HETEROCYCLES, Vol. 74, 2007, pp. 629 - 635. © The Japan Institute of Heterocyclic Chemistry
Received, 22nd August, 2007, Accepted, 4th October, 2007, Published online, 5th October, 2007. COM-07-S(W)40

EFFICIENT SYNTHESIS OF SUBSTITUTED INDOLES AND BENZAZOLES BY OXIDATIVE AROMATIZATION USING ACTIVATED CARBON—MOLECULAR OXYGEN SYSTEM

Yukiko Nomura, Yuka Kawashita, and Masahiko Hayashi*

Department of Chemistry, Graduate School of Science, Kobe University, Nada, Kobe 657-8501, Japan
*E-mail: mhayashi@kobe-u.ac.jp

Abstract—Efficient synthesis of substituted indoles was achieved by oxidative aromatization of indolines using activated carbon—molecular oxygen (O_2) system. Benzazoles (benzimidazole and benzothiazoles) were also prepared by the reaction of 1,2-phenylenediamine and 2-aminobenzenethiol with formaldehyde in the presence of activated carbon under oxygen atmosphere.

The indole moiety occurs naturally in a variety of structures.[1] There are many synthetic methods for indole framework. Fischer indole synthesis[2] is one of the most classical and established methods. Other than Fischer indole synthesis, Reissert synthesis,[3] Gassman synthesis,[4] Bartoli synthesis,[5] Madelung synthesis,[6] Nenitzescu synthesis,[7] Larock synthesis[8] and their modified methods have been reported. All of these include cyclization step. On the other hand, dehydrogenation of indolines to indoles should be alternative. Actually, recently, Kaneda and co-workers reported dehydrogenation of indolines to indoles using hydroxyapatite-bound palladium catalyst (toluene, under argon, 100 °C).[9] We recently reported oxidative aromatization using activated carbon—O_2 system. For examples, conversions of substituted pyrazolines to pyrazoles,[10] dihydropyridines to pyridines,[10] and 9,10-dihydroanthracenes to anthracenes[11] have been realized. Furthermore, direct synthesis of 2-arylbenzoxazoles,[12] 2-arylbenzimidazoles,[12] and 2-arylbenzothiazoles[13] by the reaction of substituted 2-aminophenols, 1,2-phenylenediamines, and 2-aminobenzenethiols with aryl aldehydes in the presence of activated carbon under oxygen or air atmosphere are also accomplished.

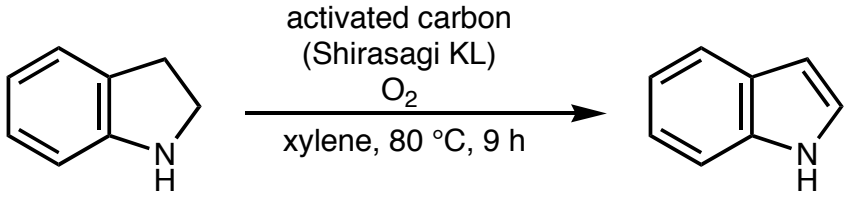
Here, we report efficient synthesis of substituted indoles and benzazoles by oxidative aromatization using activated carbon—O_2 system. Benzazoles that have no substituents at 2-position are also versatile compounds because they have potentiality to be introduced some substituents at 2-position. For

---

This paper is dedicated to Prof. Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

example, Bellina and Rossi reported palladium- and copper- mediated C-2 arylation of benzazoles.[14] At first, we examined the effect of the amount of activated carbon (Shirasagi KL, Japan EnviroChemicals, Ltd) in xylene at 80 °C for 9 h. As shown in Table 1, when the activated carbon was absent, only 6% of

Table 1. Effect of the amount of activated carbon (Shirasagi KL)[a]

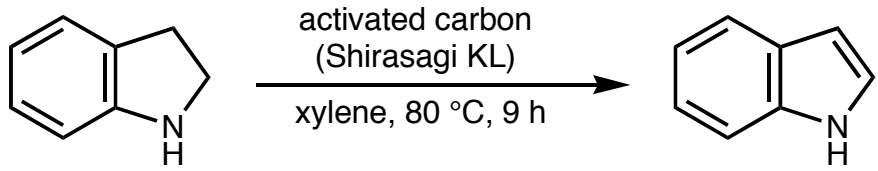


entry	activated carbon/wt%	yield/%[b]
1	none	6
2	20	11
3	50	46
4	100	89

[a] All reactions were carried out in xylene at 80 °C for 9 h.
[b] Isolated yield after silica-gel column chromatography.

indole was obtained from indoline. The yield increased to 89% in the presence of 100 weight% (wt%) of activated carbon. Then, we confirmed the effect of molecular oxygen (Table 2).

