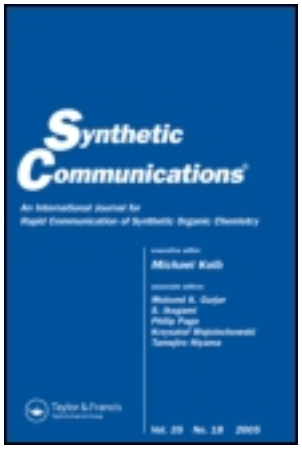


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Microwave-Assisted N-Cyclopropylation of Pyridinols with Cyclopropyl Boronic Acid

Yashwant B. Tambe [a], Somesh Sharma [a], Arunendra Pathak [a] & L. Krishnakanth Reddy [a]

[a] Jubilant Chemsys Limited, Noida, Uttar Pradesh, India

Accepted author version posted online: 21 Oct 2011. Version of record first published: 11 Jan 2012

To cite this article: Yashwant B. Tambe, Somesh Sharma, Arunendra Pathak & L. Krishnakanth Reddy (2012): Microwave-Assisted N-Cyclopropylation of Pyridinols with Cyclopropyl Boronic Acid, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:9, 1341-1348

To link to this article: http://dx.doi.org/10.1080/00397911.2010.539758

Synthetic Communications®, 42: 1341–1348, 2012

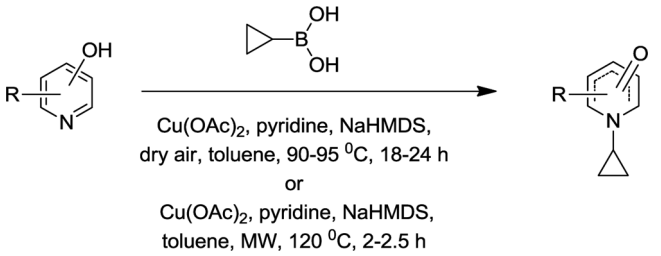
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.539758

Taylor & Francis
Taylor & Francis Group

MICROWAVE-ASSISTED N-CYCLOPROPYLATION OF PYRIDINOLS WITH CYCLOPROPYL BORONIC ACID

Yashwant B. Tambe, Somesh Sharma, Arunendra Pathak, and L. Krishnakanth Reddy
Jubilant Chemsys Limited, Noida, Uttar Pradesh, India

GRAPHICAL ABSTRACT



Abstract *Copper(II)-mediated* N-*cyclopropylation of pyridinols involving copper(II) acetate, pyridine, and NaHMDS under microwave conditions in a dry air atmosphere is described.*

Keywords Copper (II) acetate; cyclopropyl boronic acid; MW; NaHMDS

INTRODUCTION

Medicinal and organic chemists have always searched for new groups and functionalities that can provide some advantage and further the exploration in drug discovery. In this respect, the cyclopropyl group has received incredible interest because of its steric, electronic properties[1] and metabolic stability.[2] Introduction of a cyclopropyl group is always a daunting task for chemists, utilizing a number of steps. Organic chemists have used various methods for its introduction: (i) alkylation of alkoxide or phenoxide anion with cyclopropyl bromide,[3] (ii) methylenation of vinyl ethers under Simmons–Smith conditions[4] and using sulfonium ylids,[5] (iii) dehalomethylation of vinyl ether with dihalocarbene followed by reductive elimination of halo,[6] (iv) alkylation of phenoxide with 1-iodo-1-(phenylthio)cyclopropane, (iv) subsequent removal of phenylthio activating in two steps,[7] and (v) cyclopropylation of aniline under reductive amination with

Received October 25, 2010.
Address correspondence to Somesh Sharma, Jubilant Chemsys Limited, B-34, Sector-58, Noida, Uttar Pradesh, 201301, India. E-mail: somesh_sharma@jchemsys.com

(1-ethoxycyclopropoxy)trimethyl silane[8] and of cyclic amide and azoles using tris-cyclopropylbismuth reagent.[9,10]

