Pergamon

Tetrahedron Letters 42 (2001) 639–642

TETRAHEDRON
LETTERS

Microwave mediated palladium-catalysed reactions on potassium fluoride/alumina without use of solvent

Didier Villemin* and Fredéric Caillot

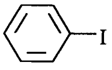
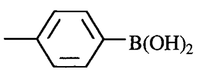
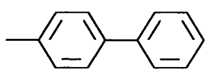
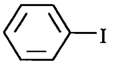
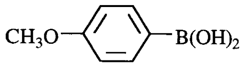
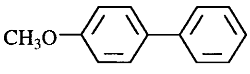
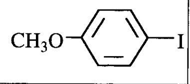
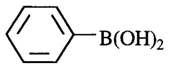
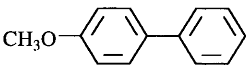
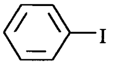
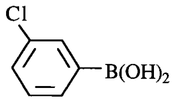
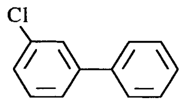
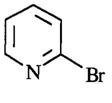
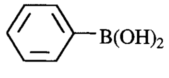
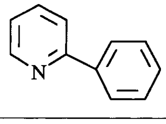
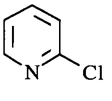
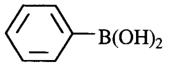
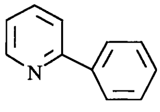
Ecole Nationale Supérieure d'Ingénieurs de Caen, ISMRA, Equipe associée au CNRS, Université de Caen, F-14050, Caen, France

Received 22 September 2000; revised 10 November 2000; accepted 14 November 2000

Abstract—Potassium fluoride on alumina was used in palladium-catalysed reactions (Suzuki, Heck, Stille, Trost–Tsuji) without solvent under mono-mode microwave irradiation. Some reactions took place in air. The organotin residue in the Stille reaction remained on the solid support. © 2001 Elsevier Science Ltd. All rights reserved.

Potassium fluoride on alumina (KF-Al_2O_3) was used as a base in various classical palladium-catalysed reactions,[1] such as the Trost–Tsuji reaction,[2a] in the synthesis of allylic thiol derivatives[2b] and more recently[2c] the Suzuki reaction. For eleven years we studied many reactions on KF-Al_2O_3[3] without solvents, Hallberg et al.[4] have shown that microwaves accelerate classical palladium reactions (Suzuki, Heck, Trost, Stille) in

Table 1. Suzuki reaction on KF-Al_2O_3 under mono-mode microwave irradiation without solvent ((A/B/$Pd(OAc)_2$ = 1/1.1/0.05; 1 mmol of A with 1 g KF-Al_2O_3)

N°	A	B	products	yield	conditions
1				98 %	15 min, 30W
2				95 %	2 min, 90W
3				82 %	2 min, 90W
4				58 %	2 min, 60W
5				66 %	5 min, 60W
6				40 %	5 min, 60W

---

* Corresponding author. Fax: +(33) 2 31 44 77; e-mail: didier.villemin@ismra.fr

0040-4039/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(00)02027-X

solution or on supported polymers. So we have decided to investigate a possible modification of these classical palladium reactions under microwave irradiation. The advantage of reactions using microwaves[5] is the simplicity of the speed of synthesis. This report describes the use of a ligand-free palladium catalyst[6] without the use of solvent under microwave irradiation. The reaction condition without use of solvent reduced toxicity and flammability. To our knowledge classical palladium reactions (Suzuki, Heck, Trost–Tsuji, Stille) under these conditions have not previously been reported.[7]

The reaction of Suzuki with palladium acetate, as the precursor of the catalyst, has produced good yields and has allowed us to obtain biphenyl derivatives (Table 1, N° 1–6). However, in the case of the acidic diphenyl derivative [with $HOOCC_6H_4B(OH)_2$ as reagent], the extraction with acetonitrile, the product, adsorbed on the support, is not easy (the yield was 10% for $C_6H_5C_6H_4COOH$ with iodobenzene) and the reaction is not of synthetic interest. The modified Suzuki reaction is possible with aromatics and heteroaromatics (Table 1, N° 5, 6). The iodide compound gave the best results but bromide and chloride can be used (Table 1, N° 5, 6).

