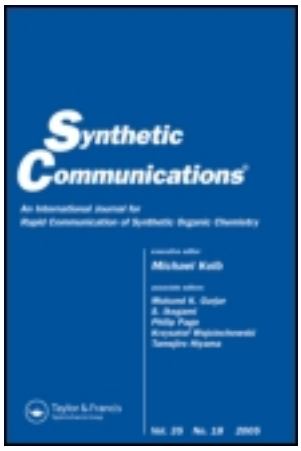


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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

Microwave-Assisted Rapid Synthesis of Neurotransmitter Release Enhancer Linopiridine and Its New Analogues

J. S. Yadav [a] & B. V. S. Reddy [a]

[a] Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad, India

Published online: 17 Aug 2006.

To cite this article: J. S. Yadav & B. V. S. Reddy (2003) Microwave-Assisted Rapid Synthesis of Neurotransmitter Release Enhancer Linopiridine and Its New Analogues, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:18, 3115-3121, DOI: 10.1081/SCC-120023425

To link to this article: http://dx.doi.org/10.1081/SCC-120023425

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS®
Vol. 33, No. 18, pp. 3115–3121, 2003

Microwave-Assisted Rapid Synthesis of Neurotransmitter Release Enhancer Linopiridine and Its New Analogues

J. S. Yadav* and B. V. S. Reddy

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad, India

ABSTRACT

A neurotransmitter release enhancer linopiridine and its new analogues have been synthesized rapidly in yields from the 1:2 coupling of oxiindole with 4-picolyl chloride hydrochloride on the surface of basic alumina doped with 37% KF under microwave irradiation in solvent-free conditions.

Key Words: Linopiridine; Microwave; Solid supports.

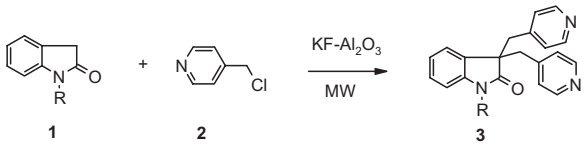
*Correspondence: J. S. Yadav, Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad, India; Fax: 91-40-27160512; E-mail: yadav@iict.ap.nic.in.

DOI: 10.1081/SCC-120023425 0039-7911 (Print); 1532-2432 (Online)

Alzheimer's disease (AD) is the most common form of dementia in the elderly.[1] It is a fatal disorder that robs its victims of their most precious organ, the brain by slowly destroying the complex web of neuronal connections that support cognitive processes such as thought and memory. This dementia is characterized by the loss of short-term memory, deterioration in intellectual performance, and behavioural problems. AD destroys its victim's personalities, leaving them unable to recall the past or process the present. In addition to memory loss, patients may exhibit agitation, combativeness, hallucinations, depression, sleeplessness and wandering. The symptoms of dementia seen in AD are associated with cholinergic loss.[2] Linopiridine stimulates the central nervous system and increases the level of the acetylcholine in the brain. It possesses the ability to enhance acetylcholine release, as the optimal site of the pendant nitrogen is the 4-position of the pyridine ring. The release enhancing effects of linopiridine are not only limited to ACh, as it also stimulates the release of dopamine, serotonin, and glutamate.[3] In consequence, a few methods have been developed[4] for the synthesis of linopiridine and its derivatives, which involve the use of stoichiometric amounts of bases and large volumes of solvents and also the products are obtained in moderate yields after a long reaction period. Furthermore, the use of harmful organic solvents is undesirable from the view of today's environmental consciousness. The use of inorganic solid supports as reaction media in organic synthesis is increasingly widespread due to improved efficiency of many surface-bound reagents.[5]

Microwave-assisted organic reactions have attracted considerable importance in organic synthesis because of the simplicity in operation, greater selectivity and rapid synthesis of a variety of organic compounds.[6] The notable features of the microwave approach are enhanced reaction rates, formation of pure products in high yields and ease of manipulation. In recent years, solvent-free microwave assisted reactions have gained more popularity as they provide an opportunity to work with open vessels. This avoids the risk of development of high pressure and provides a possibility of up-scaling the reaction and helps the induction of the reaction under dry conditions. Thus, microwave irradiation has become a powerful tool for the rapid synthesis of a variety of bioactive molecules under solvent-free conditions.[7]

