Pergamon

Tetrahedron Letters 42 (2001) 5381–5383

TETRAHEDRON LETTERS

# A rapid and general access to 3-arylpiperidines

Isabel K. Büchner and Peter Metz*

*Institut für Organische Chemie, Technische Universität Dresden, Mommsenstraße 13, D-01062 Dresden, Germany*

Received 17 May 2001; accepted 15 June 2001

**Abstract**—A short and efficient synthetic sequence to produce a wide variety of 3-arylpiperidines from three simple building blocks is described. The key step is a palladium-catalyzed arylation of cyclopentene. 

Drugs that are able to control dopamine synthesis and/or release by action upon the autoreceptor could be beneficial for the treatment of various central nervous system related diseases.[1] Especially, agents acting selectively or at least preferentially on the presynaptic or postsynaptic site might provide a means for more specific manipulation of dopamine related neural processes as compared to the effects caused by classical dopamine antagonists or agonists. A prototype for a compound showing a selectivity of this kind is (–)-3-(3-hydroxyphenyl)-*N*-propylpiperidine [(*S*)-(–)-3-PPP, preclamol], a presynaptic agonist (autoreceptor agonist) with only partial effect on the postsynaptic site (Fig. 1). Potent dopaminergic substances, such as 3-PPP and related compounds, could be effective antipsychotic agents with therapeutic effect in the treatment of schizophrenia, Parkinson's disease, depression or drug addiction.

We have recently developed a novel access to 3-arylpiperidines **1**[2] by which a wide range of these compounds is available from three simple building blocks in only four straightforward steps (Fig. 2). All starting materials are commercially available and inexpensive.

The key step in our preparation of **1** is a high yielding Heck reaction of *meta* substituted aryl halides **2** with cyclopentene to give the 3-arylcyclopentenes **3** (Scheme 1, Table 1).[3,4] Only small amounts of the unwanted regioisomers **4** were formed at room temperature (entries a–c and e). For entries d and f–i, increasing the temperature to 80°C was necessary in order to improve the yields, which resulted in slightly higher proportions of isomers **4** for the latter cases.

Using iodobenzene (**2a**) as a model substrate, some modifications of the reaction conditions were tested to study their effect on the isomerization of **3** to **4** during the palladium-catalyzed arylation (Table 2). The presence or absence of molecular sieves or triphenylphosphine had no profound influence on the isomeric ratio when the reaction was run at room temperature (entries 1–3). However, upon changing the solvent from DMF to acetonitrile at room temperature, the percentage of **3a** in the product mixture slightly decreased (entries 6 and 7), and at 80°C in DMF small amounts of 1-phenylcyclopentene were detected in addition to **3a** and **4a** (entries 4 and 5).

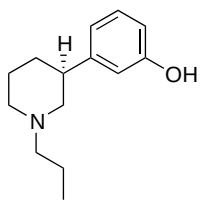



**Figure 1.** (–)-3-(3-Hydroxyphenyl)-*N*-propylpiperidine.

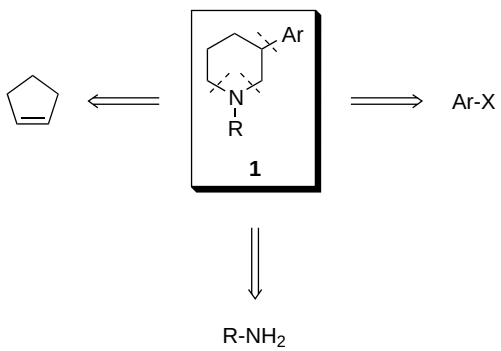
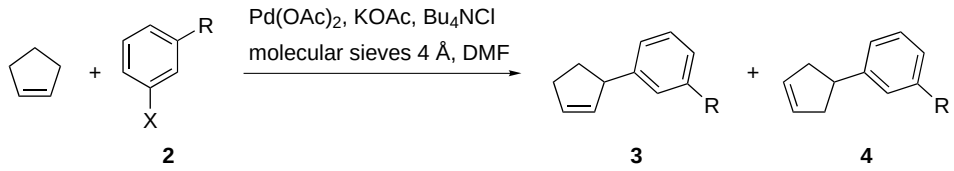



**Figure 2.** Assembly of 3-arylpiperidines from three simple building blocks.

*Keywords*: physiologically active compounds; piperidines; Heck reactions; ozonolysis.

