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Basic alumina supported tandem synthesis of bridged polycyclic quinolino/isoquinolinooxazocines under microwave irradiation

Shyamal Mondal, Rupankar Paira, Arindam Maity, Subhendu Naskar, Krishnendu B. Sahu, Abhijit Hazra, Pritam Saha, Sukdeb Banerjee, Nirup B. Mondal *

Department of Chemistry, Indian Institute of Chemical Biology, Council of Scientific and Industrial Research, 4 Raja S.C. Mullick Road, Jadavpur, Kolkata 700 032, India

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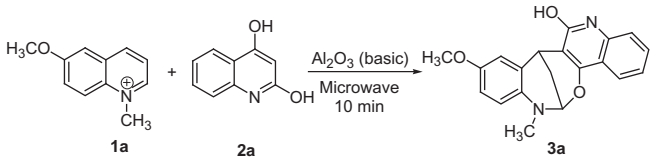
ABSTRACT

Basic alumina supported, solvent-free synthesis of novel oxazocines, medium size heterocycles, has been achieved in excellent yields by tandem C-alkylation followed by intramolecular *O*-alkylation of hydroxyquinoline/isoquinoline(s) with quinolinium salts under microwave irradiation. The method provides a facile and efficient route for the construction of polynuclear bridge-head oxazocines.

The modern trend in synthetic organic chemistry is to develop new methodologies that afford products of greater structural complexity with fewer synthetic steps,[1] and of complex molecules from relatively simple starting materials, employing operationally simple, environmentally benign reaction conditions while ensuing high yields.[2] In this respect tandem reactions,[3] where multiple transformations take place in one-pot, have emerged as an efficient tool for the synthesis of complex molecules. Significant developments in the area over the years have afforded a plethora of structurally unique compounds.[4] We have been performing tandem reactions on quinolines/tetrahydroquinolines using different catalytic systems because functionalized quinoline moiety is prevalent in numerous biologically active compounds. In this endeavor we have synthesized a number of linearly fused medium sized (seven to nine-membered) tri, tetra, penta, and hexa-cyclic substituted quinoline derivatives.[5] We noted that oxazocines, eight-membered oxa-aza-heterocycles, have received considerable attention due to their pharmacological properties like antidepressant, antithrombotic, antipsychotic, and antibreast-cancer activities.[6] The bridgehead oxazocine core is also present in a number of natural products, viz. ecteinascidine 743, bioxalomycin, tetrazomine, and quinocarcins showing good antitumor and antimicrobial activity.[7] The interesting biological activity of the bridgehead oxazocines attracted our attention and prompted us to develop a convenient protocol for easy access to this heterocyclic system utilizing the scope of addition of nucleophilic reagents to quinolinium salts that has already proved to be an efficient method for the synthesis of useful quinoline derivatives.[8]

The microwave-irradiated solid-phase heterogeneous reactions have become well-established[9] as environmentally benign reaction procedures that usually provide improved selectivity, enhanced reaction rates, cleaner products, and manipulative simplicity. We recently reported our efforts[10] for fast and facile reaction strategies that involved microwave energy as an unconventional energy source in a two-component reaction. The present study was intended to establish the viability of a two-component reaction involving a 1,3-dinucleophilic tandem reaction between *N*-alkylquinolinium salts and different bifunctional nucleophiles using microwave energy. This strategy, if successful, would provide a fast, one-pot synthesis of eight-membered rings in fused heterocycles which otherwise are accessible only through multistep synthesis. Here, in this communication, we wish to describe the first successful application of this approach.



Scheme 1. Microwave mediated synthesis of quinolinooxazocine (**3a**) catalyzed by alumina.

* Corresponding author. Tel.: +91 33 2473 3491; fax: +91 33 2473 5197.
E-mail address: nirup@iicb.res.in (N.B. Mondal).

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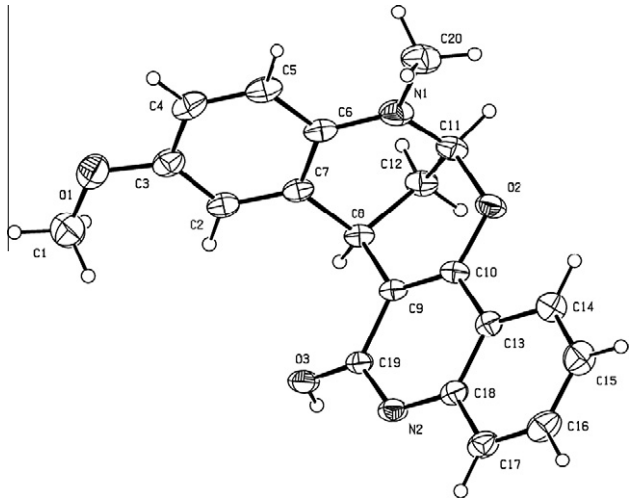


Figure 1. ORTEP diagram of quinolinooxazocine (**3a**).

