Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 4415–4418

Microwave-assisted, efficient and regioselective Pd-catalyzed C-phenylation of halopyrimidines

Susana Conde Ceide and Antonio Garrido Montalban*

Department of Chemistry, Kemia Incorporated, 5871 Oberlin Drive, Suite 100, San Diego, CA 92121, USA

Received 30 September 2005; revised 15 April 2006; accepted 19 April 2006
Available online 12 May 2006

Abstract—We herein report that flash heating microwave irradiation is a helpful tool in the formation of arylpyrimidines from the corresponding halopyrimidines. The palladium-catalyzed cross-coupling reactions of 2,4-di- and 2,4,5-trihalopyrimidines with phenylboronic acid under the above conditions are described. By use of the appropriate catalyst and the adequate halopyrimidine, good regioselectivity can be achieved in the 2-, 4-, or 5-positions of the heterocycle. In addition, we show that this methodology is amenable for the stepwise preparation of mono-, di-, and triphenylpyrimidines.

The pyrimidine skeleton is commonly found in pharmaceutical drugs, fungicides, and herbicides.[1] In particular, triphenylpyrimidines are useful in the development of advanced electronic and photonic devices.[2] Historically, functionalization of the pyrimidine system is obviated by ring formation and careful synthetic design. This has led to an extensive range of pyrimidine syntheses,[3] whereby halopyrimidines are key building blocks for further functionalization. These compounds can react with a wide variety of nucleophiles such as alkoxides, mercaptides, amines,[4] and organometallic reagents,[5] although nucleophilic substitutions of 2,4-dichloropyrimidines are generally not very regioselective.[6] However, for the synthesis of *C*-aryl derivatives involving palladium-catalyzed cross-coupling reactions of organoboronic acids with 2,4-dihalopyrimidines[7] and 2,4,6-trihalopyrimidines,[8] good selectivity has been achieved in the 4-position, under conventional conditions.

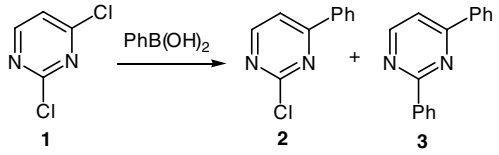
The rapid development of combinatorial and robotized parallel synthesis has led to a growing demand for fast reactions and efficient purification procedures.[9] Thus we decided to explore the utility of halopyrimidines in the microwave assisted[10] Suzuki-type cross-coupling reaction, and demonstrate that we cannot only shorten the reaction time dramatically when compared to conventional methods but also achieve good regioselectivity in the 2-, 4-, and 5-positions as a function of the catalyst and the halopyrimidine employed.

2,4-Dihalopyrimidines: It has been reported that under conventional thermal conditions with $Pd(PPh_3)_4$, the reaction takes 4 h of heating and that the 4-phenyl pyrimidine (**2**) is obtained (80%) together with 2,4-diphenyl pyrimidine (**3**, 10%) when 1 equiv of the boronic acid is used.[7b] With 2 equiv of the boronic acid, 2,4-diphenyl pyrimidine **3** is obtained after 6 h in 90% yield.[7b] Our initial experiments under microwave irradiation were thus performed using $Pd(PPh_3)_4$ as the catalyst, K_2CO_3 as the base and toluene–DMF (9:1) as the solvent in order to establish conditions that could reproduce or improve upon the above results using much shorter reaction times. Reactions were carried out at different temperatures for a period of 10 min using a Smith Microwave Synthesizer™ (Biotage BA). At 150 °C, the expected product **2** was obtained in 60% yield along with starting material (Table 1, entry 1). When the reaction was performed at 185 °C, **2** was obtained in an 85% yield accompanied by small amounts (6%) of the disubstituted pyrimidine **3** (Table 1, entry 2). At higher temperature (200 °C), the formation of **3** increased at the cost of the monosubstituted product **2** (Table 1, entry 3). With 2 equiv of the boronic acid at 185 °C, the exclusive formation of the disubstituted product **3** was observed (Table 1, entry 4). With these results in hand we then decided to try out a different palladium catalyst. It has been reported that the use of 1,4-bis(diphenylphosphino)butanepalladium dichloride,