* Corresponding author. Tel.: +49-351-463-7006; fax: +49-351-463-3162; e-mail: metz@coch01.chm.tu-dresden.de

0040-4039/01/$ - see front matter 
PII: S0040-4039(01)01045-0




**Scheme 1.**

**Table 1.** Heck reaction of *meta* substituted aryl halides **2** with cyclopentene[a]

| Entry | R | X | *T* (°C) | *t* (days) | Ratio **3**:**4**[b] | Yield **3**+**4** (%)[c] |
|---|---|---|---|---|---|---|
| **a** | H | I | rt | 1 | 94:6 | 98 |
| **b** | OMe | I | rt | 1 | 94:6 | 96 |
| **c** | CN | Br | rt | 2 | 92:8 | 95 |
| **d** | Me | I | 80 | 1 | 93:7 | 95 |
| **e** | F | I | rt | 1.5 | 92:8 | 90 |
| **f**[d] | OH | I | 80 | 1 | 87:13 | 89 |
| **g**[d] | $CH_2OH$ | I | 80 | 1 | 87:13 | 83 |
| **h**[d] | $NO_2$ | I | 80 | 1 | 86:14 | 82 |
| **i**[d] | $NH_2$ | I | 80 | 2 | 87:13 | 70 |

[a] ArX (1 mmol), cyclopentene (5 mmol), $Pd(OAc)_2$ (2.5 mol%), $Bu_4NCl$ (1 mmol), KOAc (3 mmol), DMF (5 mL), molecular sieves 4 Å (0.1 g/mmol ArX), exclusion of light, argon atmosphere.
[b] Isomeric ratio determined by GC and $^1H$ NMR.
[c] Isolated yield.
[d] $Ph_3P$ (2.5 mol%) added.

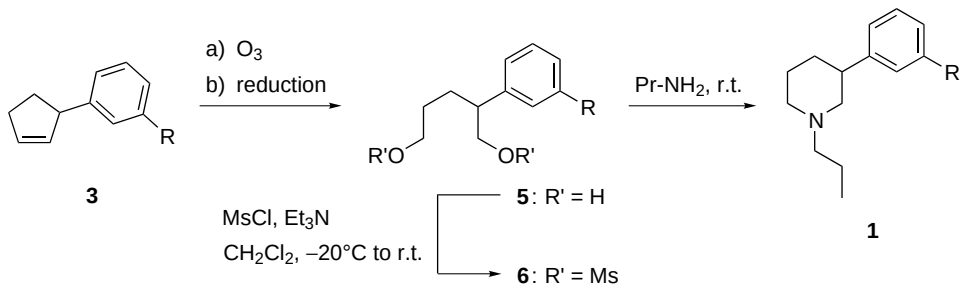
**Table 2.** Heck reaction of iodobenzene (**2a**) with cyclopentene[a]

| Entry | Solvent | *T* (°C) | Molecular sieves 4 Å (mg) | $Ph_3P$ (mmol) | Ratio **3a**:**4a**[b] |
|---|---|---|---|---|---|
| 1 | DMF | rt | 100 | 2.5 | 94:6 |
| 2 | DMF | rt | 100 | – | 94:6 |
| 3 | DMF | rt | – | 2.5 | 93:7 |
| 4 | DMF | 80 | 100 | – | 85:4:11[c] |
| 5 | DMF | 80 | – | 2.5 | 88:5:7[c] |
| 6 | MeCN | rt | 100 | 2.5 | 87:13 |
| 7 | MeCN | rt | 100 | – | 87:13 |

[a] **2a** (1 mmol), cyclopentene (5 mmol), $Pd(OAc)_2$ (2.5 mol%), $Bu_4NCl$ (1 mmol), KOAc (3 mmol), solvent (5 mL), exclusion of light, argon atmosphere.
[b] Isomeric ratio determined by GC.
[c] Ratio **3a**:**4a**:1-phenylcyclopentene.

The 3-arylcyclopentenes **3a**–**e** were ozonized followed by reductive work-up with a suitable hydride reagent to give the diols **5a**–**e** (Scheme 2, Table 3). After activation of both hydroxyl groups of **5** by mesylation under standard conditions, ring closure[5] to piperidines **1a**–**e** was smoothly achieved by treatment of the mesylates **6a**–**e** with an excess of propylamine at room temperature for 4 days.

