

HETEROCYCLES, Vol. 95, No. 2, 2017, pp. 1177-1183. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 1st September, 2016, Accepted, 14th November, 2016, Published online, 24th January, 2017
DOI: 10.3987/COM-16-S(S)66

SYNTHESIS OF 2-AROYL-1-METHYL-1*H*-IMIDAZOLES USING ARYL CARBOXYLIC ACIDS[‡]

Kin-ichi Oyama,^{a,*} Noriyuki Watanabe,^b and Kumi Yoshida^{b,*}

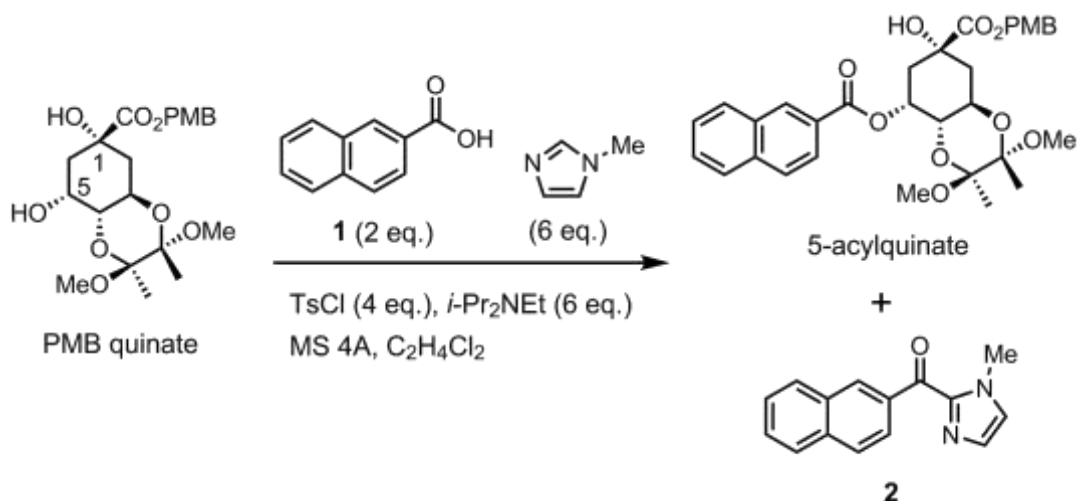
^aChemical Instrumentation Facility, Research Center for Materials Science,

^bGraduate School of Information Science, Nagoya University, Chikusa, Nagoya 464-8601, Japan; E-mail: oyama@cic.nagoya-u.ac.jp, yoshidak@is.nagoya-u.ac.jp

Abstract – A new and useful reaction for the synthesis of 2-aryl-1-methyl-1*H*-imidazoles using free aryl carboxylic acids was developed. This method was applicable to naphthoic acid and benzoic acid derivatives to give each target compound with up to 80% yield.

2-Aroylimidazoles are common structural motifs found in natural products¹ and pharmacologically active compounds.² In addition, they serve as precursors in useful organic reactions³ and as synthons for the synthesis of more complicated bioactive compounds.⁴ 2-Aroyl-1-methyl-1*H*-imidazoles have been classically prepared by reacting *N*-methylimidazole with aroyl chlorides in the presence of triethylamine.⁵ Additionally, several methods based on the addition of 2-lithioimidazole to ketones have been developed.⁶ Recently, synthesis using *N*-arylamino-substituted *N*-heterocyclic carbene⁷ and a palladium-catalyzed synthesis⁸ have been reported. However, to the best of our knowledge, synthesis using unmodified aryl carboxylic acids remains unexplored. Herein, we report a first synthetic route of 2-aryl-1-methyl-1*H*-imidazoles using *N*-methylimidazole and free aryl carboxylic acids.

We have been interested in esterification reactions of hindered and low-reactive hydroxy groups with carboxylic acids; inspired by Tanabe's report,⁹ we developed an effective synthetic method of 5-acylquinic acids using unmodified carboxylic acids in the presence of TsCl, *N*-methylimidazole, and *i*-Pr₂NEt (Scheme 1).¹⁰ During that study, an unexpected product **2** was obtained (Scheme 1). This esterification might involve an acylammonium intermediate which may be formed after tosylation.⁹ Based on these observations, we sought to establish a new synthetic methodology of 2-aryl-1-methyl-1*H*-imidazoles using unmodified aryl carboxylic acids.



