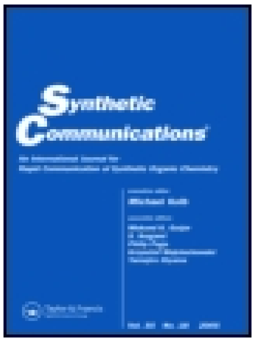

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4-Amino-3-pentadecyl-3*H*-1,2,4-triazole-3-thiones and 3-pentadecyl-1,3,4-oxadiazole-2(3*H*)-thione for the preparation of dimeric palladium(II) complexes and their applications in Tsuji–Trost and Mizoroki–Heck reactions

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ABSTRACT

The synthesis of palladium complexes derived from 4-amino-3-pentadecyl-3*H*-1,2,4-triazole-3-thiones and 3-pentadecyl-1,3,4-oxadiazole-2(3*H*)-thiones are reported. They were obtained from palladium acetate and dipotassium tetrachloropalladate(II) and their composition was assigned by elemental analysis (solid state). The resulting metallic entities were also characterized in solution based in mass spectrometry experiments. Their application in organic synthesis as cross-coupling reaction catalysts is described. One example of both conventional Tsuji–Trost and Mizoroki–Heck reactions were efficiently carried out in very high chemical yield.

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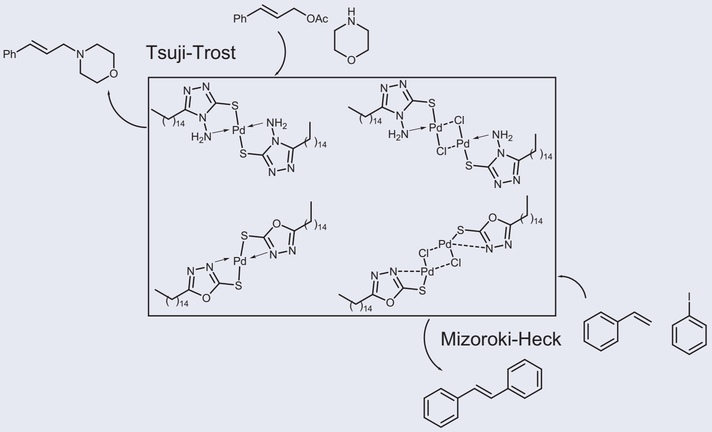
KEYWORDS
Mizoroki–Heck; palladium; palmitic acid; Tsuji–Trost

GRAPHICAL ABSTRACT



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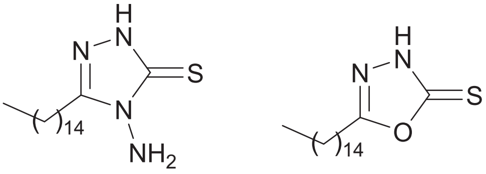


1 **2**

Figure 1. Fatty acid derivatives **1** and **2**.

Introduction

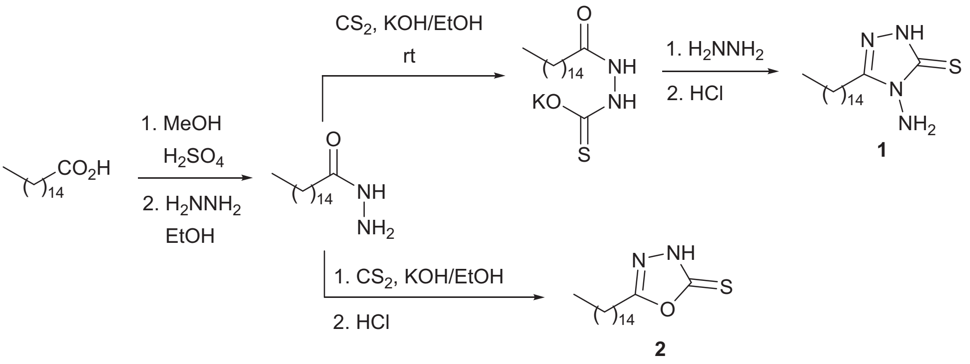
It is very well known that fatty acids possess many crucial functions in the organism. During the last two decades, the importance of these compounds in the treatment of cancer,[1] among other degenerative pathologies as, for example, Alzheimer's disease and type 2 diabetic dementia,[2] acquired an enormous dimension. In this context, several classes of molecules derived from fatty acids have received the same interest. For example, 4-amino-3-pentadecyl-3*H*-1,2,4-triazole-3-thione **1** and its corresponding 3*H*-(1,3,4)-oxadiazol-2-thione **2** (Fig. 1) have been prepared[3,4] and next their biological and other interesting properties were evaluated by several groups. These families of compounds exhibited antidepressant,[5] antitumor,[4,6] antimicrobial and antioxidant activities,[7] corrosion inhibitors of carbon steel,[8] etc.