Keywords: Microwave; Palladium; Cross-coupling; Heterocycles; Regioselectivity.
* Corresponding author. Tel.: +1 858 964 1434; fax: +1 858 964 1413; e-mail: amontalban@kemia.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.04.082

Table 1. Selectivity in the Suzuki coupling of 2,4-dichloropyrimidine (**1**)



1 **2** **3**

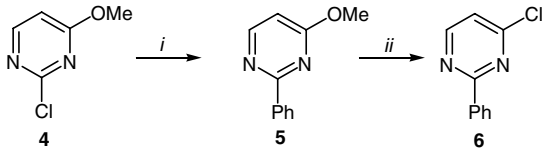
Entry	Catalyst	$PhB(OH)_2$ (No. equiv)	T (°C)	**2** (%)	**3** (%)
1	$Pd(PPh_3)_4$	1	150	60	—
2	$Pd(PPh_3)_4$	1	185	85	6
3	$Pd(PPh_3)_4$	1	200	77	12
4	$Pd(PPh_3)_4$	2	185	—	90
5	$Pd(dppb)Cl_2$	1	185	85	—
6	$Pd(dppb)Cl_2$	2	185	70	10

All reactions were performed using K_2CO_3 as base and toluene–DMF (9:1) as solvent under high frequency microwaves (2.5 GHz) for 10 min.

$Pd(dppb)Cl_2$, is superior to $Pd(PPh_3)_4$ in the Suzuki-type reactions of π-deficient heteroaryl chlorides.[11] Thus, 2,4-dichloropyrimidine was treated with this catalyst at 185 °C. Indeed, the reaction was much cleaner and with no formation of the disubstituted product **3** (Table 1, entry 5). In contrast, even with two equivalents of the phenylboronic acid, the major product turned out to be the mono-substituted derivative **2** (Table 1, entry 6). The use of $Pd(dppb)Cl_2$ as the catalyst represents a clear advantage for the formation of the monosubstituted product when compared to $Pd(PPh_3)_4$. However, all our attempts to react pinacol phenyl boronic ester with 2,4-dichloropyrimidine in the presence of any of the two catalysts were unfruitful and both reactants were recovered unaltered.

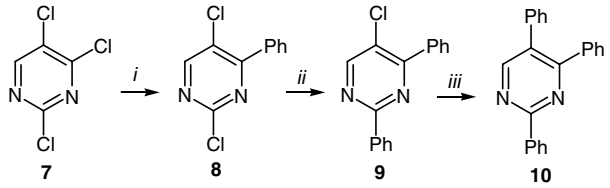
The different reactivity of the 2- versus the 4-carbon in 2,4-dihalopyrimidines toward nucleophiles, may be due to the better charge stabilization of the Meisenheimer salt derived from attack at the 4-position (thermodynamic control). The same trend is observed for the palladium-catalyzed cross-coupling reactions (vide supra). Nevertheless, high yields of the product resulting from the reaction at the less activated 2-position can be achieved when the 4-position is blocked. For example, reaction of commercially available 2-chloro-4-methoxypyrimidine (**4**) using $Pd(dppb)Cl_2$ as the catalyst under the microwave conditions established above gave compound **5**[12] in 86% yield. The methoxy group that acts as a dummy group, could be transformed back into the chloride[13] in two easy steps with an overall yield of 71% as shown in Scheme 1. In addition, the methoxy group allows the possibility of functionalizing the 5-position using the *ortho*-lithiation methodology which has been extensively described by Queguiner.[14] Next we decided to apply our findings to the Suzuki coupling of 2,4,5-trihalopyrimidines.