Table 2. Effect of oxygen[a]

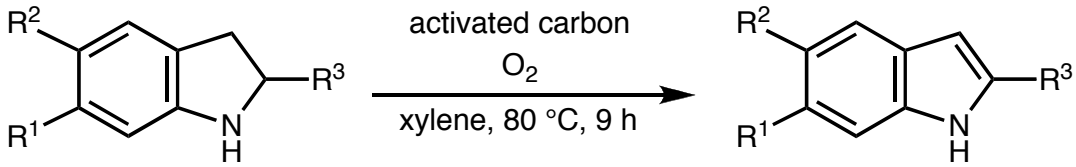


entry	activated carbon/wt%	yield/%[b]
1	Ar	16
2	air	71
3	O_2	89

[a] All reactions were carried out using 100 wt% of Shirasagi KL in xylene at 80 °C for 9 h. [b] Isolated yield after silica-gel column chromatography.

When the reaction was carried out under argon atmosphere, indole was obtained in 16%. This formation may be attributed to the existence of the oxygen in activated carbon. The reaction also proceeded even under air atmosphere (71%). When the reaction was done in the presence of molecular oxygen, 89% of indole was obtained. Using the optimized conditions, a variety of indoline derivatives were oxidized to the corresponding indoles. The results are summarized in Table 3. In all cases we examined, Shirasagi KL was more effective than Darco®KB.

Table 3. Oxidative conversion of substituted Indolines to Indoles[a]



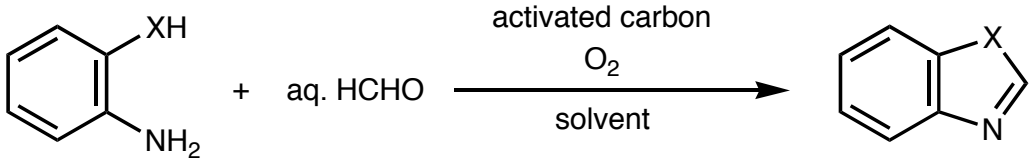
entry	R^1	R^2	R^3	yield/%[b,c]
1	H	H	H	89 (73)
2	H	H	CH_3	84 (80)
3	H	CH_3	H	98 (72)
4	H	Cl	H	75 (66)
5	H	Br	H	81 (72)
6[d]	H	NO_2	H	63[e] (nd)[f]
7[d]	NO_2	H	H	65[e] (nd)[f]

[a] All reactions were carried out using 100 wt% of Shirasagi KL in xylene at 80 °C for 9 h. [b] Isolated yield after silica-gel column chromatography unless otherwise noted. [c] The values in the parentheses are yields when Darco®KB was used instead of Shirasagi KL as an activated carbon. [d] Reactions were carried out at 120 °C. [e] Isolated yield after recrystallization. [f] nd = no data

Replacement of carbon atom of 3-position to heteroatoms such as oxygen, nitrogen and sulfur atom leads to the synthesis of benzazoles, that is, benzoxazole, benzimidazole, and benzothiazole. This inspiration encouraged us to realize the efficient synthesis of benzazoles.[15] That is, the reaction of 1,2-phenylenediamine and 2-aminobenzenethiol with formaldehyde (37 wt% solution in water containing 8% MeOH) afforded the benzimidazole and benzothiazole, respectively. The obtained results are summarized in Table 4. Unfortunately, the reaction of 2-aminophenol with formaldehyde gave benzoxazole in low yield (entry 5). Generally, in our activated carbon—O_2 system, the reaction proceed in both of acetic acid and xylene, however, in some cases, the products are unstable in acetic acid to cause the decomposition of the products. As shown in entry 2 and 4 in Table 4, in this case both of

benzimidazole and benzthiazole are tolerable in acetic acid.

Table 4. Preparation of benzimidazole, benzothiazole and benzoxazole[a]

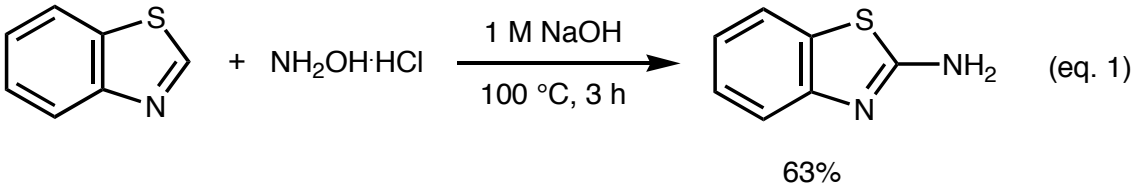


entry	X	solvent	temp/°C	time/h	yield[b]
1	NH	xylene	80	4	70
2	NH	AcOH	115	3	91
3	S	xylene	80	4	79
4	S	AcOH	115	3	68
5	O	xylene	80	4	9

[a] All reactions were carried out using 1.5 equiv. of formaldehyde (37 wt% solution in water containing 8% MeOH). [b] Isolated yield after silica-gel column chromatography.