In addition, these molecules **1** and **2** demonstrated to be good ligands in the preparation and characterization of salen-type complexes of cobalt(II), nickel(II) and copper(II) with Schiff bases derived from substituted salicylaldehydes.[9] However, to the best of our knowledge, no palladium(II) complexes of these ligands have been reported yet.[10] So, in this work, the corresponding complexes derived from heterocycles **1** and **2** will be prepared, and immediately their efficiency as catalysts[11] will be evaluated in two conventional processes such as standard Tsuji–Trost and Mizoroki–Heck reactions.

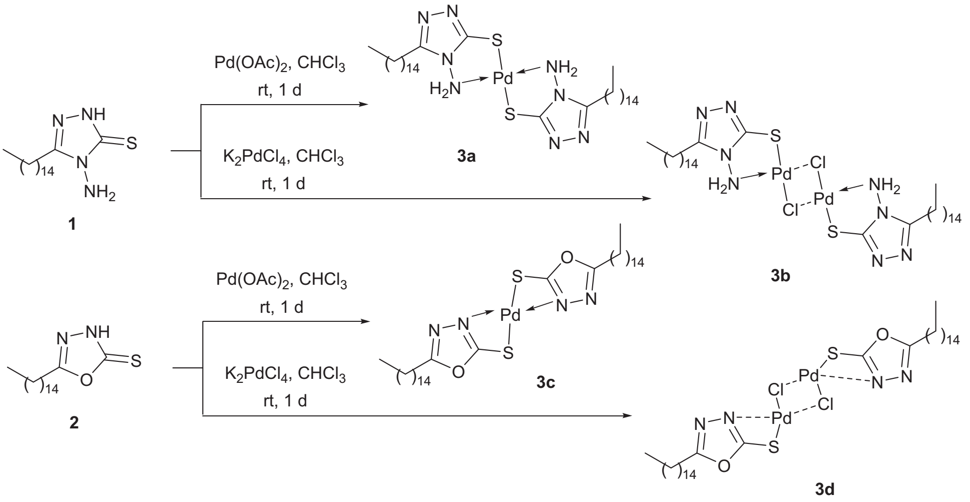
Discussion

Initially, the preparation of the heterocyclic ligands **1** and **2** was performed, according to the literature, starting from palmitic acid[3,4] (Scheme 1). This route consisted in the preparation of the corresponding hydrazide and further reaction with carbon disulfide and final acid-mediated cyclization in the presence of hydrazine or in absence of the latter.[12]

Next step was the preparation of the palladium(II) complexes. For this purpose, the formation of palladium(II) complexes from heterocyclic-2-thiones was selected as model employing, palladium(II) acetate or K_2PdCl_4 as palladium sources.[13–15] After reaction of heterocycles **1** and **2** with these salts in chloroform, at room temperature, for 24 h (Scheme 2) the resulting complexes **3a–d** were obtained. The tentative structures shown in Scheme 2 corresponded to the information obtained in solid state and in solution. No signal of acetate anion was detected by NMR of samples **3a** and **3d**. Unfortunately,



Scheme 1. Synthesis of heterocycles **1** and **2**.

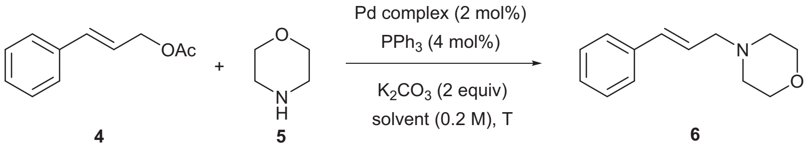


Scheme 2. Synthesis of palladium complexes **3a–d**.

NMR did not give very useful information about the real structure present in solution, possibly several complexes are present in chloroform in such a way that carbonyl group signals in ^{13}C NMR disappeared. MS was recorded using electrospray ionization (ESI) in a mixture of water/acetonitrile revealing that palladium complexes **3a** and **3b** or **3c** and **3d** exhibited a mixture of aggregates confirming the existence of dimeric species in different ratios and also coordinated with molecules of solvents employed during the analyses (MeCN and water).

After a careful washing of the four palladium complexes, with methanol/water, microanalysis was performed. The elemental analysis revealed that, in solid state, it is appropriate to draw the structure of **3a** and**3c**for complexes formed using palladium(II) acetate. Combustion data of palladium complexes **3b** and **3d** provided a high content in chlorine, so it was possible to represent these dimeric bridged structures in the solid state.