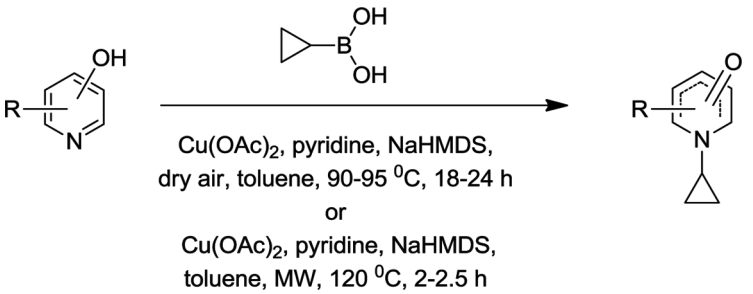
Cyclopropylation has been reported on the *N*-atom of indole, cyclic amides, and azoles in copper(II)-assisted coupling reaction conditions.[11,12] However, these substrates never posed a challenge for competitive product formation. On the other hand, pyridinols, the substrate for our studies, has *O*- and *N*-atoms in the same ring, and with Cu(II) coupling reagent (having affinity for both oxygen and nitrogen atom), challenges in the product formation and distribution is expected.

RESULTS AND DISCUSSION

In this communication, we report our investigation of *N*-cyclopropylation on substituted/unsubstituted/fused pyridinols. The preferred coupling product was obtained in coupling conditions under microwave irradiation as depicted in Scheme 1 and Table 1.

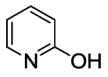
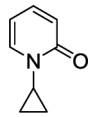
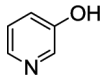
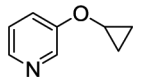
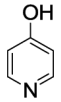
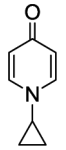
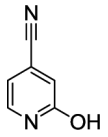
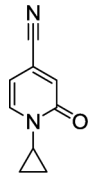
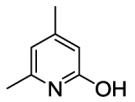
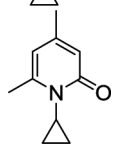
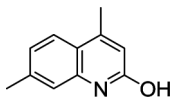
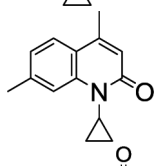
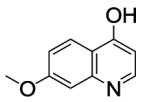
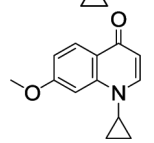
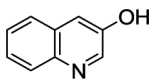
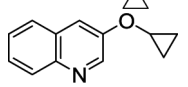
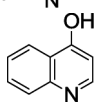
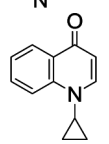
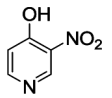
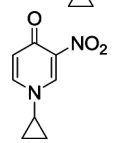
The effect of various substituents on the pyridyl system has been explored to determine the feasibility of the reaction conditions in varying electronic environments. The work was also extended to fused pyridyl systems to reveal its generality and viability. The promising results were obtained in the case of electron-donating groups as compared to electron-withdrawing groups. No product formation is observed in the cases of entries 2, 8, and 10, because of improper disposition of hydroxyl with respect to nitrogen and hydrogen bonding. In all the examples, there is a recovery of 10% of starting material under thermal conditions in contrast to microwave conditions; however, no side product formation was observed in either case. The desired product formation was further corroborated by ^{1}H NMR and ^{13}C NMR (on all examples) and heteronuclear multiple band correlation (HMBC) on representative examples (entry 1). The reaction under microwaves (MW) resulted in improved yields and shortened reaction time.

To see the influence of Li ion on product formation, LiHMDS was used as a base. There was less product conversion, and the reaction was sluggish (Scheme 2). This is due to better coordination of the Li ion with the oxygen atom in comparison to the nitrogen atom.[13] There is slight improvement in the yield (2–5%) of the product in the case of dry oxygen, and no conversion was observed in an inert atmosphere.