Scheme 1. Esterification with 2-naphthoic acid (**1**) in the presence of TsCl, *N*-methylimidazole, and *i*-Pr₂NEt

Table 1. Optimization of the condensation between 2-naphthoic acid (**1**) and *N*-methylimidazole in the presence of TsCl and *i*-Pr₂NEt



entry	NMI (eq.)	temp (°C)	time (h)	yield (%) ^a
1	3	40	1	28
2 ^b	3	40	2	0
3	3	30	2	34
4	3	40	2	40
5	3	40	3	34
6	3	60	2	24
7	6	40	2	65
8	9	40	2	63

NMI means *N*-methylimidazole.

1 (0.5 mmol) was used in all reactions.

Molar ratio: NMI/TsCl/*i*-Pr₂NEt = 3/2/3

^a Isolated yield. ^b Without *i*-Pr₂NEt.

First, the effect of *i*-Pr₂NEt in the condensation reaction of *N*-methylimidazole and 2-naphthoic acid (**1**) was examined. In the presence of TsCl in 1,2-dichloroethane at 40 °C, the reaction with *i*-Pr₂NEt for 1 h gave the desired arylimidazole **2** in 28% yield (Table 1, entry 1). However, the reaction without *i*-Pr₂NEt for 2 h gave no **2** at all despite a longer reaction time (Table 1, entry 2). These results indicated that *i*-Pr₂NEt as an amine base was essential to promote the reaction. To increase the yield, the reaction time, temperature, and equimolar amount of *N*-methylimidazole were further examined. The optimized reaction conditions were 2 h at 40 °C (Table 1, entries 2-6). By addition of 6 eq. of *N*-methylimidazole at 40 °C for 2 h, **2** was obtained in 65% yield (Table 1, entry 7).

Table 2. Synthesis of 2-aryl-1-methyl-1*H*-imidazoles (**8-12**) with various aryl carboxylic acids (**3-7**)

Reaction scheme: Ar-COOH (**3-7**) + *N*-Me-imidazole (6 eq.) $\xrightarrow[\text{C}_2\text{H}_4\text{Cl}_2, 40\text{ }^\circ\text{C}, 2\text{ h}]{\text{TsCl (4 eq.), } i\text{-Pr}_2\text{NEt (6 eq.), MS 4A}}$ Ar-CO-Imidazole (**8-12**)

entry	RCO ₂ H	product	yield (%) ^a
1		8	48%
2		9	50%
3		10	48%
4		11	56%
5		12	80%

Carboxylic acids (0.5 mmol) were used in all reactions.

^a Isolated yield.

Using the optimized reaction conditions (6 eq. of *N*-methylimidazole, 4 eq. of TsCl, and 6 eq. of *i*-Pr₂NEt in 1,2-dichloroethane at 40 °C for 2 h) we carried out the reaction using various aryl carboxylic acids to evaluate the applicability of the reaction (Table 2). In each reaction, 2-aryl-1-methyl-1*H*-imidazoles were obtained with satisfactory yields (Table 2). The difference between an electron-donating group (6-methoxy-2-naphthoic acid, **3**) and an electron-withdrawing group (6-acetoxy-2-naphthoic acid, **4**) at the 6-position of naphthoic acid did not cause an obvious difference in yields (Table 2, entries 1 and 2). Among the naphthoic acid derivatives, unsubstituted **1** afforded the highest yield (65%, Table 1, entry 7). On the other hand, with benzoic acid derivatives, an increase in the electron-withdrawing effect at the 4-position increased the yield to 48% with benzoic acid, 56% with 5-fluorobenzoic acid, and 80% with 4-nitrobenzoic acid (Table 2, entries 3-5).

In summary, we developed a new methodology for the synthesis of 2-aryl-1-methyl-1*H*-imidazoles using unmodified aryl carboxylic acids. This method was applicable to naphthoic acid and benzoic acid derivatives with up to 80% yield.