With these four complexes in hand, the study of their catalytic activity in the palladium-promoted carbon–nitrogen and carbon–carbon bond coupling reactions were



Scheme 3. Synthesis of compound **6** using palladium complexes **3a–d**.

Table 1. Synthesis of product **6** through a Tsuji–Trost reaction[a].

Entry	Pd complex (mol%)	Base	Solvent	Additive	*T* (°C)[b]	*T* (h)	Yield (%)
1	**3a** (2)	TMG	EtOH	—	80 (A)	19	70[c]
2	**3a** (2)	K_2CO_3	EtOH	—	80 (A)	19	76[c]
3	**3a** (2)	TMG	H_2O	CTAB	80 (A)	19	45[c]
4	**3a** (2)	K_2CO_3	H_2O	CTAB	80 (A)	19	43[c]
5	**3a** (2)	K_2CO_3	MeCN	—	80 (A)	19	67[c]
6	**3a** (2)	K_2CO_3	$MeCN_{dry}$	—	80 (A)	19	81
7	**3a** (2)	K_2CO_3	$MeCN_{dry}$	—	110 (A)	19	93
8	**3a** (1)	K_2CO_3	$MeCN_{dry}$	—	110 (A)	19	67
9	**3b** (2)	K_2CO_3	$MeCN_{dry}$	—	110 (A)	19	90
10	**3c** (2)	K_2CO_3	$MeCN_{dry}$	—	110 (A)	19	61
11	**3d** (2)	K_2CO_3	$MeCN_{dry}$	—	110 (A)	19	52
12	**3a** (2)	K_2CO_3	$MeCN_{dry}$	—	50 (B)	1	25
13	**3a** (2)	K_2CO_3	$MeCN_{dry}$	—	75 (B)	1	35
14	**3a** (2)	K_2CO_3	$MeCN_{dry}$	—	100 (B)	1	93
15	**3b** (2)	K_2CO_3	$MeCN_{dry}$	—	100 (B)	1	93
16	**3c** (2)	K_2CO_3	$MeCN_{dry}$	—	100 (B)	1	91
17	**3d** (2)	K_2CO_3	$MeCN_{dry}$	—	100 (B)	1	92

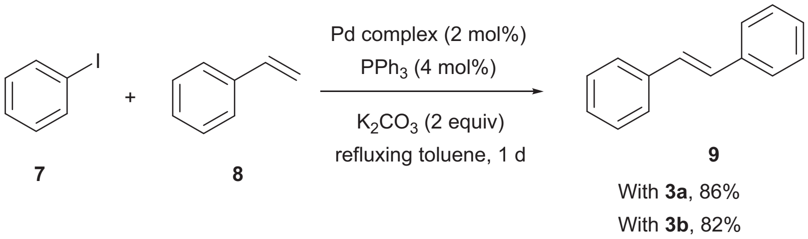
[a] The corresponding amount of palladium species **3** and PPh_3 were mixed for 1 h and then, a solution of 1 mmol of both **4** and **5**, and the additive was added. The resulting mixture was stirred at the temperature and reaction times indicated. Evaporation of the solvent and flash chromatography of the crude residue afforded pure product **6**.

[b] Method A: conventional heating in a sealed pressure tube; Method B: 50 W microwave irradiation at different temperatures.

[c] Variable proportions of cinnamyl alcohol were also isolated.

surveyed. These palladium species were freshly prepared and immediately employed in the Tsuji–Trost[16] reaction and in the Mizoroki–Heck[17] transformation.

For the first reaction, we took – as reference – the work of Billamboz et al.[18,19] in which cinnamyl acetate (**4**) was allowed to react with morpholine (**5**) using several conditions (Scheme 3 and Table 1) to afford the substitution product **6**. Two calefaction methods were employed. Method A involved a conventional heating in a sealed pressure tube, meanwhile Method B represented a 50 W microwave irradiation at different temperatures. Starting with the optimization process using palladium complex **3a**, Method A revealed that ethanol was not an appropriate solvent either with tetramethylguanidine (TMG) or potassium carbonate because large amounts ($>10\%$) of cinnamyl alcohol were isolated (Table 1, entries 1 and 2). Using water as solvent (Table 1, entries 3 and 4), an analogous situation was observed but with more than 15% content of cinnamyl alcohol. With acetonitrile the generation of this alcohol was diminished and with dry acetonitrile was suppressed (Table 1, entries 5 and 6). The increment of the temperature to 110 °C afforded a higher yield (93%) being the 2 mol% the optimal catalyst loading (Table 1, entries 7 and 8). Under this reaction conditions complex **3b** afforded similar chemical yield than that obtained one for complex **3a** (Table 1, entry 9). However, palladium dimers **3c** and **3d** did not catalyze the Tsuji–Trost reaction so efficiently (Table 1, entries 10 and 11). Using Method B reaction times were shorter and the



Scheme 4. Study of the Mizoroki–Heck reaction using complexes **3a** and **3b**.

highest yields were achieved by catalysts **3a** and **3b** at 100 °C for 1 h (Table 1, entries 12–17) although catalytic complexes **3c** and **3d** were also effective under these conditions. The presence of the triphenylphosphine was crucial for obtaining high conversions and good chemical yields of the desired product **6**.

