DOI: 10.1002/ejoc.201000961

Study on the Pd/C-Catalyzed (Retro-)Michael Addition Reaction of Activated Methylene Compounds to Electron-Poor Styrenes

Nicolai I. Nikishkin,[a] Jurriaan Huskens,[a] and Willem Verboom*[a]

Keywords: Michael addition / Palladium / C-H activation

Palladium on carbon (10 % Pd/C) efficiently catalyzes the (retro-)Michael addition of activated methylene compounds **2a–d**, such as malononitrile (**2b**), to mono- and doubly activated styrenes **1a–h** to give the adducts **3a–l**. The scope and limitations are described. The Knoevenagel condensation reaction of benzaldehyde and **2b** or ethyl cyanoacetate (**2c**) is also catalyzed by 10 % Pd/C. In these cases the Michael adducts can even be prepared in a three-component reaction. A mechanism, with as first step the oxidative addition of **2a–d** to Pd^0, is proposed.

Introduction

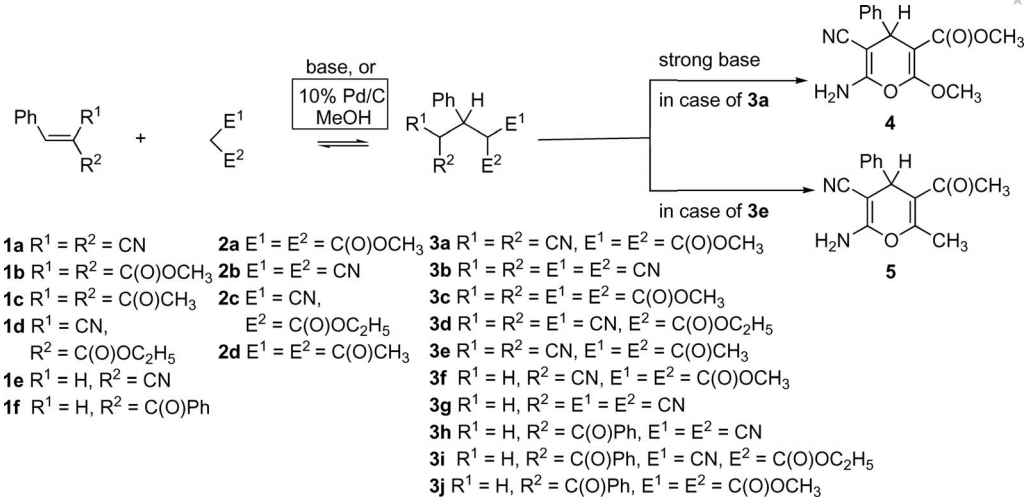
Highly substituted propanes containing two pairs of geminal electron-withdrawing groups at the 1,1- and 3,3-positions are versatile precursors for a large number of heterocyclic compounds, as, for example, 4*H*-pyranes and 4*H*-pyridines,[1,2] that are essential parts of biologically important natural products.[3,4] This type of propanes are usually prepared via a Knoevenagel condensation reaction resulting in symmetrical compounds with identical electron-withdrawing groups. However, non-symmetrical 1,1,3,3-tetrasubstituted propanes can be obtained by a Michael addition of an activated methylene compound to a Knoevenagel adduct. Over the years different studies have appeared to perform the Michael addition reaction under mild reaction conditions, e.g. making use of transition metals. It has been reported that rhodium, iridium and ruthenium polyhydride complexes are excellent catalysts for C–H bond activation of various activated methylene compounds.[5–7] Also tetrakis(triphenylphosphane)palladium(0) was reported to give satisfactory results performing the Michael addition of cyanoacetates to alkynes bearing electron-withdrawing substituents.[7] However, soluble polyhydride and low-valent transition metal complexes usually require special reaction conditions, while in addition the catalyst has to be removed from the crude reaction mixture. In the present work we report a simple palladium-catalyzed Michael addition of activated methylene compounds to mono- and doubly activated styrenes using catalytic amounts of nontoxic and easily removable palladium on activated carbon (Pd/C).