2,4,5-Trihalopyrimidines: The commercially available 2,4,5-trichloropyrimidine (**7**) was treated with 1 equiv of phenylboronic acid under the same microwave conditions as described above (Scheme 2). The 2,5-dichloro-4-phenylpyrimidine (**8**) was isolated in 58% yield, accompanied by small amounts of the 2-susbtituted- and 2,4-disubstituted-pyrimidines (7% and 10%, respectively). No significant difference with either $Pd(PPh_3)_4$ or $Pd(dppb)Cl_2$ as the catalyst was observed. Similar results have been previously described in the Stille coupling of **7** with phenyltributyltin under conventional thermal conditions.[15] When **8** was treated with a second equivalent of phenylboronic acid, 5-chloro-2,4-diphenylpyrimidine (**9**)[16] was isolated in 65% yield. Substitution at the 5-position was achieved with the more reactive catalyst, $Pd[P(t\text{-}Bu_3)]_2$,[17] to give the triphenylsubstituted pyrimidine **10**[18] in good yield (70%). Even reacting **7** with 3 equiv of phenylboronic acid and $Pd(PPh_3)_4$ as the catalyst, led only to the formation of the disubstituted product **9**. In contrast, Suzuki-type cross-coupling reactions of 2,4,6-trichloropyrimidine under conventional conditions ($Pd(OAc)_2$, Na_2CO_3, PPh_3, glyme/H_2O, 70 °C, 18–24 h) have been reported to give the 6-phenyl-, 4,6-diphenyl-, and 2,4,6-triphenyl-pyrimide in 88%, 88%, and 93% yields, respectively, depending on the amount of phenylboronic acid used.[8]



4 **5** **6**

Scheme 1. Reagents and conditions: (i) $PhB(OH)_2$, $Pd(dppb)Cl_2$, K_2CO_3, toluene–DMF (9:1), microwave irradiation, 10 min, 185 °C, 86%; (ii) HCl 6 N, 12 h, reflux then $POCl_3$, 3 h, reflux, 83%.



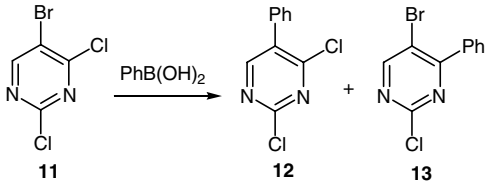
7 **8** **9** **10**

Scheme 2. Reagents and conditions: (i) $PhB(OH)_2$, $Pd(dppb)Cl_2$ or $Pd(PPh_3)_4$, K_2CO_3, toluene–DMF (9:1), microwave irradiation, 10 min, 185 °C, 58%; (ii) $PhB(OH)_2$, $Pd(dppb)Cl_2$ or $Pd(PPh_3)_4$, K_2CO_3, toluene–DMF (9:1), microwave irradiation, 10 min, 185 °C, 65%; (iii) $PhB(OH)_2$, $Pd[P(t\text{-}Bu_3)]_2$, K_2CO_3, toluene–DMF (9:1), microwave irradiation, 10 min, 185 °C, 70%.

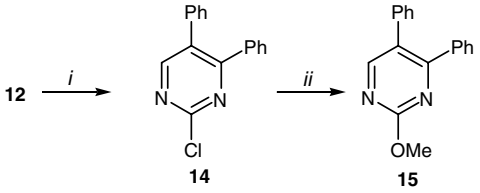
With these results in hand, we decided to explore if the same reactivity pattern would hold true for 2,4-dichloro-5-bromopyrimidine (**11**). However, when **11** was reacted with phenylboronic acid and $Pd(PPh_3)_4$ as the catalyst, we obtained a ~1:1 mixture of **12**[19] and **13**[20] (Table 2, entry 1), whereas with $Pd(dppb)Cl_2$ under the same microwave conditions, the product ratio was shifted toward **12** (Table 2, Entry 2). In both cases, a small amount of the 4,5-disubstituted product was also obtained (9%).

