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Microwave-Promoted Synthesis of 4-Arylpyrimidines by Pd-Catalysed Suzuki–Miyaura Coupling of 4-Pyrimidyl Tosylates in Water

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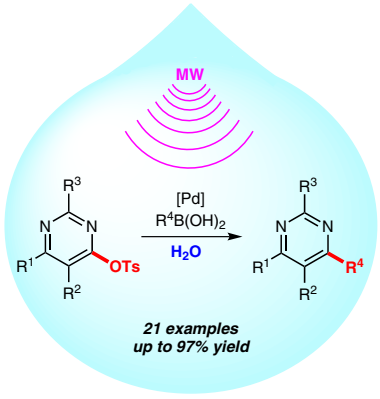

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Abstract The Suzuki–Miyaura coupling reaction of 4-pyrimidyl tosylates was investigated with aryl, heteroaryl and alkyl boronic acids. The reaction provided 4-substituted pyrimidines in good-to-excellent yields after one-hour microwave irradiation in water at 100 °C. The method constitutes a fast option for the synthesis of these heterocyclic systems.

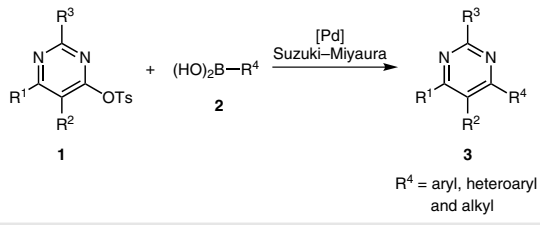
Key words Suzuki–Miyaura coupling, pyrimidines, tosylates, microwave-accelerated synthesis, cross-coupling

Cross-coupling reactions constitute a synthetic tool with an ever-increasing role in organic synthesis. A particular example is the preparation of biaryl derivatives by Pd-catalyzed Suzuki–Miyaura coupling, which has been extensively exploited over recent decades.[1] Although aryl iodides and bromides have found widespread use as the electrophilic counterpart for these coupling reactions,[2] their preparation constitutes an additional step that is highly dependent on the nature of the arene. Introduction of the halogen atom by a direct ring halogenation, in the case of electron-rich systems, may proceed in high yield under mild conditions, but often gives rise to a mixture of isomers.[3] By contrast, electron-poor systems, such as the pyrimidine ring, require considerably harsher conditions to achieve poor yields.[4] The use of Lewis acids to promote these reactions frequently leads to non-negligible mixtures of regioisomers.[5] Although methods for the halogenation of arenes have been improved,[6] the best results are based on already functionalized starting materials.[7,8] Problems of regioselectivity[5b] have been overcome in a few cases by careful selection of the arene system[9] or by using transition-metal catalysts.[10]

The above limitations of aryl halides prompted the search for other substrates for coupling reactions, with easily accessible leaving groups. Among them, aryl triflates,[11] nonaflates[12] and tosylates[13] are promising alternatives. Besides being cheaper, tosylates are stable towards heat and hydrolysis. Their main drawback is their reduced reactivity, when compared with the corresponding halides, but this limitation can be circumvented by a proper choice of catalyst and reaction conditions, in conversions involving electrophilic aryl and heteroaryl systems. For instance, 2-pyridyl tosylates and electron-rich olefins undergo Heck–Mizoroki cross-coupling reactions in good yields.[14]

Other electron-poor heterocyclic tosylates combine a good reactivity with their ready accessibility, being obtained from the corresponding hydroxyl derivatives; themselves products of cyclization with ester derivatives.[15] In a recent work we have described the ultrasound synthesis of the relatively unexploited 4-pyrimidyl tosylates **1**.[16]

In the present report, we describe a detailed study of the Pd-catalyzed Suzuki–Miyaura coupling of these derivatives with a variety of aryl, heteroaryl and alkyl boronic acids, comparing catalysts, solvents and different tosylates, for the preparation of 4-substituted pyrimidines (Scheme 1).