[a] Laboratory of Molecular Nanofabrication, MESA+ Institute for Nanotechnology, University of Twente,
P. O. Box 217, 7500 AE Enschede, The Netherlands
E-mail: w.verboom@utwente.nl

Results and Discussion

First we studied the formation of 1,1,3,3-tetrasubstituted propanes using a base-catalyzed Michael addition reaction (Scheme 1). Reaction of benzylidenemalononitrile (**1a**) with one equivalent of dimethyl malonate (**2a**) in the presence of a catalytic amount of a mild base such as triethylamine or pyridine in diethyl ether gave an equilibrium mixture containing 76% of the Michael adduct **3a**. Slow evaporation of the solvent induced crystallization of the product and shifted the equilibrium up to quantitative conversion. When the reaction was carried out with two equivalents of dimethyl malonate (**2a**) the Michael adduct **3a** was obtained in quantitative yield. When a stronger base is being used such as a hydroxide or alkoxide in-situ intramolecular cyclization of the Michael adduct **3a** to the 4*H*-pyran **4** takes place as recently described.[1] In our hands reaction of **1a** and **2a** in the presence of DBU as a base in diethyl ether afforded a 1:1 mixture of Michael adduct **3a** and 4*H*-pyran **4** according to the ^{1}H NMR spectrum. At the same time, base catalysis of a 1:1 mixture of dimethyl benzylidenemalonate (**1b**) and **2a** or malononitrile (**2b**) yielded no Michael adduct (**3c** or **3a**) at all.

During our studies on the further functionalisation of tetrasubstituted propanes, we attempted the selective reduction of the cyano groups in the Michael adduct **3a**. Since the ester moieties had to remain unaffected 10% Pd/C-catalyzed hydrogenation was chosen.[8] Upon hydrogenation of **3a** with 10 bar of H_2 the expected amino derivative could not be detected in the ^{1}H NMR spectrum of the crude reaction mixture. Instead the ^{1}H NMR spectrum showed signals at δ = 7.80 and 3.40 ppm, characteristic for benzylidenemalononitrile (**1a**) and dimethyl malonate (**2a**), respectively. Treatment of a solution of the Michael adduct **3a** in methanol with 10% Pd/C in the absence of H_2 for 15 h resulted, according to the ^{1}H NMR spectrum, in a clean mixture of **1a**/**2a**/**3a** of about 1:1:3. Apparently, a



Scheme 1. Palladium-catalyzed (retro-)Michael addition of activated methylene compounds to mono- and doubly activated styrenes.

retro-Michael reaction had occurred giving rise to the mixture. Conversely, stirring of a 1:1 mixture of **1a** and **2a** in methanol in the presence of 10% Pd/C gave rise to the same mixture, proving that equilibrium had been reached.

To study the scope of these Pd/C-catalyzed reactions, the behavior of the tetrafunctionalized propanes **3b**,**d** towards this catalyst was investigated (Scheme 1). In the case of the propanes **3b** and **3d**, according to the ^{1}H NMR spectra, 90% conversion was obtained resulting in an equilibrium mixture of 9:9:1 of **1a**/**2b**/**3b** and **1a**/**2c**/**3d**, respectively. The reverse reaction under identical conditions gave the same ratio.

In case of the retro-reaction of the Michael adducts **3a** and **3d** two different alkenes can be formed. In all cases the retro-Michael reaction occurred with the exclusive formation of the olefin bearing the strongest electron-withdrawing functionalities, hence having the highest thermodynamic stability.

