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Palladium-catalysed phenylation of heteroaromatics in water or methylformamide under microwave irradiation

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Abstract—Rapid and efficient palladium-catalysed phenylation of heteroaromatic halides takes place under focused microwave irradiation in water or monomethylformamide. © 2001 Elsevier Science Ltd. All rights reserved.

The Suzuki reaction[1] is widely used in the synthesis of natural heterocyclic compounds such as alkaloids.[2] Ligandless palladium-catalysed Suzuki reaction on phenyl halides in aqueous media was described by Bumagin et al.[3] Recently, it was published[4] that microwave irradiation allows the activation of homogenous palladium-catalysed reaction, showing that the rate of the reaction is accelerated affording faster and cleaner chemical conversions.

It is well known that water or polar solvents are particularly interesting to dissolve polar molecules, such as heterocycles. This kind of solvent absorbs microwaves very efficiently,[5] so we decided to explore the possibility for the Suzuki reaction of an heterocyclic halide in water or polar solvents under focused microwave irradiation.

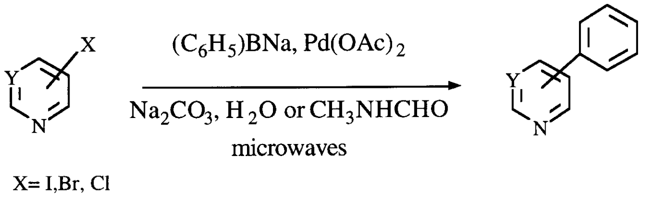
In this communication, we have used stable and commercially available sodium tetraphenylborate[6] as phenylation reagent of heteroaromatic halides with a phosphine free-palladium catalyst according to the conditions of Bumagin described for aromatic halides[3] (Scheme 1).

We have used water and monomethylformamide (MMF) as solvents. To our knowledge, MMF has not been used previously in a Suzuki coupling. MMF has a high boiling point (183°C) and is more polar ($\varepsilon=182.5$) than water ($\varepsilon=78.5$) and other amides used in microwave activated reactions[7] such as dimethylformamide (DMF, $\varepsilon=36.7$) or dimethylacetamide (DMAC, $\varepsilon=37.8$). Thus, the coupling of microwave and MMF is very strong and high temperatures can be obtained very quickly.

Because of this, we decided to carry out the Suzuki coupling reaction between different heterocycles and sodium tetraphenylborate in water or MMF as solvent under focused microwave irradiation.

All reactions were performed in a Teflon closed vessel (Ace pressure tube) under an argon atmosphere. We have used for the irradiation a resonance cavity Micro-Energie-Système (MES) at 2450 MHz as described.[9] The reactions also take place with the easy and commercially available Prolabo Synthewave 402.

The products obtained were identified by ^{1}H, ^{13}C NMR, mass spectroscopy by comparison with spectral data in the literature. The results obtained with different heterocyclic halides are presented in Table 1. Some products were previously obtained from halides by organometallic reactions catalysed by transition metals.[10–13] Comparison with literature is not easy



Scheme 1.

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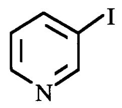
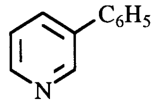
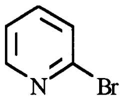
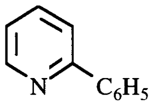
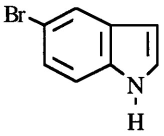
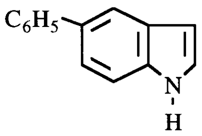
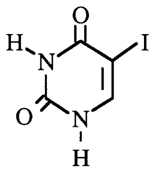
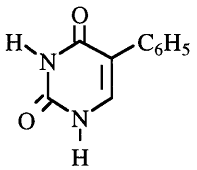
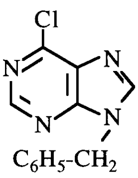
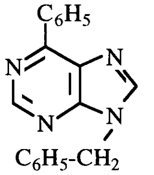
Table 1. Phenylation catalysed by palladium under mono-mode microwave irradiation[8] HetArX/$(C_6H_5)BNa/Pd(OAc)/Na_2CO_3 = 100/27/175/1$