Scheme 1 Palladium-catalyzed Suzuki–Miyaura coupling of 4-pyrimidyl tosylates **1** with boronic acids **2**

As a model reaction, the coupling of tosylate **1a** (R^1 = Me, R^2 = H, R^3 = Ph) with phenyl boronic acid **2a** (R^4 = Ph) in the presence of tetrakis(triphenylphosphine)palladium was studied in five solvents of different polarities with three different heating sources: conventional heating, heating by ultrasound irradiation and by microwave irradiation. The obtained results are listed in Table 1.

Table 1 Suzuki–Miyaura Coupling of **1a** (R^1 = Me, R^2 = H, R^3 = Ph) with Phenyl Boronic Acid **2a** in Various Solvents, Temperatures and Reaction Conditions

Entry	Solvent	Yield of **3a** (%)[a]		
		Conventional heating (100 °C, 24 h)	Ultrasound irradiation (80 °C, 1 h)[c]	Microwave heating (100 °C, 1 h)
1	H_2O	89[b]	59	97
2	EtOH	72	45	82
3	DMF	81	42	70
4	THF	40	trace	45
5	toluene	27	trace	41

[a] Yields based on the isolated product 4-methyl-2,6-diphenylpyrimidine (**3a**), starting from a mixture of **1a** (0.588 mmol), phenyl boronic acid (0.705 mmol), $Pd(PPh_3)_4$ (0.029 mmol), K_2CO_3 (0.588 mmol) and the indicated solvent (5 mL).
[b] The yield dropped to 17% when the reaction time was 1 h.
[c] Carried out in a cup horn sonicator.

In all cases, heating was required to improve yields, and no reaction was observed at room temperature. Reactions carried out under microwave or ultrasound irradiation shortened the coupling reaction time considerably, when compared with those carried out under conventional heating. Lower yields were observed for ultrasound-promoted reactions compared with MW-heated processes, probably due to the lower temperature at which the reaction was conducted; after 1 hour sonication of the reacting mixtures, the final temperatures attained were never higher than 80 °C, although, after this time the substrates were fully consumed.

Yields of palladium-catalyzed Suzuki–Miyaura reactions are strongly solvent-dependent. The reacting medium may affect the oxidative addition or the transmetalation step[17] or even change the active catalytic species.[18] In the case of the model reaction, formation of compound **3a** was favored in polar solvents, such as water, ethanol and *N*,*N*-dimethylformamide (DMF), when compared with less polar solvents such as tetrahydrofuran (THF) and toluene. In spite of the poor solubility of the coupling reagents in water, this solvent proved the best medium for the reaction, regardless of the employed heating source. Pd-catalyzed reactions in water often face the problem of catalyst aggregation and formation of inactive 'Pd-black', so that many of these reactions do not occur in aqueous media.[19] In our case, it is noteworthy that water not only had no adverse effect on this Pd-catalyzed process, but indeed proved to be the best solvent for these coupling reactions. As recognized before for several organic reactions involving hydrophobic reagents,[20] this enhanced reactivity may be ascribed to hydrophobic aggregation of the reactants in water. Having established water as the solvent of choice, and microwave heating at 100 °C for 1 hour as the optimal reaction conditions, the effect of different palladium catalysts was next investigated. Table 2 compares different catalysts in a model reaction between tosylate **1a** and phenyl boronic acid under the above conditions.