We have used a Pd(II) complex ($Pd(OAc)_2$) in the case of the Suzuki (Table 1) and Stille reactions (see Table 2)

Table 2. Stille reaction on $KF\text{-}Al_2O_3$ under mono-mode microwave irradiation without solvent. ($A/B/Pd(OAc)_2 = 1/1.2/0.035$; 1 mmol of A with 1 g $KF\text{-}Al_2O_3$)

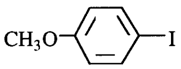
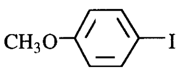
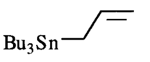
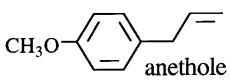
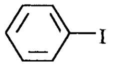
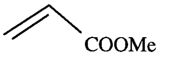
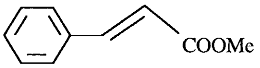
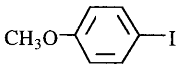
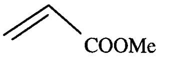
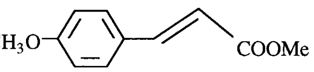
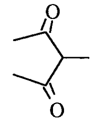
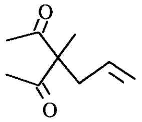
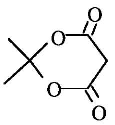
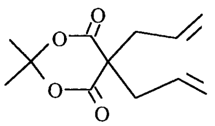
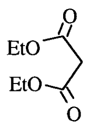
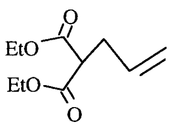
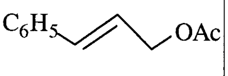
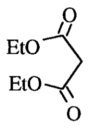
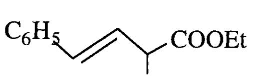
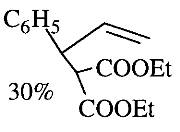
N°	A	B	products	yield	conditions
7		$(CH_3)_4Sn$		50 %	10 min, 60W
8			 anethole	68 %	10 min, 60W

Table 3. Heck and Trost–Tsuji reaction on $KF\text{-}Al_2O_3$ under mono-mode microwave irradiation without solvent ($A/B/Pd_2(dba)_3 = 1/1/0.025$; 1 mmol of A with 1 g $KF\text{-}Al_2O_3$)

N°	A	B	products	yield	conditions
9				62 %	10 min, 60W
10				68 %	10 min, 60W
11				93 %	30 min, 30W
12	2X 			98 %	30 min, 30W *
13				98 %	5 min, 60W
14			 35%  30%		5 min, 60W

* 2 eq. of allylic acetate were used

with an organometallic reagent in slight excess, in order to reduce the palladium(II) into palladium(0). In the case of Heck and Trost reactions (Table 3), a stable complex of palladium (0), [$Pd_2(dba)_3$] was used. In the Suzuki reaction and all solventless palladium-catalysed reactions described, the most important factor, in order to obtain a good yield, is to have a good dispersion of palladium complex A on KF-Al_2O_3. This dispersion was obtained by grinding the palladium catalyst with KF-Al_2O_3 before the reaction. In all palladium-catalysed reactions performed without solvent under microwave, we were unable to create reproducible results using a domestic microwave oven. This result was probably due to several factors: the small dimension of the sample irradiated (1–3 g of support), the poor control of the power and the irregular distribution of microwave irradiation. To eliminate these factors a mono-mode microwave with accurate emission control was used which gave reproducible results. We have used a mono-mode Prolabo Synthewave 402 cavity.[8]

The Stille reaction, the reactions of Heck (Table 3, N° 9–10) and the Trost–Tsuji reaction (Table 3, N° 11–14) were carried out and produced good yields under similar conditions.

The main advantage of this new methodology in the case of Stille reaction, is that the organotin residue remains adsorbed on the solid support (probably as fluorotin polymer). An elution with acetonitrile produced pure Stille reaction product, so the classical purification of the product (generally treatment with a fluoride) before biological tests is not necessary in this case.

The reactions were carried out under an inert atmosphere (argon), however some of them (Suzuki, Stille) may be carried out in air.[9] In all the reactions a slight decrease of the yield[11] has been observed [e.g.: under air the yields were respectively: N° 1 (95%), N° 2 (90%), N° 7 (50%), N° 12 (93%)]. The analyses of Suzuki, Stille and Trost–Tsuji reaction products showed that products eluted with poorly polar solvent (toluene) resulted in products free of metals (boron, tin or palladium). However, with acetonitrile some traces of palladium are observed. The comparison of yields with classical heating using a preheated oil bath has showed that reactions under microwave were faster. However the yields obtained were comparable only if the classical heating was prolonged. The increase of speed under microwave irradiation was attributed to a more direct transfer of heat.

