Pergamon

Tetrahedron Letters 40 (1999) 2623–2624

TETRAHEDRON LETTERS

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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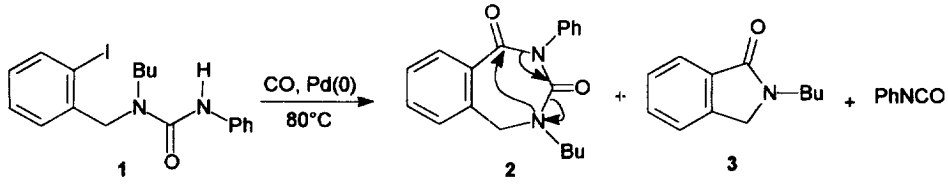
Received 7 December 1998; accepted 25 January 1999

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.

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

We now report a new and efficient synthesis of 4-butyl-phenyl-2,3,4,5-tetrahydro-*1H*-2,4-benzodiazepine-1,3-dione **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.[3] 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.[3] 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 $Pd(PPh_3)_4$ (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 ^{1}H NMR) (Scheme 1).



1 2 3

Scheme 1

PII: S0040-4039(99)00232-4

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 80°C. The structure of **2** was confirmed by X-ray analysis (Fig. 1).[6]

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.[7] As with other related *o*-substituted arylpalladium complexes,[1d,8] 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.

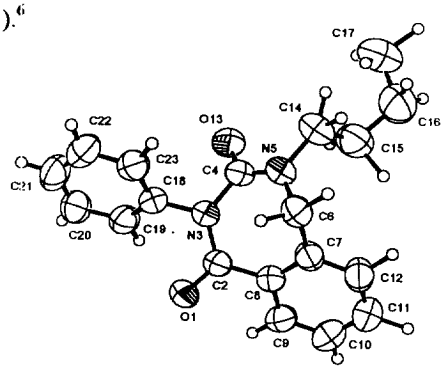


Figure 1. X-ray structure of compound **2**

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

Acknowledgement. We thank Ministero Università e Ricerca Scientifica (Progetto Nazionale di Ricerca) and National Research Council for financial support.

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^{-1}; ^1H NMR: δ 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 ($M+H^+$, 55), 190 (100).
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6. X-ray data for compound **2**: $C_{19}H_{20}N_2O_2$, M = 308.15, monoclinic, $P2_1/C$, a = 13.118(3) Å, b = 11.069(3) Å, c = 12.606(2) Å, β = 115.64 (4)°, V = 1650.2(9) $Å^3$. Data were measured on a Siemens AED diffractometer.
7. $Pd(PPh_3)_4$ (138 mg, 0.12 mmol) and compound **1** (49 mg, 0.12 mmol) gave *trans* $PdI[o\text{-}C_6H_4\text{-}CH_2N(Bu)CONHPh](PPh_3)_2$ (60 mg, 48%) in dry toluene (6 mL) at r. t. under N_2 for 2 h. IR: 3373, 1656 cm^{-1}; ^1H 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). ^{31}P NMR: δ 22.45. MS(FAB) (m/z), 1039 ($M+H^+$), 911(M-I), 910 (M-HI).
8. Brown J.M.; Pèrez-Torrente J.; Alcock N.W.; Clase H.J. *Organometallics* **1995**, *14*, 207-213.