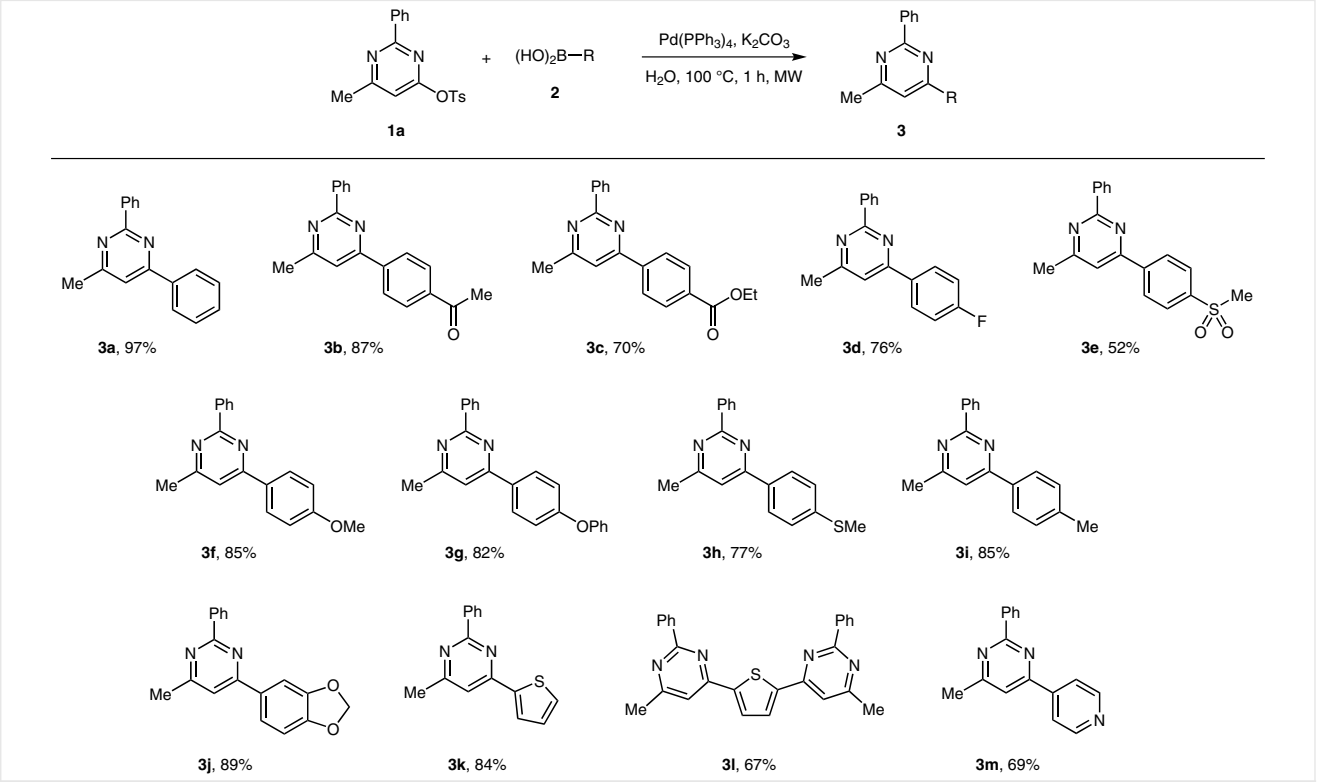
Table 2 Effect of the Palladium Catalyst on the Suzuki–Miyaura Coupling of **1a** (R^1 = Me, R^2 = Ph) with Phenyl Boronic Acid **2a** in Water

Entry	[Pd] source	[Pd] loading (mol%)[a]	Yield of **3a** (%)[b]
1	none	0	0[c]
2	$Pd(PPh_3)_4$	5	97
3	$Pd(PPh_2)Cl_2$	5	70
4	$Pd(OAc)_2$	5	0[c]
5	$Pd(OAc)_2$ + PPh_3	5	67
6	$Pd(dppf)Cl_2$	5	48
7	$Pd(PPh_3)_4$	2.5	72
8	$Pd(PPh_3)_4$	1	42

[a] Molar percentage of catalyst relative to **1a**.
[b] Yield based on the product 4-methyl-2,6-diphenylpyrimidine (**3a**), with the following reaction conditions: microwave heating at 100 °C for 1 h of a mixture of **1** (0.588 mmol), phenyl boronic acid (0.705 mmol), K_2CO_3 (0.588 mmol) and the catalyst in water (5 mL).
[c] Total consumption of starting material occurred, but no formation of **3a** was observed.

As expected, a palladium catalyst was always necessary for the formation of the coupled product. In its absence, compound **3a** was not formed (Table 2, entry 1). Palladium acetate proved completely ineffective (entry 4), but the addition of triphenylphosphine to palladium acetate led to the formation of 4-phenylpyrimidine **3a** with a reasonable yield (67%; entry 5), stressing the importance of a phosphine ligand for the stabilization of the active Pd(0) species. The possible effect of an intermediate palladium-phosphine catalyst in this process found support in the superior yield (97%; entry 2) obtained when pure $Pd(PPh_3)_4$ was employed as the catalyst (entry 7). Yields also increased with the amount of added catalyst, attaining maximum values for a 5% mol $Pd(PPh_3)_4$ loading.