Upon treatment of 1:1 mixtures of benzylidenemalononitrile (**1a**) and acetylacetone (**2d**) and of benzylideneacetylacetone (**1c**) and malononitrile (**2b**) with 10% Pd/C in methanol overnight the expected product **3e** could not be detected. However, a fast tandem intramolecular cyclization of in-situ formed Michael adduct **3e** took place to afford 4*H*-pyran **5** in 98% yield (Scheme 1). In addition to the correct mass, the formation of 4*H*-pyran **5** could be deduced from characteristic ^{1}H NMR signals at δ = 4.40 and 4.60. The corresponding base-catalyzed reaction gives rise to poor yields and requires thorough separation of the crude reaction mixtures containing products due to further based-catalyzed reaction of 4*H*-pyran **5** with **1a**,**c** to give pyrano[2,3-*b*]pyridines.[9]

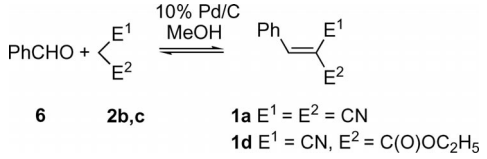
Both the character of the olefin and the activated methylene compound considerably influence the rate of the reaction. The Pd/C-catalyzed reaction of benzylidenemalononitrile (**1a**) with dimethyl malonate (**2a**) takes about 20 h before equilibrium is reached. In case of the more acidic malononitrile (**2b**) the equilibrium is already reached within 3 h. Starting from benzylidene dimethyl malonate (**1b**), the reaction is much slower. Treatment with dimethyl malonate (**2a**) did not give any reaction, even after prolonged heating. The Pd/C-catalyzed reaction with malononitrile (**2b**) proceeds very slowly; after three days there is about 30% of the Michael adduct **3a** formed which grows to 60% after six days and upon about seven days equilibrium is reached.

To further explore the scope of the Pd/C-catalyzed Michael addition reaction, a series of experiments was performed with mono-β-activated styrenes (Scheme 1). Treatment of 1:1 mixtures of cinnamonitrile (**1e**) with dimethyl malonate (**2a**) and malononitrile (**2b**) with 10% Pd/C in refluxing methanol for two days did not give rise to any reaction; the formation of the Michael adducts **3f**,**g** could not be detected. The addition of one equiv. of DBU was also unsuccessful. However, the reaction of *trans*-chalcone (**1f**) with **2b**,**c** in the presence of 10% Pd/C in methanol at room temperature gave the corresponding Michael adducts **3h** and **3i** in quantitative yield. Starting from dimethyl malonate (**2a**) the Michael adduct **3j** was only obtained in 35% yield after stirring for two days. Refluxing the reaction mixture gave rise to a complicated mixture of products. The described SmI_3-catalyzed reaction for the preparation of **3h**,**i** gives lower yields and requires chromatographic purification,[10] underlining the suitability of the Pd/C approach.

Aliphatic Michael acceptors such as isopropylidene diethyl malonate, acrylonitrile, isopropylidenemalononitrile, and neopentylidenemalononitrile failed to react with e.g. malononitrile (**2b**) under the 10% Pd/C conditions. Even after refluxing in methanol overnight, no trace of the Michael adducts could be detected in the ^{1}H NMR spectra of the crude reaction products; only starting materials were present. Apparently, the presence of the π-accepting phenyl group is a prerequisite for the reaction.

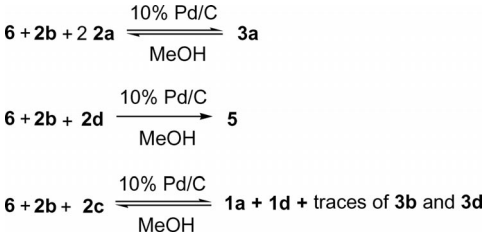
Assuming that Pd/C catalyzes the Michael addition reaction via C–H bond activation of an activated methylene compound, the influence on the Knoevenagel condensation reaction was investigated. Stirring a solution of benzaldehyde (**6**) and dimethyl malonate (**2a**) or acetylacetone (**2d**) in the presence and absence of 10% Pd/C in methanol over-

night did not give rise to any conversion. However, reaction of benzaldehyde (**6**) with ethyl cyanoacetate (**2c**) in the absence and presence of 10% Pd/C in methanol for 19 h resulted in the formation of the condensation product **1d** in 7% and 80%, respectively. The corresponding reactions with malononitrile (**2b**) for 1 h gave benzylidenemalononitrile (**1a**) in 21 and 90%, respectively (Scheme 2). These results show that the more acidic the methylene hydrogens are the faster the Knoevenagel reaction proceeds catalyzed by Pd/C.