EXPERIMENTAL

Melting points (mp) were determined on a Yanaco MP-3 instrument and are uncorrected. Infrared (IR) spectra were recorded on a JASCO FT/IR 6100 spectrometer. ¹H and ¹³C NMR spectra were recorded on a JNM ECA-500 spectrometer. Chemical shifts for ¹H NMR are reported in parts per million (ppm) downfield from tetramethylsilane (TMS: δ 0.00 ppm) as an internal reference. Chemical shifts for ¹³C NMR were reported in the scale relative to the NMR solvent (CDCl₃: δ 77.0 ppm) as an internal reference. High resolution mass spectra (HRMS) were recorded on a JEOL JMS-700 (FAB) and Bruker micrOTOF-QII (ESI) spectrometer. Flash column chromatography was performed on Fuji Silysia silica gel (PSQ 60B). Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F₂₅₄. All commercially available reagents and solvents were used directly without further purification. All reactions were carried out under an argon atmosphere. MS 4A were dried in the following manner: MS 4A was placed in a round-bottom flask. MS 4A was heated in a regular microwave for 1.5-2.0 min, and the flask was immediately evacuated. After being cooled to room temperature, the flask was backfilled with argon. The above procedure was repeated three times.

Compound 2: To a solution of 2-naphthoic acid (**1**) (86 mg, 0.5 mmol), TsCl (381 mg, 2.0 mmol), and MS 4A (ca. 0.8 g) in 1,2-dichloroethane (3.0 mL) was added *i*-Pr₂NEt (523 μL, 3.0 mmol) at room temperature. After the resulting mixture was stirred at room temperature for 30 min, *N*-methylimidazole (239 μL, 3.0 mmol) was added to the reaction mixture. After stirring for 2 h at 40 °C, the reaction mixture was quenched with saturated aqueous NH₄Cl. The crude products were extracted with AcOEt. The combined extracts were washed with saturated aqueous NaHCO₃ and dried over anhydrous Na₂SO₄. The

solvent was concentrated under reduced pressure and the residue was purified by flash column chromatography (30% AcOEt in hexane) to give **2** (77 mg, 65%) as a pale yellow oil; IR (neat) 3058, 2957, 1638, 1466, 1401, 1274, 1236, 1162, 1118, 903, 781 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.12 (s, 3H), 7.14 (s, 1H), 7.28 (s, 1H), 7.53 (ddd, $J = 8.3, 7.0, 1.0$ Hz, 1H), 7.59 (ddd, $J = 8.3, 7.0, 1.0$ Hz, 1H), 7.88 (d, $J = 8.5$ Hz, 1H), 7.92 (d, $J = 8.5$ Hz, 1H), 8.01 (d, $J = 8.5$ Hz, 1H), 8.27 (dd, $J = 8.5, 1.5$ Hz, 1H), 8.99 (brs, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 36.4, 125.9, 126.4, 126.7, 127.6, 127.8, 128.3, 129.3, 129.9, 132.4, 133.3, 134.5, 135.4, 143.3, 183.9; HRMS (ESI) Calcd for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 237.1022. Found 237.1034.

Compound 8: According to the procedure described for **2**, the reaction of 6-methoxy-2-naphthoic acid (**3**) (101 mg, 0.5 mmol) was carried out to afford **8** (64 mg, 48%) as a white solid (solvent used for flash column chromatography: 25% acetone in hexane); mp 83–85 $^\circ\text{C}$; IR (KBr) 1618, 1475, 1389, 1268, 1212, 1166, 1142, 1024, 878 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 3.96 (s, 3H), 4.11 (s, 3H), 7.13 (brs, 1H), 7.16–7.20 (m, 2H), 7.27 (brs, 1H), 7.80 (d, $J = 8.5$ Hz, 1H), 7.90 (d, $J = 8.5$ Hz, 1H), 8.27 (dd, $J = 8.5, 1.5$ Hz, 1H), 8.94 (brs, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 36.3, 55.3, 105.6, 119.3, 126.5, 126.6, 126.7, 127.7, 129.1, 131.6, 132.4, 133.3, 137.1, 143.4, 159.7, 183.6; HRMS (FAB) Calcd for $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 267.1134. Found 267.1132.

