eng. Data* **1983**, *28*, 279–281; (b) Fountain, K. R.; Pierschbacher, M. *J. Org. Chem.* **1976**, *41*, 2039–2042.
20. *General procedure for the synthesis of benzo-fused five and six-membered heterocycles.* A solution of substrate (1.0 mmol), Et_3N (2.0 mmol), $Pd(AcO)_2$ (0.02 mmol), and Ph_3P (0.08 mmol) in THF (15 mL) was pressurized by CO (400 psi) in autoclave and warmed up at 100–110 °C under magnetic stirring for the requested reaction time. The autoclave was cooled to room temperature and depressurized. The solvent was removed under reduced pressure and the crude product was purified by chromatography on Silica gel (ethyl acetate/petroleum ether 1:1). The isolated product was then characterized by ^1H NMR, ^{13}C NMR, FT-IR, GC–MS and melting point; the obtained data were in agreement with literature data.
6-Methyl-1,3-benzothiazol-2(3H)-one **10a.** White solid; mp 168−169 °C (petroleum ether); yield 73% (*via* GC). ^1H NMR (400.13 MHz; $CDCl_3$): *d* = 2.22 (s, 3H, CH_3), 6.92 (m, 2H, Ar-H_4 and Ar-H_5), 7.04 (s, 1H, Ar-H_7), 10.95 (s, 1H, NH). ^{13}C NMR (100.62 MHz; $CDCl_3$): *d* = 20.4, 110.9, 121.8, 123.2, 126.3, 131.6, 133.4, 171.0. IR (KBr): 3150 (NH), 1661 (CO). HRMS (ESI): calcd for C_8H_8NOS 166.0327 $[M+H]^+$; found 166.0326.
21. Podraza, K. F. *J. Heterocycl. Chem.* **1987**, *24*, 801.