In summary, we have demonstrated that it is possible to use KF-Al_2O_3 as a base without solvent under mono-mode microwave irradiation in classical palladium-catalysed reactions. The simplicity of experimental conditions, the resistance shown towards oxidation in the open atmosphere, the favourable safety aspects, the significant yields, rapid reaction times make this an ideal procedure for the preparation of small amounts of products.

References

1. Heck, R. F. *Palladium Reagents in Organic Synthesis*, Academic Press, 1995. Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, 1995. Cornils, B.; Hermann, W. A. *Applied Homogeneous Catalysis with Organometallic Compounds* V.C.H. 1996. Malleron, J. L.; Fiaud, J.-C.; Legros, J.-Y. *Handbook of Palladium-Catalysed Reactions*, Academic Press, 1997.
2. (a) Ferroud, D.; Genet, J. P.; Muzart, J. *Tetrahedron Lett*. **1984**, *25*, 4379–4382; Genet, J. P.; Grisoni, S. *Tetrahedron Lett*. **1986,** *27*, 4165–4168; Muzart, J.; Genet, J. P.; Denis, A. *J. Organomet. Chem*. **1987,** *326*, C23–26. (b) Goux, C.; Lhoste, P.; Sinou, D.; Muzart, J. *Sulfur Lett*. **1994**, 18, 1–8. (c) Kabalka, W.; L.Pagni, R. M.; Hair, C. M. *Org. Lett*. **1999**, *1*, 1423–1425.
3. Ben Alloum, A.; Labiad, B.; Villemin, D. *J. Chem. Soc. Chem. Commun*. **1989**, 386–387. Bram, G.; Loupy, A., Villemin, D. In *Solid Supports and Catalysts in Organic Synthesis*; K. Smith, Ed.; chap. 12, Ellis Horwood and Prentice Hall, 1992; pp. 302–326. Villemin D.; Martin, B. *Synth. Commun*. **1998**, *28*, 3195–3200 and references cited.
4. Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D. P.; Hallberg, A. *J. Org. Chem*. **1997**, *62*, 5583–5587. Larhed, M.; Hallberg, A. *J. Org. Chem*. **1996**, *61*, 9582–9584. Villemin, D.; Jaffres, P. A.; Simeon, F. *Phosphor Sulfur Silicon* **1997**, *130*, 59–63. Moberg, C.; Bremberg, U.; Hallman, K.; Svensson, M.; Norrby, P. O.; Hallberg, A.; Larhed, M.; Csoregh, I. *Pure Appl. Chem*. **1999**, *19*, 1477–1483. Vallin, K. S. A.; Larhed, M; Johansson, K.; Hallberg, A. *J. Org. Chem*. **2000**, *65*, 4537–4542. Kaiser, N. F. K.; Bremberg, U.; Larhed, M.; Moberg, C; Hallberg, A. *J. Organomet. Chem*. **2000**, 603, 2–5.
5. For a recent review on reactions under microwave irradiation without solvent: Varma, R. S. *Green Chem*. **1999**, 43–55.
6. Bumagin, N. A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437–14450.
7. Although the reaction of Heck was described with a little quantity of triethylamine[7] as solvent under microwave: DiazOrtiz, A.; Prieto, P.; Vazquez, E. *Synlett* **1997**, 269–270. Copper-palladium catalysed Sonogoshira reaction in solventlesss conditions was also recently described: Kabalka, G. W.; Wong, L.; Namboodiri, V.; Pagni, R. M. *Tetrahedron Lett*. **2000**, *41*, 5151–5154.
8. For a recent review under mono-mode microwave irradiation, see: Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis*, **1998**, 1213–1234.
9. Typical procedure (Suzuki reaction): 0.1 mmol $Pd(OAc)_2$ and 1 mmol of $ArB(OH)_2$ were mixed with a grinder (IKA A-10) with 1 g of KF-Al_2O_3 (prepared according to Ref. 10). Subsequently the mixture was placed in a pressure tube under argon and then 1 mmol of the ArI was added. The tube was irradiated with a Prolabo Synthewave 402. After the reaction was completed, the solid was extracted with toluene or acetonitrile and the solvent was evaporated in a vacuum. The residue was purified by flash chromatography on silica.

10. Villemin, D.; Ben Alloum, A. *Synthesis* **1991**, 301–303.
11. Recently different palladium catalysed reactions under heterogeneous conditions were performed in air without inhibition of catalyst: Brunner, H.; Le Cousturier de Courcy, N.; Genet, J. P. *Tetrahedron Lett*. **1999**, *40*, 4815–4818; Sripathy, V.; Chao-Jun, *Org. Lett*. **1999**, 1133–1135.