Once demonstrated the best catalytic performance of palladium complexes **3a** and **3b**, they were tested in the same proportion in the Mizoroki–Heck reaction between iodobenzene (**7**) and styrene (**8**) to give exclusively *E*-stilbene **9** in 86% and 82% yield, respectively (Scheme 4).

Conclusions

This new synthesized palladium complexes were prone to form dimeric arrangements as revealed data in solid state. In solution, this aggregates looked relatively strong and they preferentially formed dimeric structures too. The efficiency of these robust palladium(II) complexes was demonstrated in the classical Tsuji–Trost and Mizoroki–Heck reactions. The long chain (pentadecyl) was introduced with the purpose of the recovery of these complexes and their use in another catalytic process, but no results were obtained and more work is currently underway.

Experimental part

General synthetic procedure for the Tsuji-Trost reaction

Method A: Cinnamyl acetate (40 mg, 0.2 mmol), morpholine (35 mg, 0.4 mmol) K_2CO_3 (55.2 mg, 0.4 mmol), complex **3a** or **3b** (0.004 mmol, 2 mol%), and PPh_3 (2.1 mg, 0.008 mmol, 4 mol%) were suspended in dry MeCN (1 mL, 0.2M) in a pressure tube for 1 h. The mixture was heated at 110 °C in a sand bath for 19 h. Water was added (5 mL) and it was extracted with ethyl acetate (3 × 5 mL). The organic solvent was dried, filtered, evaporated and purified by column chromatography.

Method B: Cinnamyl acetate (40 mg, 0.2 mmol), morpholine (35 mg, 0.4 mmol) K_2CO_3 (55.2 mg, 0.4 mmol), complex **3a** or **3b** (0.004 mmol, 2 mol%), and PPh_3 (2.1 mg, 0.008 mmol, 4 mol%) were suspended in dry MeCN (1 mL, 0.2M). The mixture was heated at 100 °C in the microwave oven at 50 W for 1 h. Water was added (5 mL) and it was extracted with ethyl acetate (3x5 mL). The organic solvent was dried, filtered, evaporated and purified by column chromatographyfurnishing product **6**[15,16] as colorless oil, 44 mg, 93%.

General synthetic procedures for the Mizoroki–Heck reaction

Iodobenzene (41 mg, 0.2 mmol), styrene (21 mg, 0.2 mmol), K_2CO_3 (55.2 mg, 0.4 mmol), complex **3a** or **3b** (0.004 mmol, 2 mol%), and PPh_3 (2.1 mg, 0.008 mmol, 4 mol%) were suspended in toluene (3 mL) in a pressure tube. The mixture was heated at 110 °C in a sand bath for 24 h. Water was added (5 mL) and it was extracted with ethyl acetate (3 × 5 mL). The organic solvent was dried, filtered, evaporated and purified by column chromatography affording pure **9** (Commercially available compound) as colorless oil, 31 mg 86% or 30 mg 82%.

Supplementary information (SI)

Supplementary material includes the characterization data of known compounds **1** and **2** ^{1}H and ^{13}CNMR spectra of compounds **6**, **9**, and complexes **3a–d** and ESI of complexes **3a–d**.

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References

[1] (a) Amiri, M.; Yousefnia, S.; Forootan, F. S.; Peymani, M.; Ghaedi, K.; Esfahani, M. H. N. *Gene* **2018**, *676*, 171–183. (b) Torres, C.; Díaz, A. M.; Príncipe, D. R.; Grippo, P. J. *Curr. Med. Chem.* **2018**, *25*, 2608–2623. DOI: 10.2174/0929867324666170616111225.

[2] Chen, J.-J.; Gong, Y.-H.; He, L. *J. Drug Target* **2019**, *27*, 347–354. DOI: 10.1080/1061186X.2018.1491979.

[3] Yildirim, A.; Öztürk, S. *Phosphorus, Sulfur Silicon Relat. Elem.* **2015**, *190*, 1535–1550. DOI: 10.1080/10426507.2014.999067.

