Mechanically Induced Expeditious and Selective Preparation of Disubstituted Pyridine/Pyrimidine Ferrocenyl Complexes

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Summary: Disubstituted pyridine/pyrimidine ferrocenyl complexes have been obtained by mechanically induced Sukuzi coupling reactions in the solid state. It is shown that the solventless process is much faster, and more selective, than the same reaction carried out in solution. The synthesis and structure of the complex [Fe(η^5-C_5H_4-4-C_5H_4N)(η^5-C_5H_4-3-$C_4H_3N_2$)] are reported as a test case.

Mechanically induced solid-state reactions are attracting the interest of scientists engaged in the quest for solvent-free chemical processes,[1] which are important for both environmental and topochemical reasons. Even though "mechanochemical" reactions offer valuable alternative routes for the preparation of molecular materials,[2] they have been exploited mainly with inorganic[3] and organic solids.[4] Recently, however, there have been reports on coordination polymers[5a] and supermolecules[5b] obtained by grinding transition-metal inorganic salts with appropriate ligands. We have prepared by mechanical mixing of the reactants hybrid organic−organometallic hydrogen-bonded network compounds[6c] and encapsulated inorganic cations in supramolecular organometallic cages.[6a,b] In this communication we report the synthesis of disubstituted pyridine/pyrimidine ferrocenyl complexes obtained exclusively by mechanical treatment of the solid reactants, starting from the complex ferrocene-1,1′-diboronic acid, [Fe(η^5-$C_5H_4B(OH)_2)_2$] (**1**).[7] Boronic esters and acids are thermally stable, are relatively unreactive to both oxygen and water, and are thus easily handled without special precautions. They have been utilized in a number of carbon−carbon bond-forming reactions, the most popular of which is known as Suzuki coupling.[8a,b] It has been reported that the use of an alumina/potassium fluoride mixture without solvent is very effective in palladium-catalyzed reactions, in particular in the Suzuki coupling of phenyl iodides with phenylboronic acids[9a,b] and in the synthesis of thiophene oligomers via Suzuki coupling.[9c]

We show (see Scheme 1) that the use of KF/alumina as a solid-phase support for solventless Suzuki reactions offers a convenient, environmentally friendly route to the synthesis of mono- and disubstituted pyridine and pyrimidine ferrocenyl derivatives as an alternative to the preparation in solution.[10] The synthesis[11] and structure[12] of the novel *heteroligand* complex [Fe(η^5-C_5H_4-4-C_5H_4N)(η^5-C_5H_4-3-$C_4H_3N_2$)] (**6**) are reported as a test case, see Figure 1.

All reactions were carried out in the air at room temperature. In the Suzuki reaction and in all other solventless palladium-catalyzed reactions described, it is most important, in order to obtain a good yield, to have a good dispersion of the palladium complex on KF−Al_2O_3. This dispersion was obtained by grinding the palladium catalyst with KF−Al_2O_3 before the reaction and, later, by adding to the mixture of Al_2O_3/reagents/catalyst a few drops (0.1−0.2 mL) of methanol, which were subsequently evaporated under reduced pressure. The choices of the catalyst and of the base are crucial in determining the trend of the reaction (see Table 1).

There is no formation at all of the product [Fe(η^5-C_5H_4-4-C_5H_4N)(η^5-$C_5H_4B(OH)_2$)] (**2**) when $Pd(PPh_3)_4$ is used as the catalyst, whereas this compound is formed

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(7) Ferrocene-1,1′-diboronic acid (**1**) was prepared according to: Knapp, R.; Rehahn, M. *J. Organomet. Chem.* **1993**, *452*, 235. The compound (10 mg, 0.036 mmol) was dissolved in water−acetone (1:1; 7 mL). Suitable single crystals for X-ray studies were obtained by slow evaporation of the solution at room temperature.