Having established the best reaction conditions and catalyst, we next compared the reactivity of different aryl boronic acids in these cross-coupling reactions, by reacting tosylate **1a** with ten aryl- and three heteroaryl-boronic acids **2a–m** to form 4-arylpyrimidines **3a–m**. Scheme 2 summarizes the obtained results. Yields tended to increase with the nucleophilicity of the boronic acid (compounds **3f–j** in Scheme 2). Electron-withdrawing substituents on the aryl

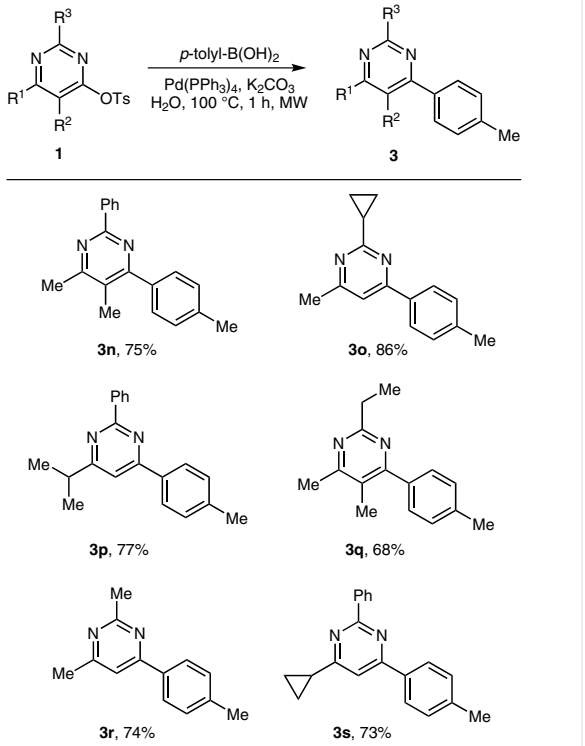


Scheme 2 Suzuki–Miyaura coupling of 4-pyrimidyl tosylate **1** with various aryl and heteroaryl boronic acids **2**

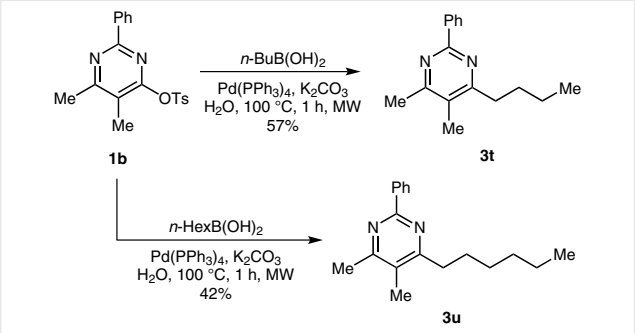
boronic acids (compounds **2a–e** in Scheme 2) decreased the yields of the reaction, as observed for other Suzuki–Miyaura coupling processes.[21]

The reactivity of six 4-pyrimidyl tosylates **1b–g** with *p*-tolyl boronic acid under the developed conditions was next investigated. As shown in Scheme 3, the desired pyrimidines **3n–s** were obtained in good to excellent yields.

Attempts to extend the method to alkyl boronic acids were less successful, with variable yields that depended on the structure of the employed tosylate or the alkyl boronic acid (Scheme 4). Thus, coupling of tosylate **1b** (R^1 = Me, R^2 = Me, R^3 = Ph) with *n*-butyl boronic acid gave the desired product **3t** (R^1 = Me, R^2 = Me, R^3 = Ph, R^4 = *n*-Bu) in 57% yield. Reaction of the same substrate **1b** with *n*-hexyl boronic acid formed **3u** (R^1 = Me, R^2 = Me, R^3 = Ph, R^4 = *n*-Hex) in 42% yield. Surprisingly, tosylate **1a**, under the same conditions, did not form any coupled product with either *n*-butyl or *n*-hexyl boronic acids. Neither **1a** nor **1b** could be made to react with ethyl or with cyclopropyl boronic acid: even after 2 h of microwave irradiation at 100 °C, significant amounts of the unreacted reagents were still present, and only traces of the desired pyrimidines were detected, as suggested by NMR analysis of the product mixture.