When we treated **12** with a second equivalent of phenylboronic acid and $Pd(PPh_3)_4$ or $Pd(dppb)Cl_2$ as the catalyst, the second substitution took place in the more reactive 4-position and the 2-chloro-4,5-diphenylpyrim-

Table 2. Selectivity in the Suzuki coupling of 2,4-dichloro-5-bromopyrimidine (**11**)

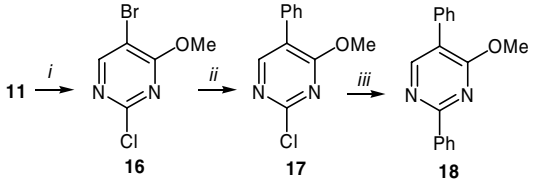


Entry	Catalyst	**12** (%)	**13** (%)
1	$Pd(PPh_3)_4$	30	23
2	$Pd(dppb)Cl_2$	60	10



Scheme 3. Reagents and conditions: (i) $PhB(OH)_2$, $Pd(PPh_3)_4$ or $Pd(dppb)Cl_2$, K_2CO_3, toluene–DMF (9:1), microwave irradiation, 10 min, 185 °C, 59%; (ii) MeOH, Na, 2 h, rt then **14**, 12 h, rt, 85%.

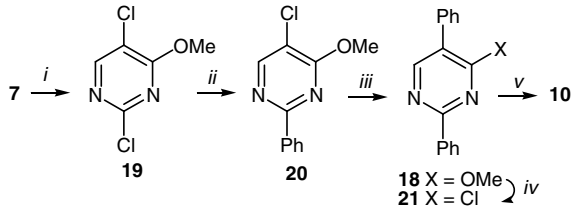
idine (**14**) was obtained in 59% yield (Scheme 3). The selectivity in **14**[21] was unambigously confirmed by comparing the spectrocopic data of its methoxy derivative **15**[22] with that of **18**. The methoxy derivative **18** was prepared via the known pyrimidine **16**[23] followed by sequential cross-coupling reactions as depicted in Scheme 4.[24]



Scheme 4. Reagents and conditions: (i) MeOH, Na, 2 h, rt then **11**, 12 h, rt, 90%; (ii). $PhB(OH)_2$, $Pd(dppb)Cl_2$, K_2CO_3, toluene–DMF (9:1), microwave irradiation, 10 min, 185 °C, 60%; (iii) $PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, toluene–DMF (9:1), microwave irradiation, 10 min, 185 °C, 81%.

For the introduction of the third phenyl ring in the 2-position of **14**, either $Pd[P(t\text{-}Bu_3)]_2$, $Pd(PPh_3)_4$ or $Pd(dppb)Cl_2$ as the catalyst proved successful. In fact when we reacted **11** with 3 equiv of phenylboronic acid and $Pd(PPh_3)_4$ as the catalyst, the trisubstituted product **10** was obtained in a 62% yield. Thus the order of the stepwise introduction of three phenyl rings into the 2-, 4-, and 5-positions of the pyrimidine system can be achieved depending on the choice of the starting trihalopyrimidine and catalyst.

In order to obtain the first arylation at the 2-position of **7**, for example, first selective methoxylation at the 4-position to give 2,5-dichloro-4-methoxypyrimidine (**19**)[25] followed by treatment with 1 equiv of phenylboronic acid and $Pd(PPh_3)_4$ as the catalyst can be used. As expected the 5-chloro-4-methoxy-2-phenylpyrimidine (**20**)[26] was the only product isolated (78%). The second phenyl ring in the 5-position was introduced by using $Pd[P(t\text{-}Bu_3)]_2$ as the catalyst to give **18** in 83% yield. The methoxy group could easily be transformed into the chloride **21**[27] after which the third phenyl ring was introduced via Suzuki coupling using $Pd(PPh_3)_4$ to give **10** in 81% yield (Scheme 5).