Table 1
Tandem reaction[a] of **1a** and **2a** under thermal condition

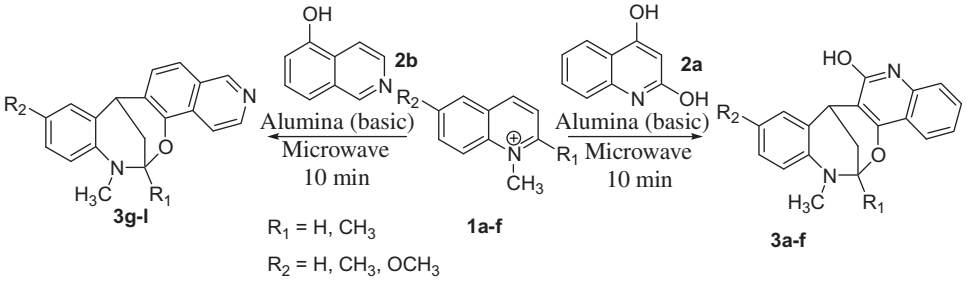
Entry	Solvent	Base	Yield[b] of **3a** (%)
1	Methanol	Cs_2CO_3	60
2	THF	Cs_2CO_3	55
3	CH_3CN	Cs_2CO_3	75
4	Pyridine	Cs_2CO_3	80
5	Methanol	Basic Al_2O_3	54
6	THF	Basic Al_2O_3	50
7	CH_3CN	Basic Al_2O_3	56
8	Pyridine	Basic Al_2O_3	65
9[c]	Nil	Basic Al_2O_3	92

[a] Reactions were carried using 1 mmol of quinolinium salt, 1.2 equiv of hydroxyquinoline and 1 g basic alumina.
[b] Isolated yields.
[c] Basic alumina was activated at 450 °C for 12 h and then the reaction was carried out according to Scheme 1.

It was reasoned that basic alumina can be used as a basic catalyst under microwave energy for activation of the hydroxyquinoline, which could participate in a 1,3-dinucleophilic addition reaction with *N*-alkyl quinolinium salts. On the basis of that reasoning, we chose *N*-alkyl quinolinium salt **1a** (1 mmol) and hydroxyquinoline **2a** (1.2 equiv) as reactants of this study. Those were mixed with basic alumina (0.5 g) and irradiated in a monomode Discover microwave reactor (CEM Corp., Matthews, NC, USA) at 100 °C for 10 min. Usual work-up with ethyl acetate followed by chromatographic purification afforded the reaction product **3a** in 92% yield. The molecular formula was deduced to be $C_{20}H_{18}N_2O_3$ by elemental and high resolution mass spectral analysis, indicating the annulation of the reactants to form the desired quinolinooxazocine (Scheme 1). The ^{1}H NMR spectrum of **3a** exhibited two characteristic[11] peaks (δ 2.03 and δ 2.13) for the geminal aliphatic methylene protons, two 3H singlets assigned to N–CH_3 (δ 3.09) and O–CH_3 protons (δ 3.64), two broad singlets for N–CH–O and the benzylic protons (δ 5.89 and δ 4.13), and a peak for phenolic OH proton at δ 11.35. The ^{13}C NMR spectrum of **3a** showed 20 distinct peaks in agreement with the proposed structure. ^{13}C DEPT data established a peak at δ 25.1 for the methylene carbon, one peak at δ 36.9 for N–CH_3, and one for the methoxy carbon at δ 55.3. Of the rest 17 peaks, nine were assigned to aromatic methine carbons and other eight peaks were identified for quaternary carbons. The bridged structure was eventually fully elucidated by single crystal X-ray analysis. The ORTEP representation of the compound **3a**, indicating the molecular structure, is depicted in Figure 1. When the 2-methyl quinolinium salt **1d** was used as the starting material, the product **3d** displayed in its ^{1}H NMR spectrum signals resembling those of **3a** except for the disappearance of the signal at δ 5.89; instead a singlet at δ 1.90 was observed for the methyl group.

We conducted several reactions with or without basic alumina but in conjugation with other bases and in different organic solvents to study the effectiveness of basic alumina. When the reaction was carried out thermally with quinolinium salt **1a** (1 mmol), hydroxyquinoline **2a** (1.2 equiv) and cesium carbonate

Table 2
Synthesis of quinolino/isoquinolinooxazocines under microwave irradiation



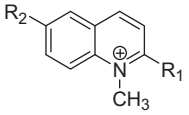
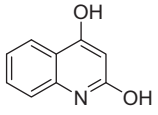
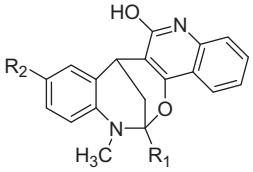
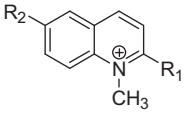
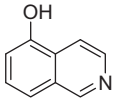
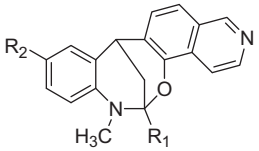
Entry[a]	Quinolinium salts	Hydroxyquinoline/isoquinolines	Products	Yields[b] (%)
				