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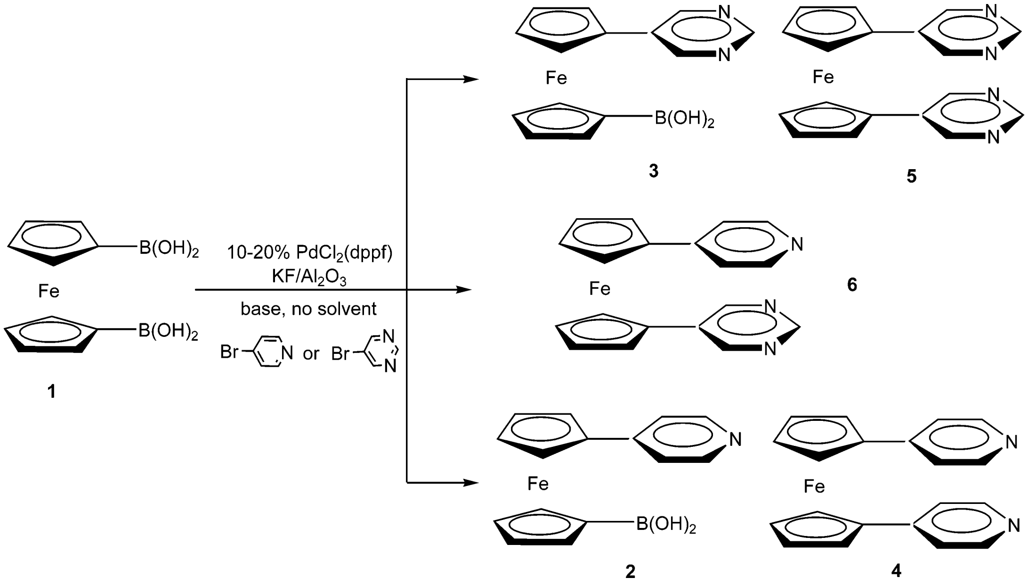
Scheme 1. Solid-State Synthesis of Mono- and Disubstituted Pyridine and Pyrimidine Ferrocenyl Derivatives



in 57% isolated yield when commercial $PdCl_2$(dppf) is employed. Both potassium hydroxide and potassium fluoride[13] are effective in inducing the solid-phase coupling reactions product $[Fe(\eta^5\text{-}C_5H_4\text{-}4\text{-}C_5H_4N)(\eta^5\text{-}C_5H_4B(OH)_2)]$ (**2**), but KOH is less effective than KF for the formation of the product $[Fe(\eta^5\text{-}C_5H_4\text{-}3\text{-}C_4H_3N_2)(\eta^5\text{-}C_5H_4B(OH)_2)]$ (**3**).

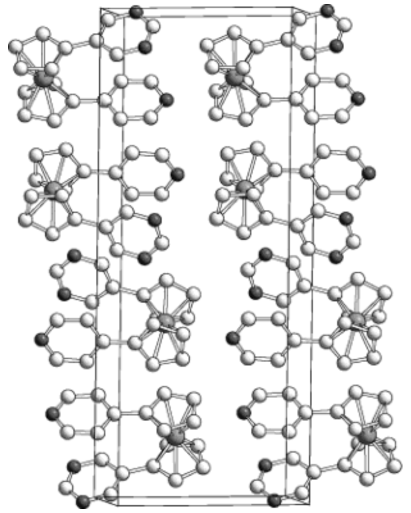


Figure 1. Structure of the *heteroligand* complex $[Fe(\eta^5\text{-}C_5H_4C_6H_4\text{-}4\text{-}C_5H_4N)(\eta^5\text{-}C_5H_4\text{-}3\text{-}C_4H_3N_2)]$ (**6**). Note how the two ligands adopt a near-eclipsed conformation in the solid state.

Table 1. Experimental Data for the Mechanically Induced Reaction between $[Fe(\eta^5\text{-}C_5H_4B(OH)_2)_2]$ (1)/ $[Fe(\eta^5\text{-}C_5H_4\text{-}4\text{-}C_5H_4N)(\eta^5\text{-}C_5H_4B(OH)_2)]$ (2) and 4-Bromopyridine/5-Bromopyrimidine

compd	cat.	base	yield (%)
2	$Pd(PPh_3)_3$	KOH	0
2	$PdCl_2$(dppf)[a]	KOH	57
2	$PdCl_2$(dppf)	KF	50
3	$PdCl_2$(dppf)	KOH	25
3	$PdCl_2$(dppf)	KF	40
4	$PdCl_2$(dppf)	KOH	30
5	$PdCl_2$(dppf)	KOH	32
6	$PdCl_2$(dppf)	KOH−KF	20

[a] dppf = 1,1′-bis(diphenylphosphino)ferrocene.

From this analysis it is shown that the use of $PdCl_2$(dppf) as catalyst and KOH/KF as base represents a reasonable standardization of the solid-state synthetic procedure in the preparation of monosubstituted ferrocenyl boronic compounds **2** and **3**. In the synthesis of the symmetric compounds **4** and **5** KOH is used, whereas the synthesis of the disubstituted pyridine/pyrimidine ferrocenyl complex **6** requires both KOH and KF. One may argue that the reaction cannot be consid-