Scheme 5. Reagents and conditions: (i) MeOH, Na, 2 h, rt then **7**, 12 h, rt, 92%; (ii) $PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, toluene–DMF (9:1), microwave irradiation, 10 min, 185 °C, 78%; (iii) $PhB(OH)_2$, $Pd[P(t\text{-}Bu_3)]_2$, K_2CO_3, toluene–DMF (9:1), microwave irradiation, 10 min, 185 °C, 83%; (iv) HCl 6 N, 12 h, reflux then $POCl_3$, 3 h, reflux, 79%; (v) $PhB(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, toluene–DMF (9:1), microwave irradiation, 10 min, 185 °C, 81%.

In conclusion, we have developed a fast microwave assisted method that, starting from easily available halopyrimidines, allows us to introduce aryl groups selectively in the 2-, 4-, or 5-positions of the pyrimidine system depending on the choice of halopyrimidine and the catalyst employed. We have extended this reaction to demonstrate the preparation of mono, di, and triphenylpyrimidines. We are currently examining the scope of this methodology in the N- and O-arylation of pyrimidines.

Typical procedure for the Suzuki coupling reactions: A 2.0–5.0 mL microwave vial was charged with the halopyrimidine (0.5 mmol), phenylboronic acid (1.1 equiv), potassium carbonate (3.0 equiv), the corresponding catalyst (ca. 5 mol %) in 1.8 mL toluene and 0.2 mL DMF. The vial was purged three times with nitrogen and then heated under microwave irradiation (2.5 GHz) for 10 min using a Smith Microwave Synthesizer™(Biotage BA) at different temperatures. After this time, the reaction mixture was allowed to cool, filtered and the solvents were removed in vacuo. Ethyl acetate was added and the organic layer was washed with brine, separated, and dried ($MgSO_4$). The mixture was purified by reverse phase chromatography.

Acknowledgment

We are grateful to Kemia Inc., for support of this work.