As for reaction mechanism, to clarify the mechanism, especially, to obtain the information concerning the role of activated carbon, we examined the oxidative aromatization using more than ten kinds of activated carbons those have different surface areas, micropore volumes, and contents of oxygen functional group. Then we revealed that the multiplier effect of surface area and contents of oxygen functional group evolved as CO in micropore played very important role to make the reaction proceed effectively. From the above reason, Shirasagi KL and Darco®KB are effective than other activated carbon. The reason why Shirasagi KL was more effective than Darco®KB is also explained based on the same reason. Concerning the contamination of trace amount of metals those exist in original materials, we concluded that the contaminated metals are not so effective by the following experiments. We washed several kinds of activated carbons with acid to remove the contained metals, then after confirmation of removal of metals by ICP spectroscopy, we examined the oxidative aromatization reactions using activated carbon before and after washing. The results indicated that activated carbon before and after washing showed about the same reactivity. So we concluded that the contaminated metals are not so effective in this reaction. Anyway the detailed reaction mechanism of the activated carbon—O_2 system seems very complicated, so the mechanism, especially concerning on the role of micropore in activated carbon in oxidative aromatization reaction will be discussed in near future.

We then introduce amino group at 2-position of benzothiazole by the reaction with hydroxylamine hydrochloride as shown in eq. 1. Further study for introduction of a variety of groups at 2-position of benzothiazole is now under progress.



In conclusion, the present oxidative synthesis of substituted indoles and benzazoles has advantage from the viewpoints of operational simplicity, cost performance, and environmental friendly.

EXPERIMENTAL SECTION

Typical procedure for oxidative aromatization of 5-methylindoline to 5-methylindole (entry 3 in Table 3). A three-necked flask was charged with 5-methylindoline (260 μL, 2 mmol), xylene (4 mL), and 266 mg (100 wt%) of activated carbon (Shirasagi KL, Japan EnviroChemicals, Ltd) under an oxygen atmosphere using a balloon. The whole was warmed to 80 °C and stirred for 9 h at this temperature. After confirmation of the consumption of starting material by TLC analysis, activated carbon was filtered off using Celite. After washing with ethyl acetate and acetone, the filtrate was evaporated and the resulting solid was purified by silica-gel column chromatography to give 5-methylindole (258 mg, 98%) as a brown crystal: mp 57—58 °C (lit.,[16] mp 57—59 °C).

Typical procedure for the synthesis of benzothiazole (entry 3 in Table 4). A mixture of 2-aminobenzenethiol (535 μL, 5 mmol) with formaldehyde (608 mg of 37 wt% solution in water containing 8% MeOH, 7.5 mmol), and 625 mg (100 wt%) of activated carbon (Shirasagi KL, Japan EnviroChemicals, Ltd) was placed in a three-necked flask under an oxygen atmosphere using a balloon. After stirring at this temperature for 3 h, activated carbon was filtered off using Celite. After washing with ethyl acetate and acetone, the filtrate was evaporated and the resulting oil was purified by silica-gel column chromatography to give benzothiazole in 79% yield (536 mg) as a yellow oil.

ACKNOWLEDGEMENTS

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" and No. B17340020 from the Ministry of Education, Culture, Sports, Science and Technology, Japan. The authors also thank Japan EnviroChemicals, Ltd for kind gift of Shirasagi KL.