Scheme 3 Suzuki–Miyaura coupling of 4-pyrimidyl tosylates **1** with *p*-tolyl boronic acid



Scheme 4 Suzuki–Miyaura coupling of 4-pyrimidyl tosylate **1b** with alkyl boronic acids

These erratic results prompted us to abandon further attempts to obtain 4-alkylpyrimidine derivatives under the developed conditions. Nevertheless, in spite of lying beyond the scope of the present work, the improvement of the reaction conditions for this transformation is currently a subject of investigation in our group.

In conclusion, the relatively unexploited 4-pyrimidyl tosylates are good substrates for Suzuki–Miyaura cross-coupling reactions, allowing a rapid and versatile access to 4-arylpyrimidines,[22] 4-heteroaylpyrimidines and, in some cases, 4-alkylpyrimidines. Although the coupling reactions proved in general rather slow under conventional heating at 100 °C, variations of the solvent, heating methods, catalyst, and the aryl boronic partner improved the rates of formation and the yields of the coupled products. Optimal reaction conditions employed water as the best solvent, microwave heating at 100 °C, a $Pd(PPh_3)_4$ catalyst, and electron-rich aryl or heteroaryl boronic acids for the preparation of 4-arylpyrimidines in high yields. This process should prove a valuable alternative for the synthesis of these and related pyrimidine derivatives.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588810.

References and Notes

(1) Johanson Seechurn, C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062.
(2) King, A. O.; Yasuda, N. In *Organometallics in Process Chemistry*; Springer-Verlag: Berlin/Heidelberg, **2004**, 205–245.
(3) Arsenyan, P.; Paegle, E.; Belyakov, S. *Tetrahedron Lett.* **2010**, *51*, 205.
(4) Liu, Z.; Li, S.; Li, D.; He, X.; Hu, Y. *Tetrahedron* **2007**, *63*, 1931.
(5) (a) Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 15770. (b) Qiu, D.; Mo, F.; Zheng, Z.; Zhang, Y.; Wang, J. *Org. Lett.* **2010**, *12*, 5474.
(6) Smith, K.; Butters, W.; Paget, E.; Goubet, D.; Fromentin, E.; Nay, B. *Green Chem.* **1999**, *1*, 83.
(7) Niu, F.; Zhang, H.; Yang, H.; Fu, H. *Synlett* **2014**, *25*, 995.
(8) Accessible 4-chloropyrimidines are good coupling partners in Suzuki–Miyaura reactions, see: (a) Achelle, S.; Ramondenc, Y.; Marsais, F.; Plé, N. *Eur. J. Org. Chem.* **2008**, 3129. (b) Lee, D.-H.; Choi, M.; Yu, B.-W.; Ryoo, R.; Taher, A.; Hossain, S.; Jin, M.-J. *Adv. Synth. Catal.* **2009**, *351*, 2912. (c) Lee, D.-H.; Jung, J.-Y.; Jin, M.-J. *Green Chem.* **2010**, *12*, 2024. (d) Anderson, S. C.; Handy, S. T. *Synthesis* **2010**, 2721.
(9) (a) Jakab, G.; Hosseini, A.; Hausmann, H.; Schreiner, P. R. *Synthesis* **2013**, *45*, 1635. (b) Ganguly, N. C.; De, P.; Dutta, S. *Synthesis* **2005**, 1103. (c) Rajesh, K.; Somasundaram, M.; Saiganesh, R.; Balasubramanian, K. K. *J. Org. Chem.* **2007**, *72*, 5867.
(10) (a) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434. (b) Imazaki, Y.; Shirakawa, E.; Ueno, R.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 14760. (c) Pan, J.; Wang, X.; Zhang, Y.; Buchwald, S. L. *Org. Lett.* **2011**, *13*, 4974. (d) Du, B.; Sun, J. P. *J. Org. Chem.* **2013**, *78*, 2786.
(11) (a) Shu, C.; Sidhu, K.; Zhang, L.; Wang, X.; Krishnamurthy, D.; Senanayake, C. H. *J. Org. Chem.* **2010**, *75*, 6677. (b) Lee, D.; Ryu, T.; Park, Y.; Lee, P. H. *Org. Lett.* **2014**, *16*, 1144.
(12) (a) Domínguez, M.; Reissig, H.-U. *Synthesis* **2014**, *46*, 1110. (b) Hommes, P.; Reissig, H.-U. *Eur. J. Org. Chem.* **2016**, 338.
(13) (a) Ke, H.; Chen, X.; Zou, G. *J. Org. Chem.* **2014**, *79*, 7132. (b) Molinaro, C.; Scott, J. P.; Shevlin, M.; Wise, C.; Ménard, A.; Gibb, A.; Junker, E. M.; Lieberman, D. *J. Am. Chem. Soc.* **2015**, *137*, 999.
(14) Gøgsig, T. M.; Lindhardt, A. T.; Dekhane, M.; Grouleff, J.; Skrydstrup, T. *Chem. Eur. J.* **2009**, *15*, 5950.
(15) (a) Bartrum, H. E.; Blakemore, D. C.; Moody, C. J.; Hayes, C. J. *J. Org. Chem.* **2010**, *75*, 8674. (b) Yang, J.; Liu, S.; Zheng, J.-F.; Zhou, J. *Eur. J. Org. Chem.* **2012**, 6248.
(16) Vidal, M.; García-Arriagada, M.; Rezende, M. C.; Domínguez, M. *Synthesis* **2016**, *48*, 4246.
(17) (a) Littke, A. F.; Dai, C. Y.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.
(18) Proutiere, F.; Schoenebeck, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 8192.
(19) (a) Adrio, L. A.; Nguyen, B. N.; Guilera, G.; Livingston, A. G.; Hii, K. K. *Catal. Sci. Technol.* **2012**, *2*, 316. (b) Bedford, R. B.; Bowen, J. G.; Davidson, R. B.; Haddow, M. F.; Seymour-Julen, A. E.; Sparkes, H. A.; Webster, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 6591. (c) Li, Z.; Gelbaum, C.; Heaner, W. L. IV; Fisk, J.; Jaganathan, A.; Holden, B.; Pollet, P.; Liotta, C. *Org. Process Res. Dev.* **2016**, *20*, 1489.
(20) For overlooks and reviews on various organic reactions carried out in water, see: (a) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Hartmuth, C. K.; Sharpless, K. B. *Angew. Chem. Int. Ed.*