Compound 9: According to the procedure described for **2**, the reaction of 6-acetoxy-2-naphthoic acid (**4**) (115 mg, 0.5 mmol) was carried out to afford **9** (74 mg, 50%) as a yellow solid (solvent used for flash column chromatography: 25% acetone in hexane); mp 106–108 $^\circ\text{C}$; IR (KBr) 1766, 1625, 1396, 1189, 1136, 1010, 888 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 2.37 (s, 3H), 4.12 (s, 3H), 7.15 (brs, 1H), 7.28 (brs, 1H), 7.30 (dd, $J = 9.0, 2.0$ Hz, 1H), 7.61 (d, $J = 2.0$ Hz, 1H), 7.88 (d, $J = 9.0$ Hz, 1H), 8.03 (d, $J = 9.0$ Hz, 1H), 8.30 (dd, $J = 9.0, 2.0$ Hz, 1H), 9.01 (brs, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 21.2, 36.4, 118.3, 121.7, 126.7, 126.8, 127.5, 129.2, 130.3, 131.5, 133.1, 134.4, 135.9, 143.2, 150.2, 169.2, 183.4; HRMS (FAB) Calcd for $\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 295.1083. Found 295.1073.

Compound 10: According to the procedure described for **2**, the reaction of benzoic acid (**5**) (61 mg, 0.5 mmol) was carried out to afford **10** (45 mg, 48%) as pale yellow oil (solvent used for flash column chromatography: 30% AcOEt in hexane); IR (neat) 1643, 1447, 1399, 1262, 1168, 902 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.08 (s, 3H), 7.10 (s, 1H), 7.23 (s, 1H), 7.48 (t, $J = 7.5$ Hz, 2H), 7.56 (t, $J = 7.5$ Hz, 1H), 8.26 (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 44.5, 116.8, 117.8, 118.8, 120.0, 121.5, 125.2, 129.9, 162.7; HRMS (FAB) Calcd for $\text{C}_{11}\text{H}_{11}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 187.0871. Found 187.0868.

Compound 11: According to the procedure described for **2**, the reaction of 4-fluorobenzoic acid (**6**) (70 mg, 0.5 mmol) was carried out to afford **11** (57 mg, 56%) as a yellow solid (solvent used for flash column chromatography: 25% AcOEt in hexane); mp 63–66 $^\circ\text{C}$; IR (KBr) 3050, 1649, 1599, 1397, 1268, 1214, 1152, 905, 774 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.08 (s, 3H), 7.12 (s, 1H), 7.16 (t, $J = 9.0$ Hz, 2H),

7.23 (s, 1H), 8.38 (dd, $J = 9.0, 5.8$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 36.5, 115.1 (d, $J = 21.5$ Hz), 126.9, 129.3, 133.5 (d, $J = 9.5$ Hz), 142.9, 165.6 (d, $J = 252.6$ Hz), 182.3; HRMS (FAB) Calcd for $\text{C}_{11}\text{H}_{10}\text{FN}_2\text{O}$ $[\text{M}+\text{H}]^+$ 205.0777. Found 205.0779.

Compound 12: According to the procedure described for **2**, the reaction of 4-nitrobenzoic acid (**7**) (84 mg, 0.5 mmol) was carried out to afford **12** (92 mg, 80%) as a yellow solid (solvent used for flash column chromatography: CHCl_3); mp 166–167 °C; IR (KBr) 3107, 1640, 1599, 1514, 1352, 1251, 1141, 906 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 4.12 (s, 3H), 7.17 (d, $J = 1.0$ Hz, 1H), 7.27 (d, $J = 1.0$ Hz, 1H), 8.31 (d, $J = 9.0$ Hz, 2H), 8.45 (d, $J = 9.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 36.6, 123.1, 127.8, 130.0, 131.7, 142.4, 142.5, 149.8, 181.9; HRMS (ESI) Calcd for $\text{C}_{11}\text{H}_9\text{N}_3\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$ 254.0536. Found 254.0544.

ACKNOWLEDGMENTS

This work was financially supported in part by a SUNBOR GRANT (Suntory Institute for Bioorganic Research) and the Ministry of Education, Culture, Sports, Science and Technology, Japan (Global COE in Chemistry, Nagoya University, Priority Areas No. 18032037, Creative Scientific Research (B) No. 24380062, and Young Scientists (B) No. 18780086).

