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## A New and Efficient Palladium-catalyzed Synthesis of a 2,3,4,5-Tetrahydro-1H-2,4-benzodiazepine-1,3-dione Derivative

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Abstract: The palladium-catalyzed intramolecular cyclization of 1-butyl-1(o-iodobenzyl)-3-phenylurea 1 at 80°C in the presence of carbon monoxide at atmospheric pressure gives the corresponding 2,3,4,5-tetrahydro-1H-2,4-benzodiazepine-1,3-dione derivative 2 in 91% yield. Yield and selectivity are strongly affected by the solvent. © 1999 Elsevier Science Ltd. All rights reserved.

Palladium-catalyzed ring formation leading to seven-membered nitrogen heterocycles<sup>1</sup> has recently proved to be a valuable technique in view of the pharmaceutical interest in this class of compound.<sup>2</sup>

We now report a new and efficient synthesis of 4-butyl-phenyl-2,3,4,5-tetrahydro-1H-2,4-benzodiazepine-1,3dione 2, based on palladium-catalyzed intramolecular C-N bond formation. As far as we know, only the corresponding N,N'-dibenzyl substituted derivative has been synthesized, although in low yield.<sup>3</sup> The difficulty in preparing these compounds is probably due to their ability to undergo further transformations. The parent 2,3,4,5-tetrahydro-1H-2,4-benzodiazepine-1,3-dione could not be obtained owing to spontaneous rearrangement and ring contraction leading to the corresponding 1-oxo-2-isoindolinecarboxamide.<sup>3</sup> A suitable precursor to compound 2 is 1-butyl-1(*o*-iodobenzyl)-3-phenyl urea 1, readily prepared in two steps from *o*iodobenzyl chloride, *n*-butylamine and phenylisocyanate in 77% overall yield. Thus, compound 1 (98 mg, 0.24 mmol) and CO were heated in anisole at 80°C and atmospheric pressure for 3 h in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> (27.7 mg, 0.024 mmol) as catalyst and KOAc (35.3 mg, 0.36 mmol) as a base and gave product  $2^4$  (42% isolated yield) along with 2-butyl-2,3-dihydro-isoindol-1-one  $3^5$  in 3.5/1 ratio (from <sup>1</sup>H NMR) (Scheme 1).



Scheme 1

Compound 3 was proved to derive from compound 2 by prolonged heating (16 h) of a pure sample of 2 in anisole at 80°C, which afforded a mixture of 2 and 3 in 1.2/1 ratio. Under these conditions, compound 2 transformed into 3 by rearrangement and ring contraction, with concomitant phenylisocyanate elimination. The phenylisocyanate was isolated as diphenylurea after work-up. The achievement of a high yielding synthesis required the choice of a suitable solvent, however. We thus shifted to a polar solvent such as DMF, which was expected to stabilize the polar seven-membered ring, thus preventing rearrangement and ring contraction. We were pleased to observe that our expectation was fulfilled with yield of 2 reaching 91% in 2 h and 30 min at

The sequence leading to compound 2 requires an initial oxidative addition of Pd(0) to substrate 1 giving the corresponding trans-Pd(II) complex which has been isolated and characterized.<sup>7</sup> As with other related o-substituted arylpalladium complexes,<sup>1d,8</sup> neither the nitrogen nor oxygen of the ortho-side chain are co-ordinated to the metal. The complex undergoes carbon monoxide insertion and the NH attack on the acylpalladium complex thus formed gives 2 and liberates palladium.



Figure 1. X-ray structure of compound 2

In conclusion, the palladium-catalyzed cyclization of 1 in DMF allows us to obtain 2 with high selectivity under mild conditions.

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## **References and notes**

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- 2. Weissberger A.; Taylor E.C., eds. The Chemistry of Heterocyclic Compounds, vol. 43 (Rosowsky ed), Wiley, New York, 1984.
- 3. Felix M.A.; Fryer R.I. J. Heterocyclic Chem. 1968, 5, 291-293 and references therein.
- 4. 2: Mp (AcOEt) 114-115 °C; IR: 1680, 1651 cm<sup>-1</sup>; <sup>1</sup>H NMR: 8 0.85 (t, 3H), 1.21 (sext., 2H), 1.54 (quint., 2H), 3.45 (t, 2H), 4.00-5.00 (v br s, 2H), 7.26 (dd, 1H), 7.35-7.54 (m, 7H), 7.99 (dd, 1H). MS(CI) m/z (Rel. int.), 309 (M+H<sup>+</sup>, 55), 190 (100).
- 5. Butula Lj.; Kolbah D.; Butula I. Croat. Chem. Acta 1972, 44, 481-485.
- 6. X-ray data for compound 2:  $C_{19}H_{20}N_2O_2$ , M = 308.15, monoclinic,  $P_{21}/C$ , a = 13.118(3) Å, b = 11.069(3) Å, c = 12.606(2) Å,  $\beta$  = 115.64 (4)°, V = 1650.2(9) Å<sup>3</sup>. Data were measured on a Siemens AED diffractometer.
- 7. Pd(PPh<sub>1</sub>)<sub>4</sub> (138 mg, 0.12 mmol) and compound 1 (49 mg, 0.12 mmol) gave trans PdI[o-C<sub>6</sub>H<sub>4</sub>-CH<sub>2</sub>N(Bu)CONHPh](PPh<sub>3</sub>)<sub>2</sub> (60 mg, 48%) in dry toluene (6 mL) at r. t. under N<sub>2</sub> for 2 h. IR: 3373, 1656 cm<sup>-1</sup>; <sup>1</sup>H NMR: δ 0.85 (t, 3H), 1.04-1.16 (br sext., 2H), 1.26-1.40 (m, 2H), 2.62 (br t, 2H), 4.50 (s, 2H), 5.35 (s, 1H), 6.30 (t, 1H), 6.45 (d, 1H), 6.64 (t, 1H), 6.80-6.90 (m, 3H), 6.96 (t, 1H), 7.14 (t, 2H), 7.19-7.24 (br t, 12H), 7.28-7.33 (br t, 6H), 7.39-7.44 (m, 12H). <sup>31</sup>P NMR: δ 22.45. MS(FAB) (m/z), 1039 (M+H<sup>+</sup>), 911(M-I), 910 (M-HI).
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