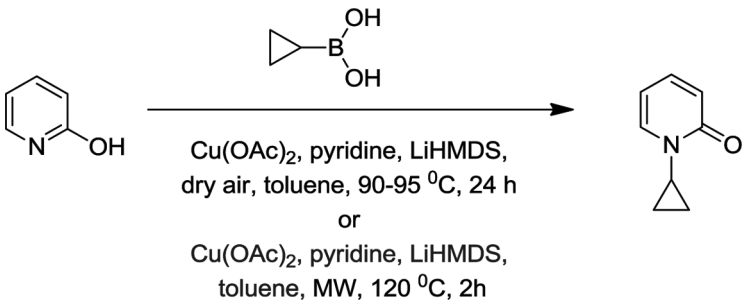


Scheme 1.

Table 1. Copper(II)-catalyzed *N*-cyclopropylation of various pyridinol derivatives

Entry	Substrate	Product	Yield (%) (time in h) conventional heating (90–95 °C)	Yield (%) (time in h) microwave heating (120 °C)
1			40 (24)	75 (2)
2			No conversion	No conversion
3			48 (24)	80 (2)
4			30 (26)	65 (2.5)
5			45 (18)	80 (2)
6			40 (18)	75 (2)
7			45 (22)	75 (2.5)
8			No conversion	No conversion
9			40 (24)	74 (2)
10			No conversion	No conversion

Notes. Reaction conditions: Substrate (1.0 equiv.), cyclopropyl boronic acid (2.0 equiv.), $Cu(OAc)_2$ (1.0 equiv.), pyridine (5.0 equiv.), NaHMDS (1.0 equiv.), dry air, and toluene.



Scheme 2.

CONCLUSION

In summary, we have successfully demonstrated copper-mediated *N*-cyclopropylation on substituted fused or unfused pyridinol systems in MW conditions. Efforts are under way to develop this chemistry for *O*-cyclopropylation with other transition-metal catalysts and ligands.

EXPERIMENTAL

^{1}H NMR, HMBC, and ^{13}C NMR spectra were recorded on a Bruker 400-MHz Ultrashield Advance II 400 model. The chemical shifts are reported in δ parts per million (ppm) relative to tetramethylsilane (TMS). The Fourier transform (FT)-infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR system Spectrum Bx. Mass spectra were recorded on a SQD-3100 Waters instrument for positive ion mode with Acquity ultrahigh performance liquid chromatography (UPLC) for purity. The laboratory-grade solvents and reagents were used without further purification. Thin-layer chromatography (TLC) was performed on silica-gel 60 F_{254} precoated plates (250-μm layers). TLC visualization was performed with ultraviolet (UV) light. A Biotage Initiator Sixty Exp 355434 instrument was used to carry out the reaction under microwaves. Flash chromatography was performed using Biotage SNAP cartridge KP-Sil 10 g on the Biotage system in MeOH/dichloromethane (DCM). Purity of the isolated compound is more than 95% by TLC.

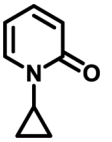
Conventional Heating Condition

Pyridinol or quinolinol (5.0 mmol, 1.0 eq), cyclopropylboronic acid (10.0 mmol, 2.0 eq), copper(II) acetate (5.0 mmol, 1.0 eq), pyridine (25.0 mmol, 5.0 eq), and toluene (10 mL) were added to a 25-mL round-bottom flask. To the mixture, NaHMDS (5.0 mmol, 1.0 eq) was added under nitrogen atmosphere. Dry air was introduced to the reaction mixture. The mixture was stirred at 100 °C for 24 h under an atmosphere of dry air, and then allowed to cool to ambient temperature. The reaction mass was passed through a celite pad. The celite pad was washed with ethyl acetate (2 × 5 mL). The organic layer was washed with water (2 × 5 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification was done on Biotage SNAP cartridge KP-Sil (10 g) using Biotage system in MeOH/DCM solvent system to afford the desired *N*-cyclopropyl pyridinone or quinolinone.