REFERENCES

- ‡ This paper is dedicated to Prof. Masakatsu Shibasaki on the occasion of his 70th birthday.
- (a) K. Bartik, J.-C. Braekman, D. Dalozze, C. Stoller, J. Huysecom, G. Vandevyver, and R. Ottinger, *Can. J. Chem.*, **1987**, **65**, 2118; (b) L. Arabshahi and F. J. Schmitz, *Tetrahedron Lett.*, **1988**, **29**, 1099; (c) R. Durán, E. Zubía, M. J. Ortega, S. Naranjo, and J. Salvá, *Tetrahedron*, **1999**, **55**, 13225.
 - (a) G. Caliendo, G. Cirino, G. Grecol, E. Novellino, E. Perissutti, A. Pinto, V. Santagada, and L. Sorrentino, *Eur. J. Med. Chem.*, **1995**, **30**, 315; (b) M. Kim, J. Lee, K. Jung, H. Kim, W. Aman, J.-S. Ryu, and J.-M. Hah, *Bioorg. Med. Chem. Lett.*, **2014**, **24**, 3600.
 - (a) R. Y. Ning, J. F. Blount, P. B. Madan, and R. I. Fryer, *J. Org. Chem.*, **1977**, **42**, 1791; (b) S. Ohta, S. Hayakawa, and M. Okamoto, *Tetrahedron Lett.*, **1984**, **25**, 5681; (c) S. Ohta, S. Hayakawa, H. Moriwaki, S.-i. Tsuboi, and M. Okamoto, *Heterocycles*, **1985**, **23**, 1759.
 - (a) M. Nagaraj, M. Boominathan, S. Muthusubramanian, and N. Bhuvanesh, *Synlett*, **2012**, **23**, 1353; (b) S. Demirayak and I. Kayagil, *J. Heterocycl. Chem.*, **2005**, **42**, 319.
 - (a) E. Regel and K.-H. Büchel, *Liebigs Ann. Chem.*, **1977**, 145; (b) G. Steiner, A. Krajete, H. Kopacka, K.-H. Ongania, K. Wurst, P. Preishuber-Pflügl, and B. Bildstein, *Eur. J. Inorg. Chem.*, **2004**, 2827; (c) K. Ushiroda, K. Maruta, T. Takazawa, T. Nagano, M. Taiji, T. Kohno, Y. Sato, S. Horai, K. Yanagi, and R. Nagata, *Bioorg. Med. Chem. Lett.*, **2011**, **21**, 1978.

6. (a) S. Ohta, S. Hayakawa, K. Nishimura, and M. Okamoto, [*Tetrahedron Lett.*, 1984, **25**, 3251](#); (b) B. Abarca-Gonzalez, R. A. Jones, M. Medio-Simon, J. Quilez-Pardo, J. Sepulveda-Arques, and E. Zaballos-Garcia, [*Synth. Commun.*, 1990, **20**, 321](#); (c) S. Ushijima, S. Dohi, K. Moriyama, and H. Togo, [*Tetrahedron*, 2012, **68**, 1436](#); (d) R. C. Samanta, S. D. Sarkar, R. Fröhlich, S. Grimme, and A. Studer, [*Chem. Sci.*, 2013, **4**, 2177](#).
7. T. Zarganes-Tzitzikas, C. G. Neochoritis, J. Stephanidou-Stephanatou, and C. A. Tsoleridis, [*J. Org. Chem.*, 2011, **76**, 1468](#).
8. J. Tjutrins and B. A. Arndtsen, [*J. Am. Chem. Soc.*, 2015, **137**, 12050](#).
9. K. Wakasugi, A. Iida, T. Misaki, Y. Nishii, and Y. Tanabe, [*Adv. Synth. Catal.*, 2003, **345**, 1209](#).
10. K.-I. Oyama, N. Watanabe, T. Yamada, M. Suzuki, Y. Sekiguchi, T. Kondo, and K. Yoshida, [*Tetrahedron*, 2015, **71**, 3120](#).