Scheme 2. Palladium-catalyzed Knoevenagel reaction.

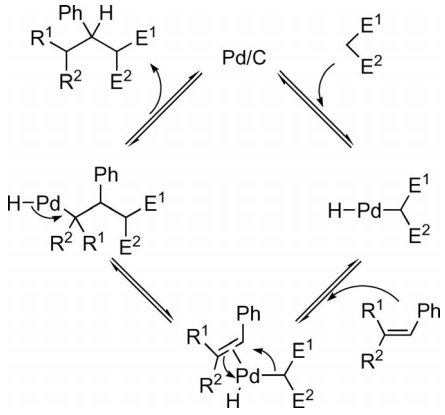
This led us to investigate a three-component reaction in which the Knoevenagel condensation product is formed in-situ. Reaction of a mixture of benzaldehyde (**6**) with malononitrile (**2b**) and two equivalents of dimethyl malonate (**2a**) in the presence of 10% Pd/C gave as expected the Michael adduct **3a** in quantitative yield (Scheme 3).



Scheme 3. Palladium-catalyzed three-component reactions.

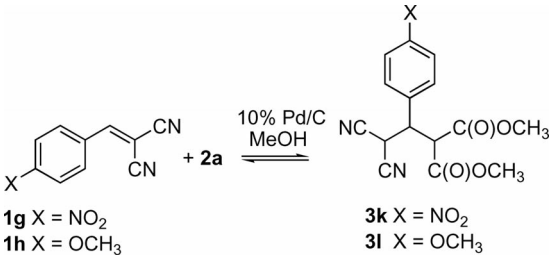
The same reaction in which **2a** was replaced by one equivalent of acetylacetone (**2d**) afforded the 4*H*-pyran **5** in quantitative yield in line with the results described above. The corresponding reaction of a 1:1:1 mixture of benzaldehyde, **2b**, and ethyl cyanoacetate (**2c**) gave a 1:1 mixture of the Knoevenagel adducts **1a**,**d** and traces of the different Michael adducts. The latter is explainable by the fact that the Michael adducts are in equilibrium with the Knoevenagel adducts in a 1:9 ratio (vide supra).

A possible mechanistic rationale that explains this unprecedented catalytic activity of palladium on carbon in a Michael addition reaction is shown in Scheme 4. Oxidative addition of an activated methylene compound to Pd^0 will furnish a Pd^{II} species. Further coordination of an activated alkene followed by a migratory insertion of the deprotonated Michael-donor into a double bond and subsequent reductive elimination will afford the Michael adduct and recover the active catalyst. The same type of oxidative addition of C–H acids to Pd^0 was also proposed as the key step in catalytic additions to allenes,[11,12] or methylenecyclopropanes.[13]



Scheme 4. Proposed catalytic cycle.

To investigate the influence of substituents on the aromatic ring of the Michael acceptor on the formation of the π-complex with palladium (Scheme 4), claimed as the prerequisite for this reaction, a series of experiments with 2-(4-nitrobenzylidene)malononitrile (**1g**) and 2-(4-methoxybenzylidene)malononitrile (**1h**), as extreme examples of substrates bearing electron-withdrawing and -donating groups, respectively, was performed (Scheme 5).



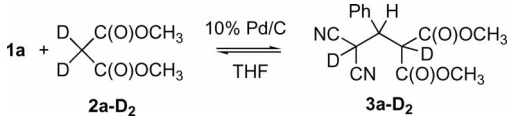
Scheme 5. Palladium-catalyzed Michael reaction with substituted benzylidenemalononitriles.

Upon reaction of **1g** with an equimolar amount of **2a** in the presence of Pd/C (10%) the desired Michael adduct **3k** was formed in 90% yield after stirring overnight. However, a different behavior was observed in case of **1h**. Stirring a 1:1 mixture of **1h** and **2a** in the presence of Pd/C (10%), the equilibrium was only set after four days; in the reaction mixture 43% of the Michael adduct **3l** was detected. Apparently, the reaction rate was considerably decreased by the presence of the strongly electron-donating methoxy group.