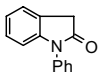
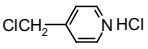
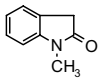
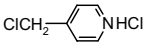
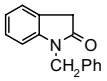
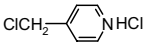
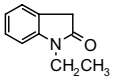
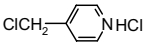
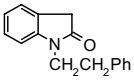
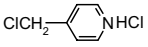
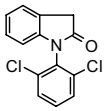
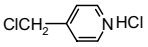
In this report, we wish to describe our results on the microwave-assisted synthesis of linopiridine and its new derivatives from oxyindole and 4-picolyl chloride hydrochloride using $KF–Al_2O_3$. Thus, treatment of oxiindole with 4-picolyl chloride hydrochloride in the presence of basic alumina impregnated with 37% KF under microwave irradiation afforded linopiridine in 90% yield (Sch. 1).



R = Phenyl, 2,6-dichlorophenyl, benzyl, phenethyl, ethyl, methyl

Scheme 1.

Table 1. Microwave-assisted synthesis of linopiridine and its analogues.[a]

			Microwave irradiation	
Entry	Oxiindole	Picolychloride	Time (min)	Yield[b] (%)
a			3.0	90
b			3.0	87
c			3.0	85
d			4.0	90
e			4.0	88
f			5.0	92

[a]All products were characterized by ^{1}H NMR, IR, and mass spectra.
[b]Pulsed irradiation (1 min with 20 s interval) using BPL, BMO-700T microwave oven.

In a similar fashion, various substituted oxiindoles reacted smoothly with 4-picolyl chloride in solvent-free conditions to afford the corresponding linopiridine analogues in high yields. The scope and generality of this process is illustrated with respect to alkyl, aryl, and benzyl substituted oxiindoles and 4-picolyl chloride and the results are presented in the Table 1.

Microwave irradiations were carried out using BPL, BMO-700T domestic microwave oven operated at 2450 MHz (450 W). The reactions were carried out both under microwave as well as thermal conditions. The reaction rates and yields were dramatically enhanced by microwave irradiation. The rate enhancement under microwave may be attributed to the absorption of more microwave energy by polar media, which generates heat energy as required to promote the reaction. The reaction temperature was reached to 110°C after 3 min pulsed irradiation (1 min with 20 s intervals) at the same power. The same reaction, under thermal conditions, at 110°C took 8–12 h to afford yields comparable with those that are obtained by microwave irradiation.

In summary, the article describes a convenient and rapid method for the synthesis of linopiridine and its analogues from oxiindoles and 4-picolyl chloride using a solid supported reagent system $KF–Al_2O_3$. The present method avoids high temperature reaction conditions, the use of solvent and extended reaction times. The time saving ability together with very short response times and the minimization of thermal decomposition of products are the main advantages of microwave heating and further improvement will be facilitated by the availability of a continuous microwave reactor.

EXPERIMENTAL

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finning MAT 1020 mass spectrometer operating at 70 eV. CHN analyses were recorded on a Vario EL analyzer. Microwave irradiation was carried out using BPL, BMO-700T, operated at 450 W (2450 MHz). 37% $KF–Al_2O_3$ was prepared using known literature procedure.[8]

General Procedure

Oxiindole derivative (5 mmol) and 4-picolyl chloride hydrochloride (10 mmol) were admixed with 2.0 g of $KF–Al_2O_3$ (37% KF absorbed on basic alumina) and subjected to microwave irradiation for 3–5 min as required to complete the reaction. After completion of the reaction as indicated by TLC, the reaction mixture was filtered and washed with

dichloromethane (2×15 mL). The combined organic layers were concentrated in vacuo and purified by column chromatography on silica gel to afford pure linopiridine derivative 1.