REFERENCES

1. T. L. Gilchrist, "Heterocyclic Chemistry", third edition, 1997, Longman, Chapter 6; A. R. Katritzky and A. F. Pozharskii, "Handbook of Heterocyclic Chemistry", second edition, 2000, Pergamon, Chapter 4.4; T. Eicher and S. Hauptmann, "The Chemistry of Heterocycles", 2003, Wiley-VCH, Chapter 5; "Name Reactions in Heterocyclic Chemistry", ed. by J. J. Li, 2005, John Wiley & Sons, Chapter 3.
2. E. Fischer and F. Jourdan, *Ber.*, 1883, **16**, 2241; E. Fischer and O. Hess, *Ber.*, 1884, **17**, 559; B. Robinson, *Chem. Rev.*, 1969, **69**, 227; B. Robinson, "The Fischer Indole Synthesis", John Wiley & Sons, 1982, 923pp; D. L. Huge, *Org. Prep. Proced. Int.*, 1993, **25**, 607; B. Miller and E. R. Matjeka, *Tetrahedron Lett.*, 1977, 131; C.-y Chen, C. H. Senanayake, T. J. Bill, R. D. Larsen, T. R. Verhoeven, and P. J. Reider, *J. Org. Chem.*, 1994, **59**, 3738; D. L. Hughes and D. Zhao, *J. Org. Chem.*, 1993, **58**, 228; H. Fujii, A. Mizusuna, R. Tanimura, and H. Nagase, *Heterocycles*, 1997, **45**, 2109.
3. A. Reissert, *Ber.*, 1897, **30**, 1030.
4. P. G. Gassman, T. J. van Bergen, D. P. Gilbert, and B. W. Cue, *J. Am. Chem. Soc.*, 1974, **96**, 5495.
5. G. Bartoli, G. Palmieri, M. Bosco, and R. Dalpozzo, *Tetrahedron Lett.*, 1989, **30**, 2129; M. Bosco, R. Dalpozzo, G. Bartoli, G. Palmieri, and M. Petrini, *J. Chem. Soc., Perkin Trans 2*, 1991, 657: G. Bartoli, M. Bosco, R. Dalpozzo, G. Palmieri, and E. Marcantoni, *J. Chem. Soc., Perkin Trans 1*, 1991, 2757; G. Bartoli, *Acc. Chem. Res.*, 1984, **17**, 109. See also, A. Dobbs, *J. Org. Chem.*, 2001, **66**, 638.
6. W. Madelung, *Ber.*, 1912, **45**, 1128. See also, W. J. Houlihan, V. A. Parrino, and Y. Uike, *J. Org. Chem.*, 1981, **46**, 4511; K. Miyashita, K. Tsuchiya, K. Kondoh, H. Miyabe, and T. Imanishi, *Heterocycles*, 1996, **42**, 513; K. Miyashita, K. Kondoh, K. Tsuchiya, H. Miyabe, and T. Imanishi, *J. Chem. Soc., Perkin Trans 1*, 1996, 1261; I. Hughes, *Tetrahedron Lett.*, 1996, **37**, 7595.
7. C. D. Nenitzescu, *Bull. Soc. Chim. Romania*, 1929, **11**. 37. See also, R. Adams and W. P. Samuels, Jr., *J. Am. Chem. Soc.*, 1955, **77**, 5375; K. A. Parker and S-K. Kang, *J. Org. Chem.*, 1979, **44**, 1536.
8. R. C. Larock and E. K. Yum, *J. Am. Chem. Soc.*, 1991, **113**, 6689; R. C. Larock, *Pure Appl. Chem.*, 1999, **71**, 1435; R. C. Larock, *J. Organomet. Chem.*, 1999, **576**, 114; K. R. Roesch and R. C. Larock, *J. Org. Chem.* 2001, **66**, 412.
9. T. Hara, K. Mori, T. Mizugaki, K. Ebitani, and K. Kaneda, *Tetrahedron Lett.*, 2003, **44**, 6207.
10. N. Nakamichi, Y. Kawashita, and M. Hayashi, *Org. Lett.*, 2002, **4**, 3955; N. Nakamichi, Y. Kawashita, and M. Hayashi, *Synthesis*, 2004, 1015.; M. Hayashi and Y. Kawashita, *Lett. Org. Lett.*, 2006, **3**, 571.
11. N. Nakamichi, H. Kawabata, and M. Hayashi, *J. Org. Chem.*, 2003, **68**, 8272.
12. Y. Kawashita, N. Nakamichi, H. Kawabata, and M. Hayashi, *Org. Lett.*, 2003, **5**, 3713.

13. Y. Kawashita, C. Ueba, and M. Hayashi, *Tetrahedron Lett*., 2006, **47**, 4231.
14. F. Bellina, S. Cauteruccio, and R. Rossi, *Eur. J. Org. Chem*., 2006, 1379.
15. Previously reported synthesis of benzazoles. For benzimidazole: M. Kočevar, P. Sušin, and S. Polanc, *Synthesis*, 1993, 773; P. Y. S. Lam, G. Vincent, D. Bonne, and C. G. Clark, *Tetrahedron Lett*., 2003, **44**, 4927. For benzothiazole: C. S. Davis, A. M. Knevel, and G. L. Jenkins, *J. Org. Chem*., 1962, **27**, 1919; T. Itoh, K. Nagata, M. Miyazaki, and A. Ohsawa, *Heterocycles*, 2000, **52**, 1037. For benzoxazole: M. I. El-Sheikh, A. Marks, and E. R. Biehl, *J. Org. Chem*., 1981, **46**, 3256; M. F. Haley and K. Yates, *J. Org. Chem*., 1987, **52**, 1825. See also, C. Grundmann and A. Kreutzberger, *J. Am. Chem. Soc*., 1955, **77**, 6559; J. I. G. Cadogan, C. L. Hickson, and H. McNab, *J. Chem. Soc., Perkin Trans 1*, 1985, 1885: H. Singh and R. Sarin, *Tetrahedron*, 1986, **42**, 1449; G. Frachey, C. Crestini, R. Bernini, R. Saladino, and E. Mincione, *Heterocycles*, 1994, **38**, 2621.
16. G. R. Brown and A. J. Foubister, *Synthesis*, 1982, 1036.