Microwave Heating Condition

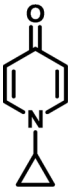
Similar reaction conditions (molar concentration and atmosphere) were maintained in microwave vial (10–20 ml) to carry out the reaction in a Biotage MW. The MW reactions were carried out at 1-g scale in 5 ml of toluene. The purification was done as described previously.

1-Cyclopropylpyridin-2(1H)-one (1)



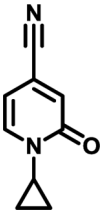
^{1}H NMR (400 MHz, DMSO-d_6): δ 7.50 (d, 1H, $J = 6.8$ Hz), 7.36 (t, 1H, $J = 7.2$ Hz), 6.34 (d, 1H, $J = 9.2$ Hz), 6.15 (t, 1H, $J = 6.8$ Hz), 3.35 (m, 1H), 0.96 (m, 2H), 0.81 (m, 2H) ppm; ^{13}C NMR (100 MHz, MeOD): δ 165.13, 140.41, 137.61, 118.99, 107.03, 32.25, and 5.86 ppm; MS: $m/z = 136.06$ (M + 1); HRMS: obs. 136.0688, cal. 136.0762; IR (neat, cm^{-1}): 1636, 1547, 1399, 1362, 1257, 1183, 1068, 1018, 856, 524.

1-Cyclopropylpyridin-4(1H)-one (3)



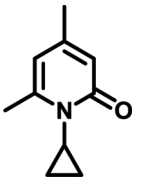
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, 2H, $J = 7.6$ Hz), 6.34 (d, 2H, $J = 7.6$ Hz), 3.39 (m, 1H), 1.08 (m, 2H), 1.00 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.35, 140.78, 118.46, 36.96 and 7.11 ppm; MS: $m/z = 136.04$ (M + 1); HRMS: obs. 136.0675, cal. 136.762; IR (neat, cm^{-1}): 1638, 1545, 1458, 1400, 1362, 1256, 1199, 1183, 1068, 1018, 884, 856, 694, 524.

1-Cyclopropyl-2-oxo-1,2-dihydropyridine-4-carbonitrile (4)



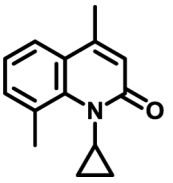
^{1}H NMR (400 MHz, DMSO-d_6): δ 7.77 (d, 1H, $J = 7.2$ Hz), 6.99 (d, 1H, $J = 1.2$ Hz), 6.46 (dd, 1H, $J = 1.6$ Hz, 7.2 Hz), 3.33 (m, 1H), 1.00 (m, 2H), 0.87 (m, 2H) ppm; ^{13}C NMR (100 MHz, MeOD): δ 162.90, 139.96, 124.81, 124.67, 115.45, 105.72, 32.79, and 5.93 ppm; MS: $m/z = 161.22$ (M + 1); HRMS: obs. 161.0805, cal. 161.0715; IR (neat, cm^{-1}): 2244, 1662, 1587, 1514, 1330, 1302, 1200, 1032, 876, 792, 737, 627.

1-Cyclopropyl-4,6-dimethylpyridin-2(1H)-one (5)



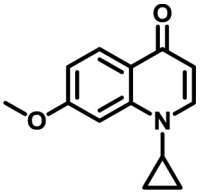
^{1}H NMR (400 MHz, DMSO-d_6): δ 5.97 (s, 1H), 5.91 (s, 1H), 2.76 (m, 1H), 2.37 (s, 3H), 2.02 (s, 3H), 1.08 (m, 2H), 0.72 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.30, 150.15, 147.32, 117.03, 109.56, 27.73, 21.03, 20.51, and 10.32 ppm; MS: $m/z = 164.18$ (M + 1); HRMS: obs. 164.1022, cal. 164.1075; IR (neat, cm^{-1}): 1656, 1577, 1548, 1347, 1240, 1033, 892, 823, 613, 525.