3a. *N*-Phenyl-3,3-di(4-pyridylmethyl)-2-indolinone. Solid, m.p. 180–182°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.20 (d, 2H, $J = 13.8$ Hz), 3.45 (d, 2H, $J = 13.8$ Hz), 6.25 (dd, 1H, $J = 8.0$, 1.7 Hz), 6.55 (dd, 2H, $J = 8.0$, 1.7 Hz), 6.85 (d, 4H, $J = 8.4$ Hz), 7.05–7.18 (m, 2H), 7.30–7.45 (m, 4H), 8.30 (d, 4H, $J = 8.4$ Hz). ^{13}C NMR ($CDCl_3$) δ: 43.48, 55.83, 109.62, 123.15, 124.46, 125.53, 126.84, 128.68, 128.94, 128.98, 129.93, 134.34, 144.95, 149.57, 176.95. IR (KBr) ν: 3070, 2921, 1714, 1602, 1563, 1493, 1465, 1414, 1366, 1212, 992, 795. EIMS: m/z: 391, 299, 271, 220, 193, 152, 127, 98, 69, 43. Anal. calcd. for $C_{26}H_{21}N_3O$ (391.47): C, 79.77; H, 5.41; N, 10.73. Found: C, 80.0; H, 5.43; N, 10.81.

3b. *N*-Methyl-3,3-di(4-pyridylmethyl)-2-indolinone. Solid, m.p. 89–90°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.80 (s, 3H), 3.18 (d, 2H, $J = 14.5$ Hz), 3.38 (d, 2H, $J = 14.5$ Hz), 6.40 (d, 1H, $J = 8.2$ Hz), 6.81 (d, 4H, $J = 8.2$ Hz), 7.10–7.21 (m, 2H), 7.30 (dd, 1H, $J = 8.2$, 1.6 Hz), 8.30 (d, 4H, $J = 8.2$ Hz). IR (KBr) ν: 3051, 2933, 1710, 1610, 1578, 1497, 1460, 1414, 1365, 1215, 978, 879, 795. EIMS: m/z: 329 [M^+]. Anal. calcd. for $C_{21}H_{19}N_3O$ (329.4): C, 76.57; H, 5.81; N, 12.76. Found: C, 76.61; H, 5.83; N, 12.8.

3c. *N*-Benzyl-3,3-di(4-pyridylmethyl)-2-indolinone. Viscous liquid, ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.18 (d, 2H, $J = 14.5$ Hz), 3.40 (d, 2H, $J = 14.5$ Hz), 4.48 (s, 2H), 6.20 (d, 1H, $J = 7.8$ Hz), 6.35 (d, 2H, $J = 8.1$ Hz), 6.80 (d, 4H, $J = 8.3$ Hz), 7.02–7.20 (m, 4H), 7.32–7.48 (m, 2H), 8.20–8.38 (d, 4H, $J = 8.3$ Hz). EIMS: m/z: 405 [M^+]. IR (KBr) ν: 3067, 2929, 1712, 1607, 1568, 1490, 1465, 1440, 1365, 1212, 987, 877, 790. Anal. calcd. for $C_{27}H_{23}N_3O$(405.49): C, 79.98; H, 5.72; N, 10.36. Found: C, 8.01; H, 5.75; N, 10.35.

3d. *N*-Ethyl-3,3-di(4-pyridylmethyl)-2-indolinone. Solid, m.p. 140–142°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 0.70 (t, 3H, $J = 6.5$ Hz), 3.15 (d, 2H, $J = 14.0$ Hz), 3.30–3.45 (m, 4H), 6.40 (d, 1H, $J = 8.0$ Hz), 6.80 (d, 4H, $J = 8.5$ Hz), 7.05–7.20 (m, 2H), 7.35 (d, 1H, $J = 8.0$ Hz), 8.30 (d, 4H, $J = 8.5$ Hz). ^{13}C NMR ($CDCl_3$) δ: 25.43, 42.49, 55.01, 108.04, 122.06, 123.41, 124.77, 128.23, 128.53, 143.30, 144.57, 148.86, 176.77. EIMS: m/z: 343 [M^+], 251, 223, 195, 149, 93, 71, 57. IR (KBr) ν: 3055, 2920, 1717, 1607, 1565, 1497, 1443, 1210, 1010, 793. Anal. calcd. for $C_{22}H_{21}N_3O$ (343.42): C, 76.94; H, 6.16; N, 12.24. Found: C, 77.0; H, 6.13; N, 12.31.