The obtained experimental data clearly shows that the presence of a strongly electron-withdrawing group in the aromatic ring of the Michael acceptor facilitates its coordination to the palladium center. This decreases the HOMO–LUMO gap of Michael donor and Michael acceptor and hence significantly increases the reaction rate.

To further support the proposed mechanism the palladium-catalyzed reaction of methylene-deuterated dimethyl malonate (**2a-D_2**) with benzylidenemalononitrile (**1a**) in THF as an aprotic solvent was carried out and the deuterated Michael adduct **3a-D_2** was obtained (Scheme 6). In the ^{1}H NMR spectrum the expected positions of the deuterium atoms in adduct **3a-D_2** were confirmed by the absence of

two doublets at δ = 4.90 and δ = 4.14 (in **3a**) and the presence of a singlet at δ = 3.95 for the benzylic hydrogen atom. The formation of **3a-D$_2$** indicates that oxidative insertion of Pd^0 into one of the C–D bonds of **2a-D$_2$** has taken place. Upon carbopalladation of **1a** with the Pd^{II} species, in the resulting complex reductive coupling takes place in which the D is transferred to the "malononitrile" carbon atom. The role of Pd^0 in the first step was also proven in an exchange experiment using a solution of **2a** in CD_3OD in which the presence of Pd^0 is prerequisite for H–D exchange.



Scheme 6. Deuterium-labeled Michael addition reaction.

Conclusions

In conclusion, we have demonstrated an efficient and very simple palladium-on-carbon-catalyzed (retro-)Michael addition reaction of activated methylene compounds to doubly and mono-activated styrenes that in some cases is superior to base catalysis. The catalyst is very robust, not air-sensitive, and can easily be removed.

Experimental Section

General Remarks: The solvents and all reagents were obtained from commercial sources and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity INOVA (300 MHz) spectrometer. ^{1}H NMR chemical shift values (300 MHz) are reported as δ using the residual solvent signal as an internal standard ($CDCl_3$, δ = 7.257). ^{13}C NMR chemical shift values (75 MHz) are reported as δ using the residual solvent signal as an internal standard ($CDCl_3$, δ = 77.0 ppm). Electrospray ionization (positive mode) mass spectra were recorded on a WATERS LCT mass spectrometer. The styrene derivatives **1b**,[14] **1c**,[15] **1g**,[16] and **1h**[15] and the Michael adducts **3a**,[17] **3c**,[18] **3h**,[10] **3i**,[10] **3j**,[19] **3k**,[20] and **3l**[19] were prepared according to literature procedures.

General Procedure for the Palladium-Catalyzed (Retro-)Michael Reactions: A mixture of a Michael donor (1 mmol), a Michael acceptor (1 mmol), and 10%-Pd/C (0.106 g) in methanol (10 mL) was stirred overnight (unless specified). (In case of the retro-reaction 1 mmol of the Michael adduct was used under the same conditions.) Thereafter the catalyst was filtered off and the solvent removed in vacuo. The residue was analyzed by ^{1}H NMR spectroscopy. The spectra correspond with those reported for the different compounds in literature. For the 4*H*-pyranes **4** and **5** see ref.[1,9]

General Procedure for the Palladium-Catalyzed Three-Component Reactions: A mixture of an aromatic aldehyde (1 mmol), two corresponding activated methylene compounds (1 mmol of each), and 10% Pd/C (0.106 g) in methanol (10 mL) was stirred overnight. The catalyst was filtered off from the resulting mixture and the solvent removed in vacuo. The residue was analyzed by ^{1}H NMR spectroscopy. The spectra correspond with those reported for the different compounds in literature.