1-Cyclopropyl-4,8-dimethylquinolin-2(1H)-one (6)



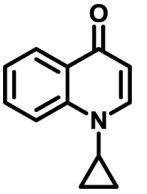
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, 1H, $J = 7.6$ Hz), 7.32 (d, 1H, $J = 7.2$ Hz), 7.13 (t, 1H, $J = 7.6$ Hz), 6.44 (s, 1H), 3.44 (m, 1H), 2.72 (s, 3H), 2.38 (s, 3H), 1.20 (m, 2H), 0.60 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.31, 146.69, 141.35, 133.91, 126.93, 123.51, 122.66, 122.42, 121.45, 32.67, 22.44, 19.35, and 12.44 ppm; MS: $m/z = 214.26$ (M + 1); HRMS: obs. 214.1290, cal. 214.123; IR (neat, cm^{-1}): 1650, 1583, 1440, 1381, 1277, 1165, 1025, 862, 747.

1-Cyclopropyl-7-methoxyquinolin-4(1H)-one (7)



^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 (d, 1H, $J = 8.8$ Hz), 7.88 (d, 1H, $J = 7.6$ Hz), 7.36 (d, 1H, $J = 6.0$ Hz), 7.02 (dd, 1H, $J = 2.4$ Hz, 8.8 Hz), 5.92 (d, 1H, $J = 8.0$ Hz), 3.92 (s, 3H), 3.49 (m, 1H) 1.20 (m, 2H), 1.00 (m, 2H) ppm; ^{13}C NMR (100 MHz, MeOD): δ 178.31, 163.23, 143.91, 143.51, 127.25, 119.89, 113.87, 108.23, 98.39, 54.84, 33.86, and 7.16 ppm; MS: $m/z = 216.14$ (M + 1); HRMS: obs. 216.1132, cal. 216.1025.

1-Cyclopropylquinolin-4(1H)-one (9)



^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15 (dd, 1H, $J = 1.2$ Hz, 8.0 Hz), 8.03 (d, 1H, $J = 8.8$ Hz), 7.98 (d, 1H, $J = 8.0$ Hz), 7.77 (m, 1H), 7.41 (t, 1H, $J = 7.6$ Hz), 6.00 (d, 1H, $J = 7.6$ Hz), 3.53 (m, 1H), 1.19 (m, 2H), 1.02 (m, 2H) ppm; ^{13}C NMR (100 MHz, MeOD): δ 178.82, 144.22, 141.55, 132.32, 125.41, 124.06, 116.93, 108.42, 33.95, 7.22 ppm; MS: $m/z = 186.08$ (M + 1), HRMS: obs. 186.0938, cal. 186.0919.

ACKNOWLEDGMENT

We are thankful to Jubilant Chemsys Limited for funding our research work and providing the infrastructure support.

REFERENCES

1. (a) Brown, H. C.; Fletcher, R. S.; Johannesen, R. B. I-strain as a factor in the chemistry of ring compounds. *J. Am. Chem. Soc.* **1951**, *73*, 213–221; (b) Roberts, J. D.; Chambers, V. C. Small-ring compounds, VII: Physical and chemical properties of cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl derivatives. *J. Am. Chem. Soc.* **1951**, *73*, 5030–5034.
2. Shaffer, C. L.; Harriman, S.; Koen, Y. M.; Hanzlik, R. P. Formation of cyclopropanone during cytochrome P450-catalysed N-dealkylation of a cyclopropylamine. *J. Am. Chem. Soc.* **2002**, *124*, 8268–8274.
3. Lesher, G. Y. N,N′-Heptamethylenebis(4-methoxybenzamide). U.S. Patent 4009208, February 22, 1977.
4. (a) Shostakovskii, S. M.; L'vov, A. I.; Kimel'fel'd, Y. M. Cyclopropyl aryl ethers. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1966**, 1754, Chem. Abstr. **66**, 37558; (b) Retinskii, A. A.; Shostakovskii, S. M.; Kositsyna, E. I. Phenyl cyclopropyl ethers in electrophilic substitution. *Izv Akad. Nauk SSSR, Ser Khim.* **1972**, 1778; (Chem. Abstr. 77, 151590; (c) Furukawa, J.; Kawabata, N.; Nishimura, J. Synthesis of cyclopropanes by the reaction of olefins with dialkylzinc and methylene iodide. *Tetrahedron* **1968**, *24*, 53–58.
5. Cimetiere, B.; Julia, M. Alkene cyclopropanation with sulfonium ylids. *Synlett* **1991**, 271.
6. (a) Retinskii, A. A.; Shostakovskii, S. M. Reduction of 1-alkyl(aryl)oxy-2,2-dichlorocyclopropane. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1967**, 413; *Chem. Abstr.* **67**,