2005, *44*, 3275. (b) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68. (c) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563. (d) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725.

(21) Berionni, G.; Maji, B.; Knochel, P.; Mayr, H. *Chem. Sci.* **2012**, *3*, 878.

(22) **4-(4-Acetylphenyl)-6-methyl-2-phenylpyrimidine** (**3b**)

A 10-mL microwave vial was charged with 4-pyrimidyl tosylate **1a** (0.588 mmol), the aryl boronic acid **2** (0.705 mmol), tetrakis(triphenylphosphine)palladium (0.029 mmol), powdered potassium carbonate (0.588 mmol) and water (5 mL). The resulting reaction mixture was irradiated for 1 h at 100 °C. The reaction mixture was then extracted three times with dichloromethane (ca. 15 mL each). The combined organic phases were dried with anhydrous sodium sulfate and filtered. The solvent was removed on a rotary evaporator and the crude product was purified by column chromatography (silica gel; *n*-hexane/EtOAc, 10:1) to obtain a yellow solid. Yield: 122 mg (87%); mp 148–150 °C; R_f = 0.72 (*n*-hexane/EtOAc, 5:1). IR (ATR): 3070, 2920, 1683, 1589, 1572 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.61–8.52 (m, 2 H, Ph), 8.25 (d, *J* = 8.4 Hz, 2 H, ArH), 8.06 (d, *J* = 8.4 Hz, 2 H, ArH), 7.60–7.47 (m, 3 H, Ph), 7.45 (s, 1 H, H-5), 2.64 (s, 3 H, $COCH_3$), 2.63 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$, 101 MHz): δ = 198.1, 168.6, 164.8, 162.7, 141.8, 138.8, 138.2, 131.1, 129.2, 128.9, 128.8, 127.8, 114.8, 27.2, 25.1. HRMS (ESI-TOF): *m*/*z* [M + H^+] calcd for $C_{19}H_{17}N_2O$: 289.1341; found: 289.1342.