In conclusion, the synthetic sequence described here constitutes a simple and efficient route to produce a wide variety of 3-arylpiperidines **1**. Electron-withdraw-




**Scheme 2.**

**Table 3.** Conversion of 3-arylcyclopentenes **3** to 3-arylpiperidines **1**

| Entry | R | Yield **5** (%)[a] | Yield **6** (%)[a] | Yield **1** (%)[a] |
|---|---|---|---|---|
| **a** | H | 90[b] | 100 | 85 |
| **b** | OMe | 83[c] | 97 | 62 |
| **c** | CN | 50[d] | 95 | 63 |
| **d** | Me | 81[c] | 95 | 70 |
| **e** | F | 68[c] | 100 | 90 |

[a] Isolated yield.
[b] (a) $O_3$, $CH_2Cl_2$, −78°C; (b) $LiAlH_4$, ether, rt.
[c] (a) $O_3$, MeOH, −78°C; (b) $NaBH_4$, MeOH, rt.
[d] (a) $O_3$, MeOH, −78°C; (b) $NaBH_4$, MeOH, reflux.

ing as well as electron-donating substituents in the *meta* position of the aryl moiety are both tolerated. Using an enantioselective version of the Heck reaction,[6,7] the absolute configuration of **1** would be controlled as well. Studies toward the asymmetric synthesis of **1** along these lines will be reported in due course.

## Acknowledgements

Financial support of this work by the BMBF, SMWK, Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

## References

1. (a) Lahti, A. C.; Weiler, M. A.; Corey, P. K.; Lahti, R. A.; Carlsson, A.; Tamminga, C. A. *Biol. Psychiatry* **1998**, *43*, 2–11; (b) Pirtosek, Z.; Merello, M.; Carlsson, A.; Stern, G. *Adv. Neurol.* **1996**, *69*, 535–540; (c) Clark, D.; Hjort, S.; Carlsson, A. *J. Neural Transm.* **1985**, *62*, 171–207; (d) Clark, D.; Hjort, S.; Carlsson, A. *J. Neural Transm.* **1985**, *62*, 1–52.
2. For recent synthetic work in this area, see: (a) Cervetto, L.; Demontis, G. C.; Giannaccini, G.; Longoni, B.; Macchia, B.; Macchia, M.; Martinelli, A.; Orlandini, E. *J. Med. Chem.* **1998**, *41*, 4933–4938; (b) Wong, Y.-S.; Marazano, C.; Gnecco, D.; Genisson, Y.; Chiaroni, A.; Das, B. C. *J. Org. Chem.* **1997**, *62*, 729–733; (c) Sonesson, C.; Lin, C.-H.; Hansson, L. O.; Waters, N.; Svensson, K.; Carlsson, A.; Smith, M. W.; Wikström, H. *J. Med. Chem.* **1994**, *37*, 2735–2753; (d) Grayson, N. A.; Bowen, W. D.; Rice, K. C. *Heterocycles* **1992**, *34*, 2281–2292; (e) Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1992**, *57*, 4015–4017; (f) Law, H.; Leclerc, G. A.; Neumeyer, J. L. *Tetrahedron: Asymmetry* **1991**, *2*, 989–992.
3. (a) Larock, R. C.; Gong, W. H.; Baker, B. E. *Tetrahedron Lett.* **1989**, *30*, 2603–2606; (b) Larock, R. C.; Baker, B. E. *Tetrahedron Lett.* **1988**, *29*, 905–908.
4. For current reviews, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066; (b) de Meijere, A.; Bräse, S. *J. Organomet. Chem.* **1999**, *576*, 88–110.
5. (a) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633–640; (b) Veith, H. J.; Collas, M.; Zimmer, R. *Liebigs Ann. Recueil* **1997**, 391–394.
6. Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A. *Synthesis* **1997**, 1338–1345.
7. For current reviews, see: (a) Shibasaki, M.; Vogl, E. M. In *Comprehensive Asymmetric Catalysis I–III*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, 457–487; (b) Shibasaki, M.; Vogl, E. M. *J. Organomet. Chem.* **1999**, *576*, 1–15; (c) Loiseleur, O.; Hayashi, M.; Keenan, M.; Schmees, N.; Pfaltz, A. *J. Organomet. Chem.* **1999**, *576*, 16–22.