References and notes

1. Joule, J. A.; Mills, K.; Smith, G. F. *Heterocyclic Chemistry*; Chapman & Hall: London, 1995.

2. Itami, K.; Yamazaki, D.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2004**, *126*, 15396–15397.
3. (a) Müller, T. J. J.; Braun, R.; Ansorge, M. *Org. Lett.* **2000**, *2*, 1967–1970; (b) Dodson, R. M.; Seyler, J. K. *J. Org. Chem.* **1951**, *16*, 461–465; (c) Adams, J. L.; Boehm, J. C.; Kassis, S.; Gorycki, P. D.; Webb, E. F.; Hall, R.; Sorenson, M.; Lee, J. C.; Ayrton, A.; Griswold, D. E.; Gallagher, T. F. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3111–3116.
4. (a) Breault, G. A.; Ellston, R. P. A.; Green, S.; James, S. R.; Jewsbury, P. J.; Midgley, C. J.; Pauptit, R. A.; Minshull, C. A.; Tucker, J. A.; Pease, J. E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2961–2966; (b) Ludovici, D. W.; De Corte, B. L.; Kukla, M. J.; Ye, H.; Ho, C. Y.; Lichtenstein, M. A.; Kavash, R. W.; Andries, K.; Bethune, M.-P.; Azjin, H.; Pauwels, R.; Lewi, P. J.; Heeres, J.; Koymans, L. M. H.; de Jonge, M. R.; Van Aken, K. J. A.; Daeyaert, F. F. D.; Das, K.; Arnold, E.; Janssen, P. A. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2235–2239; (c) Wojtowicz-Rajchel, H.; Suchowiak, M.; Fiedorow, P.; Golankiewicz, K. *J. Chem. Soc. Perkin Trans. 2* **1998**, 841–845; (d) Tjarks, W.; Gabel, D. *J. Med. Chem.* **1991**, *34*, 315–319; (e) Schinazi, R. F.; Prusoff, W. H. *J. Org. Chem.* **1985**, *50*, 841–847; (f) Hilbert, G. E.; Jansen, E. F. *J. Am. Chem. Soc.* **1934**, *56*, 134–139.
5. Organotins: (a) Majeed, A. J.; Antonsen, O.; Benneche, T.; Undheim, K. *Tetrahedron* **1989**, *45*, 993–1006; (b) Benneche, T. *Acta Chem. Scand.* **1990**, *44*, 927–931; Organozincs: (c) Sandosham, J.; Undheim, K.; Rise, F. *Heterocycles* **1993**, *35*, 235–244; (d) Simkovsky, N. M.; Ermann, M.; Roberts, S. M.; Parry, D. M.; Baxter, A. D. *J. Chem. Soc. Perkin. Trans. 1* **2002**, 1847–1849; (e) Turck, A.; Ple, N.; Lepretre-Gaquere, A.; Queguiner, G. *Heterocycles* **1998**, *49*, 205–214; Organolithiums: (f) Ple, N.; Turck, A.; Couture, K.; Queguiner, G. *J. Org. Chem.* **1995**, *60*, 3781–3786; (g) Mattson, R. J.; Sloan, C. P. *J. Org. Chem.* **1990**, *55*, 3410–3412; (h) Taylor, H. M.; Jones, C. D.; Davenport, J. D.; Hirsch, K. S.; Kress, T. J.; Weaver, D. *J. Med. Chem.* **1987**, *30*, 1359–1365; Organozirconocenes: (i) Mangalagiu, I.; Benneche, T.; Undheim, K. *Acta. Chem. Scand.* **1996**, *50*, 914–917; Organoalanes: (j) Lu, Q.; Mangalagiu, I.; Benneche, T.; Undheim, K. *Acta. Chem. Scand.* **1997**, *51*, 302–306.
6. A good way to introduce selectivity is by using the 5-bromo-2,4-dichloropyrimidine. It has been reported that the first substitution takes place in the 4-position followed by the 2-position. The bromine could subsequently be removed via a simple hydrogenation: Yamai, K. *J. Pharm. Soc. Jpn.* **1942**, *62*, 315–333; *Chem. Abstr.* **1951**, *45*, 5150.
7. (a) Parry, P. R.; Wang, C.; Batsanov, A. S.; Bryce, M. R.; Tarbit, B. *J. Org. Chem.* **2002**, *67*, 7541–7543; (b) Jiang, B.; Yang, C.-g. *Heterocycles* **2000**, *53*, 1489–1498; (c) Gong, Y.; Pauls, H. W. *Synlett* **2000**, 829–831.
8. Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125–7128.
9. Bursavich, M. G.; Lombardi, S.; Gilbert, A. M. *Org. Lett.* **2005**, *7*, 4113–4116.