[4] Ahmad, A.; Varshney, H.; Rauf, A.; Sherwani, A.; Owais, M. *Arab. J. Chem.* **2017**, *10*, S3347–S3357. DOI: 10.1016/j.arabjc.2014.01.015.

[5] Jubie, S.; Dhanabal, P.; Azam, M. A.; Kumar, N. S.; Ambhore, N.; Kalirajan, R. *Med. Chem. Res.* **2015**, *24*, 1605–1616. DOI: 10.1007/s00044-014-1235-2.

[6] Salah El-Din Mohamed, F.; Hashem, A. I.; Swellem, R. H.; Abd El-Moaen Mohamed Nawwar, G. *LDDD.* **2014**, *11*, 304–315. DOI: 10.2174/1570180811310000072.

[7] (a) Abd El Salam, H. A.; Yakout El-Sayed, M. A.; Nawwar, G. A. M.; El-Hashash, M. A.; Mossa, A.-T. H. *Monatsh. Chem.* **2017**, *148*, 291–304. (b) Othman, A. A.; Kihel, M.; Amara, A. *Arabian J. Chem.* **2016**, *9*, s1840–s1846. DOI: 10.1016/j.arabjc.2012.05.005.

[8] (a) Sobhi, M.; El-Sayed, R.; Abdallah, M. *J. Surfact. Deterg.* **2013**, *16*, 937–946. (b) Khiati, Z.; Othman, A. A.; Sanchez-Moreno, M.; Bernard, M.-C.; Joiret, S.; Sutter, E. M. M.; Vivier, V. *Corrosion Sci.* **2011**, *53*, 3092–3099. DOI: 10.1016/j.corsci.2011.05.042.

[9] Patil, N.; Akkasali, R. *Int. J. Chem. Sci.* **2010**, *8*, 1193–1199.

[10] For recent reviews about palladium-catalysed processes, see: (a) Devendar, P.; Qu, R.-Y.; Kang, W. M.; He, B.; Yang, G. F. *J. Agric. Food Chem.* **2018**, *66*, 8914–8934. (b) Biffis, A.; Centomo, P.; Del Zotto, A.; Zecca, M. *Chem. Rev.* **2018**, *118*, 2249–2295. (c) Roy, D.; Uozumi, Y. *Adv. Synth. Catal.* **2018**, *360*, 602–625. DOI: 10.1002/adsc.201700810.

[11] Biffis, A.; Centomo, P.; Del Zotto, A.; Zecca, M. *Chem. Rev.* **2018**, *118*, 2249–2295. DOI: 10.1021/acs.chemrev.7b00443.

[12] Espinosa, J. C.; Navalón, S.; Álvaro, M.; Dhakshinamoorthy, A.; García, H. *ACS Sustainable Chem. Eng.* **2018**, *6*, 5607–5614. DOI: 10.1021/acssuschemeng.8b00638.

[13] Riera, X.; Moreno, V.; Freisinger, E.; Lippert, B. *Inorg. Chim. Acta* **2002**, *339*, 253–264. DOI: 10.1016/S0020-1693(02)00957-X.

[14] Faraglia, G.; Sitran, S.; Montagner, D. *Inorg. Chim. Acta* **2005**, *358*, 971–980. DOI: 10.1016/j.ica.2004.09.063.

[15] Tirmizi, S. A.; Nadeem, S.; Hameed, A.; Wattoo, M. H. S.; Anwar, A.; Ansari, Z. A.; Ahmad, S. *Spectroscopy* **2009**, *23*, 299–306. DOI: 10.1155/2009/763231.

[16] For general reviews about Tsuji-Trost reaction, see: (a) Qian, J.; Jiang, G. *CCAT* **2017**, *6*, 25–30. (b) Trost, B. M. *Tetrahedron* **2015**, *71*, 5708–5733. DOI: 10.1016/j.tet.2015.06.044.

[17] For general reviews about Mizoroki-Heck reaction, see: (a) Jagtap, S. *Catalysts* **2017**, *7*, 1–53. (b) Watson, W. J. *Org. Process Res. Dev.* **2010**, *14*, 748–748. DOI: 10.1021/op1000918.

[18] Billamboz, M.; Mangin, F.; Drillaud, N.; Chevrin-Villette, C.; Banaszak-Léonard, E.; Len, C. *J. Org. Chem.* **2014**, *79*, 493–500. DOI: 10.1021/jo401737t.

[19] Cazorla, C.; Billamboz, M.; Bricout, H.; Monflier, E.; Len, C. *Eur. J. Org. Chem.* **2017**, *2017*, 1078–1085. DOI: 10.1002/ejoc.201601311.