3e. *N*-Phenethyl-3,3-di(4-pyridylmethyl)-2-indolinone. Solid, m.p. 122–123°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.35 (t, 2H, $J = 6.8$ Hz), 3.15 (d, 2H, $J = 14.6$ Hz), 3.35 (d, 2H, $J = 14.6$ Hz), 3.50 (t, 2H,

$J = 6.8$ Hz), 6.35 (dd, 1H, $J = 8.0$, 1.6 Hz), 6.80 (d, 4H, $J = 8.3$ Hz), 7.0 (dd, 2H, $J = 8.0$, 1.5 Hz), 7.15 (t, 2H, $J = 7.9$ Hz), 7.25–7.40 (m, 4H), 8.22–8.38 (d, 4H, $J = 8.3$ Hz). ^{13}C NMR ($CDCl_3$) δ: 33.06, 41.07, 42.67, 54.77, 108.32, 121.99, 123.66, 125.02, 126.41, 128.37, 128.56, 142.62, 144.26, 148.96, 176.67. EIMS: m/z: 419 [M^+], 328, 237, 209, 181, 149, 123, 109, 80, 43. IR (KBr) ν: 3029, 2937, 1708, 1615, 1469, 1365, 1167, 990, 765. Anal. calcd. for $C_{28}H_{25}N_3O$ (419.52): C, 80.16; H, 6.01; N, 10.0. Found: C, 80.18; H, 6.05; N, 10.05.

3f. *N*-(2,6-Dichlorophenyl)-3,3-di(4-pyridylmethyl)-2-indolinone. Solid, m.p. 191–192°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.30 (m, 4H), 6.18 (dd, 1H, $J = 8.0$, 1.8 Hz), 6.88 (brs, 4H), 7.15–7.40 (m, 6H), 8.38 (brs, 4H). ^{13}C NMR ($CDCl_3$) δ: 43.01, 54.40, 109.59, 122.75, 123.41, 124.55, 125.93, 128.32, 128.78, 128.98, 130.58, 135.15, 143.06, 144.37, 149.34, 175.64. EIMS: m/z: 460 [M^+], 436, 365, 339, 163, 107, 69, 57. IR (KBr) ν: 3058, 2921, 1714, 1602, 1563, 1493, 1465, 1439, 1414, 1366, 1212, 1112, 992, 879, 795. Anal. calcd. for $C_{26}H_{19}Cl_2N_3O$ (460.36): C, 67.83; H, 4.16; Cl, 15.4; N, 9.13. Found: C, 67.80; H, 4.18; Cl, 15.45; N, 9.11.

ACKNOWLEDGMENT

BVS thanks CSIR, New Delhi, for the award of fellowship.

REFERENCES

1. Evans, D.A.; Funkenstein, H.; Albert, M.S. Prevalence of Alzheimer's disease in a community population of older persons. JAMA **1989**, *262*, 2551.
2. Siddiqui, M.F.; Levey, A.I. Drugs of Future **1999**, *24*, 417.
3. Chorvat, R.J.; Earl, R.A.; Zaczek, R. Drugs of Future **1995**, *20*, 1145.
4. (a) Meyers, M.J.; Nickolson, V.J. US Patent 4 760 083, 1988; (b) Wilkerson, W.W.; Kergaye, A.A.; Tam, S.W. J. Med. Chem. **1993**, *36*, 2899; c) Bryant III, W.M.; Huhn, G.F.; Jensen, J.H.; Pierce, M.E. Synth. Commun. **1993**, *23*, 1617.
5. Cornelis, A.; Laszlo, P. Synlett. **1994**, 155.
6. (a) Abramovitch, R.A. Org. Prep. Proceed. Int. **1991**, *23*, 685; (b) Caddick, S. Tetrahedron **1995**, *51*, 10403; (c) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. Synthesis **1998**, 1213; (d) Varma, R.S. Green Chemistry **1999**, 43.
7. (a) Yadav, J.S.; Reddy, B.V.S. Tetrahedron Lett. **2002**, *43*, 1905; (b) Yadav, J.S.; Reddy, B.V.S; Madan, Ch.; Kumar, G.M. Synlett

2001, 1781; (c) Yadav, J.S.; Reddy, B.V.S. New Journal of Chemistry **2000**, *24*, 489; (d) Yadav, J.S.; Reddy, B.V.S.; Madan, Ch. Synlett **2001**, 1131.

8. Schmitting, E.A.; Sawyer, J.S. Tetrahedron Lett. **1991**, *32*, 7207.

Received in the USA November 12, 2002

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016