21464; (b) Retinskii, A. A.; Tolmasova, V. P.; Kotomanova, G. P.; Shostakovskii, S. M. Synthesis and some conversion of gem-dihalocyclopropyl ethers. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1968**, 164; *Chem. Abstr*. **69**, 18643.

7. Hollingworth, G. J.; Dinnell, K.; Dickinson, L. C.; Elliott, J. M.; Kulagowski, J. J.; Swain, C. J.; Thomson, C. G. A convenient method for the preparation of aryl cyclopropyl ethers from phenols. *Tetrahedron Lett.* **1999**, *40*, 2633–2636.
8. (a) Kang, J.; Kim, K. S. N-Cyclopropylation of aromatic amines. *J. Chem. Soc., Chem. Commun.* **1987**, 897–898; (b) Gillaspy, M. L.; Lefker, B. A.; Hada, W. A.; Hoover, D. J. A simple method for the formation of cyclopropylamine: The first synthesis of tricyclopropylamine. *Tetrahedron Lett.* **1995**, *36*, 7399–7402; (c) Yoshida, Y.; Umeza, K.; Hamada, Y.; Atsumi, N.; Tabuchi, F. Practical synthesis of N-cyclopropylanilines via direct condensation of anilines with [(1-ethoxycyclopropyl)oxy]trimethylsilane. *Synlett* **2003**, 2139–2142.
9. Gagnon, A.; St-Onge, M.; Little, K.; Duplessis, M.; Barabe, F. Direct N-cyclopropylation of cyclic amides and azoles Employing a cyclopropylbismuth reagent. *J. Am. Chem. Soc.* **2007**, *129*, 44–45.
10. (a) Liang, G. B.; Qian, X.; Feng, D.; Biftu, T.; Eiermann, G.; He, H.; Leiting, B.; Lyons, K.; Petrov, A.; Sinha-Roy, R.; Zhang, B.; Wu, J.; Zhang, X.; Thornberry, N. A.; Weber, A. E. Optimization of 1,4-diazepan-2-one containing dipeptidyl peptidase IV inhibitors for the treatment of type 2 diabetes. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1903–1907; (b) Tran, T. P.; Ellsworth, E. L.; Stier, M. A.; Domagala, J. M.; Showalter, H. D. H.; Gracheck, S. J.; Shapiro, M. A.; Joannides, T. E.; Singh, R. Synthesis and structural–activity relationship of 3-hydroxyquinazoline-2,4-dione antibacterial agents. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4405–4409.
11. Tsuritani, T.; Strotman, N. A.; Yamamoto, Y.; Kawasaki, M.; Yasuda, N.; Mase, T. N-Cyclopropylation of indoles and cyclic amides with copper(II) reagent. *Org. Lett.* **2008**, *10*, 1653–1655.
12. Benard, S.; Neuville, L.; Zhu, J. Copper-mediated N-cyclopropylation of azoles, amides, and sulfonamides by cyclopropylboronic acid. *J. Org. Chem.* **2008**, *73*, 6441–6444.
13. Izatt, R. M.; Bradshaw, J. S.; Dalley, N. K. Coordination chemistry of lithium ion: A crystal and molecular structure review. *Chem. Rev.* **1991**, *91*, 137–164.