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(11) All details are provided as Supporting Information. Example cases are as follows: the monopyridyl boronic acid $[Fe(\eta^5\text{-}C_5H_4\text{-}4\text{-}C_5H_4N)(\eta^5\text{-}C_5H_4B(OH)_2)]$ (**2**) and the monopyrimidyl boronic acid $[Fe(\eta^5\text{-}C_5H_4\text{-}4\text{-}C_3H_3N_2)(\eta^5\text{-}C_5H_4B(OH)_2)]$ (**3**) were obtained from $[Fe(\eta^5\text{-}C_5H_4B(OH)_2)_2]$ (**1**) and 4-bromopyridine and 5-bromopyrimidine, respectively, through a solventless Suzuki coupling in the presence of 10 mol % of (ddpf)$PdCl_2$ catalyst, as described in Scheme 1. $[Fe(\eta^5\text{-}C_5H_4C_6H_4\text{-}4\text{-}C_5H_4N)(\eta^5\text{-}C_5H_4\text{-}3\text{-}C_4H_3N_2)]$ (**6**) to a KF/Al_2O_2 mixture (0.725 g, 40 wt %)[16] and $PdCl_2$[1,1′-bis(diphenylphosphino)ferrocene] (0.1 equiv, 0.05 mmol, 40.8 mg) was added **2** (1 equiv, 0.5 mmol, 153.5 mg). The solid mixture was ground at room temperature in the open air until homogeneous; 5-bromopyrimidine (1.3 equiv, 0.65 mmol, 103.35 mg) was then added with grinding. The mixture was ground at room temperature for an additional 10−15 min to ensure efficient mixing. KF (1.3 equiv, 0.65 mmol, 37.7 mg) was added to accelerate the reaction. To make the mixture more homogeneous 0.1−0.2 mL of methanol was added and the slurry ground at room temperature for an additional 10 min and then evaporated under reduced pressure with a rotary evaporator. This last step was repeated 3−4 times. The reaction was followed by TLC. The mixture was separated via flash chromatography on alumina (CH_2Cl_2:MeOH = 95:5), yielding the pure product as a red solid. ^1H NMR (200 MHz, $CDCl_3$): δ 4.4035 (d, J = 3.3, 4H, Cp H), 4.647 (d, J = 7.5, 4H, Cp H), 7.01−7.19 (m, 2H, Py H), 8.38−8.45 (m, 2H, Py H), 8.54−8.63 (m, 2H, Pyr H), 8.99 (s, 1H, Pyr H). Anal. Calcd for $C_{19}H_{15}N_3Fe$: H, 4.43; C, 66.89; N, 12.32. Found: H, 4.51; C, 66.91; N, 12.20. Single crystals of **6** suitable for single-crystal X-ray diffraction were obtained by slow evaporation at room temperature of a solution obtained by dissolving the compound (20 mg, 0.033 mmol) in 3 mL of methanol.

(12) The solid-state structure of $[Fe(\eta^5\text{-}C_5H_4C_6H_4\text{-}4\text{-}C_5H_4N)(\eta^5\text{-}C_5H_4\text{-}3\text{-}C_4H_3N_2)]$ (**6**) was determined at 293 K by single-crystal X-ray diffraction on a Nonius CAD4 diffractometer equipped with a graphite monochromator (Mo Kα radiation, λ = 0.710 73 Å): monoclinic, space group $P2_1/a$, $Z = 4$, a = 7.452(2) Å, b = 22.337(4) Å, c = 9.385(1) Å, β = 103.21(2)°, V = 1521.0(6) Å^3, 2663 independent reflections (2828 measured), R1 = 0.0551, wR2 = 0.1838, GOF = 0.762. All non-H atoms were refined anisotropically. The SHELX-97 package was used for structure solution and refinement based on F^2 (Sheldrick, G. M. SHELX-97: Program for Crystal Structure Determination; University of Göttingen, Göttingen, Germany, 1997).

(13) Both potassium hydroxide and potassium fluoride were purchased from Fluka and used without further purification.

ered entirely solventless, because a tiny amount of MeOH is required for the process to take place. The role of small quantities of solvent to accelerate solid-state processes has been discussed.[14] It is also well-known that the preparation of inclusion compounds often requires *kneading*: i.e., the use of small quantities of solvent.[15] To the best of our knowledge, this is the first case of the total synthesis in the solid state, starting from $[Fe(\eta^5\text{-}C_5H_4B(OH)_2)_2]$ (**1**), of disubstituted ferrocenyl derivatives. It is worth mentioning that the previously reported solution process requires prolonged heating and that the process can only be accelerated by microwave heating.[10]

The advantages of the mechanically induced reaction described above with respect to that in solution can be summarized as follows: shorter reaction time, less workup, no need for solvent, higher or comparable yields, and, most importantly, the possibility of combining different synthetic steps in order to obtain homo- and heteroligand ferrocenyl complexes.

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Supporting Information Available: Details about the solution and mechanochemical preparations of compounds **1**−**6** as well as details of X-ray crystal structures, including tables of crystal data and structure refinement parameters, atomic coordinates, and bond lengths and angles. This material is available free of charge via the Internet at http://pubs.acs.org.

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