Dimethyl 1,1-Dicyano-1,3-dideuterio-2-phenylpropane-3,3-dicarboxylate (3a-D$_2$): A mixture of methylene-deuterated dimethyl malonate **2a-D$_2$**[21] (0.134 g, 1 mmol), benzylidenemalononitrile (**1a**) (0.154 g, 1 mmol), and 10%-Pd/C (0.106 g) in dry THF (10 mL) was stirred for 20 h and then filtered. After removal of the solvent the ^{1}H NMR spectrum of the residue showed the formation of 76% of **3a-D$_2$**. ^{1}H NMR: δ = 7.40 (m, 5 H), 3.95 (s, 1 H), 3.86 (s, 3 H), 3.50 (s, 3 H) ppm. ^{13}C NMR: δ = 168.0, 166.6, 134.9, 133.7, 131.0, 129.9, 129.5, 128.6, 111.6, 111.5, 53.8, 53.4, 53.3, 52.8, 45.0, 44.9, 44.8, 27.9 ppm.

[1] N. S. Babu, N. Pasha, K. T. V. Rao, P. S. Sai Prasad, N. Lingaiah, *Tetrahedron Lett.* **2008**, *49*, 2730.
[2] H. Yi-Feng, X. Min, *Curr. Org. Chem.* **2010**, *14*, 379.
[3] P. R. Blakemore, C. Kilner, N. R. Norcross, P. C. Astles, *Org. Lett.* **2005**, *7*, 4721.
[4] A. Gogoll, C. Johansson, A. Axen, H. Grennberg, *Chem. Eur. J.* **2001**, *7*, 396.
[5] T. Naota, H. Taki, M. Mizuno, S. Murahashi, *J. Am. Chem. Soc.* **1989**, *111*, 5954.
[6] S. Paganelli, A. Schionato, C. Botteghi, *Tetrahedron Lett.* **1991**, *32*, 2807.
[7] S. Murahashi, T. Naota, Y. Nakano, *Synlett* **2009**, 3355.
[8] R. C. Larock, in: *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd ed., Wiley-VCH, New York, **1999**.
[9] N. Martin, C. Seoane, J. L. Soto, *Tetrahedron* **1988**, *44*, 5861.
[10] Y. M. Ma, Y. M. Zhang, *Synth. Commun.* **2002**, *32*, 819.
[11] Y. Yamamoto, M. AI-Masum, N. Asao, *J. Am. Chem. Soc.* **1994**, *116*, 6019; M. Meguro, S. Kamijo, Y. Yamamoto, *Tetrahedron Lett.* **1996**, *37*, 7453.
[12] B. M. Trost, V. J. Gerusz, *J. Am. Chem. Soc.* **1995**, *117*, 5156.
[13] N. Tsukada, A. Shibuya, I. Nakamura, Y. Yamamoto, *J. Am. Chem. Soc.* **1997**, *119*, 8123.
[14] E. S. Putilova, N. A. Troitskii, S. G. Zlotin, *Russ. Chem. Bull., Int. Ed.* **2005**, *54*, 1233 (*Izv. Akad. Nauk, Ser. Khim.* **2005**, 1199).
[15] A. B. Smith, Z. Liu, *Org. Lett.* **2008**, *10*, 4363.
[16] S. M. Saad, J. M. Abdalla, N. E. Nashed, *Mikrochimica Acta* **1984**, *83*, 27.
[17] M. N. Elinson, S. K. Feducovich, T. A. Zaimovskaya, A. N. Vereshchagin, S. V. Gorbunov, G. I. Nikishin, *Russ. Chem. Bull., Int. Ed.* **2005**, *54*, 1593 (*Izv. Akad. Nauk, Ser. Khim.* **2005**, 1547).
[18] C. F. Bernasconi, J. L. Zitomer, J. P. Fox, K. A. Howard, *J. Org. Chem.* **1984**, *49*, 482.
[19] H. Sasai, T. Arai, Y. Satow, K. N. Houk, M. Shibasaki, *J. Am. Chem. Soc.* **1995**, *117*, 6194.
[20] T. Lemek, H. Mayr, *J. Org. Chem.* **2003**, *68*, 6880.
[21] D. J. Hupe, E. R. Pohl, *J. Am. Chem. Soc.* **1984**, *106*, 5634.

Received: July 8, 2010
Published Online: October 22, 2010