10. (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284; (b) Larhed, M.; Hallberg, A. *Drug Discovery Today* **2001**, *6*, 406–416; (c) Santagada, V.; Perissutti, E.; Caliendo, G. *Curr. Med. Chem.* **2002**, *9*, 1251–1283.
11. (a) Sugi, Y.; Bando, K.-i. *Chem. Lett.* **1976**, *5*, 727–730; (b) Ali, N. M.; McKillop, A.; Mitchell, M. B.; Rebelo, R. A.; Wallbank, P. J. *Tetrahedron* **1992**, *48*, 8117–8126; (c) Mitchell, M. B.; Wallbank, P. J. *Tetrahedron Lett.* **1991**, *32*, 2273–2276.
12. Yamanaka, H.; Ogawa, S.; Sakamoto, T. *Heterocycles* **1981**, *4*, 573–576.
13. Geerts, J. P.; van der Plas, H. C.; van Veldhuizen, A. *Org. Magn. Reson.* **1975**, *7*, 86–88.
14. (a) Ple, N.; Turck, A.; Heynderickx, A.; Queguiner, G. *J. Heterocyclic Chem.* **1994**, *31*, 1311–1315; (b) Ple, N.; Turck, A.; Martin, P.; Barbey, S.; Queguiner, G. *Tetrahedron Lett.* **1993**, *34*, 1605–1608; (c) Turck, A.; Ple, N.; Trohay, D.; Ndzi, B.; Queguiner, G. *J. Heterocyclic Chem.* **1992**, *29*, 699–702; (d) Ple, N.; Turck, A.; Bardin, F.; Queguiner, G. *J. Heterocyclic Chem.* **1992**, *29*, 467–470; (e) Turck, A.; Ple, N.; Mojovic, L.; Queguiner, G. *J. Heterocyclic Chem.* **1990**, *27*, 1377–1381.
15. Solberg, J.; Undheim, K. *Acta Chem. Scand.* **1989**, *43*, 62–68.
16. To determine the selectivity of the second substitution, we removed the remaining chloride of **9** [white solid; ^{1}H NMR ($CDCl_3$): 7.50–7.55 (m, 6H), 8.01–8.02 (m, 2H), 8.50–8.51 (m, 2H), 8.81 (s, 1H); MS [$C_{16}H_{11}ClN_2$]: *m*/*z* (M+): Calcd 266, found 266] by hydrogenation. The chemical shifts of the ^{1}H NMR spectrum of the corresponding product were identical to the one obtained for **3**.
17. Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387–3388.
18. Padwa, A.; Smolanoff, J.; Wetmore, S. I., Jr. *J. Org. Chem.* **1973**, *38*, 1333–1340.
19. Allen, D. W.; Buckland, D. J.; Hutley, B. G.; Oades, A. C.; Turner, J. B. *J. Chem. Soc. Perkin Trans. 1* **1977**, 621–624.
20. Compound **13**: white solid. ^{1}H NMR ($CDCl_3$): 7.51–7.53 (m, 3H), 7.81–7.82 (m, 2H), 8.80 (s, 1H); MS [$C_{10}H_6BrClN_2$]: *m*/*z* (M+): Calcd 268, found 268.
21. Coppola, G. M.; Hardtmann, G. E.; Huegi, B. S. *J. Heterocycl. Chem.* **1980**, *17*, 1479–1482.
22. Compound **15**: white solid. ^{1}H NMR ($CDCl_3$): 4.15 (s, 3H), 7.19 (m, 2H), 7.27–7.38 (m, 6H), 7.48 (d, $J = 8.0$ Hz, 2H). 8.56 (s, 1H); MS [$C_{17}H_{14}N_2O$]: *m*/*z* (M+): Calcd 262, found 262.
23. Strekowski, L. *Roczniki Chem.* **1975**, *49*, 1017–1024.
24. Compound **17**: white solid. ^{1}H NMR ($CDCl_3$): 4.08 (s, 3H), 7.44–7.53 (m, 5H), 8.36 (s, 1H); MS [$C_{11}H_9ClN_2O$]: *m*/*z* (M+): Calcd 220, found 220. Compound **18**: white solid. ^{1}H NMR ($CDCl_3$): 4.16 (s, 3H), 7.26–7.28 (t, $J = 8.8$ Hz, 1H), 7.40–7.50 (m, 5H), 7.62 (d, $J = 8.8$ Hz, 2H), 8.51 (s, 2H), 8.61 (s, 1H); MS [$C_{17}H_{14}N_2O$]: *m*/*z* (M+): Calcd 262, found 262.
25. (a) Hoffman-La Roche Patent CH 397694, **1966**; *Chem Abstr*. **1966**, 64, 19633d; (b) Kloetzer, W.; Schantl, J. *Monatsh. Chem.* **1963**, *94*, 1190–1197.
26. To determine the selectivity in **20** [white solid; ^{1}H NMR ($CDCl_3$): 4.12 (s, 3H), 7.45–7.55 (m, 5H), 8.39 (s, 1H); MS $C_{11}H_9ClN_2O$]: *m*/*z* (M+): Calcd 220, found 220], we compared the spectroscopic data of its dechlorinated analogue with that of **5**. Both compounds showed identical chemical shifts in the ^{1}H and ^{13}C NMR spectra.
27. Brovarets, V. S.; Vydzhak, R. N.; Zyuk, K. V.; Drach, B. S. *Russ. J. Gen. Chem.* **1993**, *63*, 884–886.