Entry	Starting Halide	Product	Solvent /Conditions	Yield (%)	Literature
1			MMF, 100 W, 12 min	85	10
2			H2O, 160 W, 12 min MMF, 100 W, 12 min	73 84	10
3			H2O, 160 W, 10 min MMF, 100 W, 8 min	78 84	11
4			MMF, 100W, 8 min	70	12
5			MMF, 160 W, 12 min	60	13

because of the variety of organometallics used. In an experiment (no. 2) we obtained a final temperature of 105°C in water and 195°C in MMF. The reaction performed for 12 min in a preaheated oil bath (105°C for H_2O and 195°C for MMF) gave, respectively, yields of 42 and 53%. In general, under microwave irradiation better yields were obtained in MMF, perhaps because the temperature gradient and the ionisation of solvent are higher. According to the stoichiometry and the yields, it would appear that the four phenyl groups of the sodium tetraphenylboronate are available for phenylation.

In conclusion, commercially available and non-toxic sodium tetraphenylborate can be used in water or monomethylformamide for a rapid and efficient phenylation of heteroaromatic halide under mono-mode microwave irradiation.

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References

1. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483; Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263–303; Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press, 1995; Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: New York, 1995; Cornils, B.; Hermann, W. A. *Applied Homogeneous Catalysis with Organometallic Compounds*; VCH: Weinheim, 1996; Malleron, J. L.; Fiaud, J.-C.; Legros, J.-Y. *Handbook of Palladium-catalysed Reactions*; Academic Press: New York, 1997.
2. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933; Snieckus, V. *Pure Appl. Chem.* **1994**, *66*, 2155–2158.
3. Bumagin, N. A.; Bykov, V. V. *Tetrahedron* **1997**, *42*, 14437–144350.
4. Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582–9584; Villemin, D.; Jaffres, P. A.; Simeon, F. *Phosphorus Sulfur Silicon* **1997**, *130*, 59–63; Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 5583–5587; Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. *J. Org. Chem.* **1999**, *64*, 1082–1083; Olofsson, K.; Kim, S.; Larhed, M.; Curran, D.; Hallberg, A. *J. Org. Chem.* **1999**, *64*, 4539–4541.

5. *Microwave-enhanced Chemistry*, Kingston, H. M. S.; Haswell, S. J., Eds.; ACS Monography, 1998.
6. Sodium tetraphenylborate was introduced for the palladium-catalysed phenylation of allyl acetate catalysed by palladium by: Legros, J.-Y.; Fiaud, J.-C. *Tetrahedron Lett*. **1990**, *31*, 7453–7456.
7. Bose, A. J.; Manhas, M. S.; Ghosh, M.; Shah, M.; Raju, V. S.; Bari, S. S.; Nerwaz, S. N.; Banik, B. K.; Chaudhary, A. G.; Barahat, K. J. *J. Org. Chem*. **1991**, *56*, 6968–6970; Banik, B.; Barakat, K.; Wagle, D.; Manhas, M.; Bose, A. *J. Org. Chem*. **1999**, *64*, 5746–5753.
8. *Typical procedure for the synthesis of 5-phenyluracil*: A mixture of 5-iodouracil (0.5 mmol), $(C_6H_5)_4BNa$ (0.135 mmol), Na_2CO_3 (0.875 mmol) and $Pd(OAc)_2$ (5×10^{-3} mmol) was introduced in MMF (2 ml) under an argon atmosphere. The mixture was stirred and irradiated in a microwave resonance cavity[9] at 100 W during 12 min. The crude reaction product was purified by chromatography on silica gel.
9. Villemin, D.; Martin, B. *Synth. Commun*. **1995**, *25*, 2319–2326.
10. Takao, K.; Yoshinori Murata, N.; Yamanaka, H. *Tetrahedron* **1993**, *49*, 9713–9720; Katritzky, A. R., Hands, V. R. *J. Chem. Soc*. **1958**, 2202; Hanessian, S.; Kagotani, M. *Synthesis* **1987**, 409–411.
11. Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem*. **1997**, *62*, 8024–8030.
12. Matsui, M.; Kamiya, K.; Shibata, K.; Muramatsu, H. *J. Org. Chem*. **1990**, *55*, 1396–1399.
13. Gundersen, L. L.; Bakkestuen, A. K.; Aasen, A. J.; Oeveras, H.; Rise, F. *Tetrahedron* **1994**, *50*, 9743–9756; Havelkova, M.; Hocek, M.; Cesnek, M.; Dvorak, D. *Synlett* **1999**, 1145–1147.