1	**1a** (R^1 = H, R^2 = OCH_3)	**2a**	**3a**	92
2	**1b** (R^1 = H, R^2 = CH_3)	**2a**	**3b**	90
3	**1c** (R^1 = H, R^2 = H)	**2a**	**3c**	90
4	**1d** (R^1 = CH_3, R^2 = OCH_3)	**2a**	**3d**	88
5	**1e** (R^1 = CH_3, R^2 = CH_3)	**2a**	**3e**	87

Table 2 (*continued*)

Entry[a]	Quinolinium salts	Hydroxyquinoline/isoquinolines	Products	Yields[b] (%)
6	**1f** (R^1 = CH_3, R^2H) 	**2a** 	**3f** 	87
7	**1a**	**2b**	**3g**	88
8	**1b**	**2b**	**3h**	89
9	**1c**	**2b**	**3i**	88
10	**1d**	**2b**	**3j**	86
11	**1e**	**2b**	**3k**	86
12	**1f**	**2b**	**3l**	85

[a] Reactions were carried using 1 mmol of quinolinium salt, 1.2 equiv of hydroxyquinoline and 0.5 g basic alumina under microwave irradiation.
[b] Isolated pure yield.

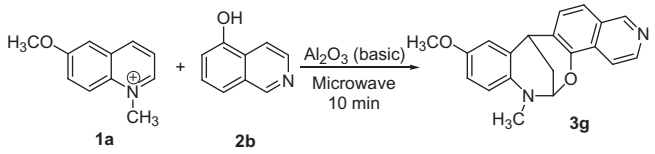
(used as base in lieu of basic alumina) for 5 h in solvents like MeOH, THF, or CH_3CN, considerable decrease in yield was observed (Table 1, entry 1–3). However, when the same was performed in dry pyridine with cesium carbonate as base, it afforded somewhat better yield of the quinolinooxazocine (entry 4). The thermal reaction of **1a** and **2a** in other organic solvents in combination with basic alumina also lowered the yield of **3a** (entries 5–8).

After achieving the optimal reaction condition for the tandem synthesis of quinolinooxazocine **3a**,[12] we carried out reactions of other quinolinium salts (**1b–f**) with hydroxyquinoline (**2a**) under the protocol to afford **3b–f** in excellent yields (Table 2). The remarkable advantage of this solid-phase reaction is that the reaction products were separated from alumina by simple extraction with ethyl acetate.

To extend the scope of the reaction further, the alumina catalyzed solid phase reaction was carried out with **1a** and **2b** under microwave irradiation (entry 7, Table 2) to afford isoquinolinooxazocine **3g** in 88% yield (Scheme 2).

However, an attempt to carry the tandem reaction with 2-hydroxyquinoline, 4-hydroxyquinoline, and 3-hydroxyisoquinoline under identical conditions failed to produce any result. We presume the failure was probably due to keto-amine tautomerism in the quinoline molecules. As described in the report of Moghaddam et al.[11e] the mechanism possibly involves the formation of an iminium intermediate via C-alkylation followed by intramolecular cyclization to give the desired product.

The usefulness of this methodology lies in the fact that the tandem reaction is carried out rapidly under microwave promoted environmentally benign, solvent-free condition to give quinolino/isoquinolinooxazocines (entry **3a–l**)[13] in excellent yields. The catalytic effect of basic alumina was found to be more prominent in solid phase reactions than liquid phase reactions (Table 2). The reaction is compatible with various substituents. In conclusion the methodology is expected to provide a general route for the facile, one-pot synthesis of a wide range of quinolino/isoquinolinooxazocines.



Scheme 2. Microwave mediated synthesis of isoquinolinooxazocine (**3g**) catalyzed by alumina.

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Supplementary data

Crystallographic data in CIF format are available free of charge via the internet at CCDC 825258. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.012.

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12. General procedure for the synthesis of quinolino/isoquinolinooxazocines **3a**–**l**: A mixture of *N*-methyl quinolinium salts **1a**–**f** (1 mmol) and hydroxyquinolines **2a**–**b** (1.2 equiv) was placed in a round bottom flask (25 ml) and dissolved in minimum amount of methanol. Basic alumina (0.5 g) was then added to the mixture and the solvent was evaporated to dryness under reduced pressure. The flask was fitted with a septum, and the reaction mixture was irradiated in the mono-mode Discover microwave reactor (CEM Corp., Matthews, NC, USA) at 100 °C for 10 min while the reaction was monitored by TLC. The mixture was then cooled and ethyl acetate was added, and the slurry was stirred at room temperature for another 10 min. The mixture was then filtered through a sintered glass funnel. The filtrate was evaporated to dryness and the residue was chromatographed over a column of silica gel (60–120 mess) eluting with a mixture of hexane and ethyl acetate in different ratios to yield the products **3a**–**l**.
13. *(a) Spectral data for* **3a**: White crystals (yield: 92%); mp 171–172 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.03 (d, 1H, J = 12.6 Hz, CH_2), 2.13 (d, 1H, J = 12.6 Hz, CH_2), 3.09 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 4.13 (bs, 1H, CH), 5.89 (bs, 1H, CH), 6.62 (m, 2H, CH), 6.95 (d, 1H, J = 2.4 Hz, CH), 7.14 (t, 1H, J = 7.8 Hz, CH), 7.23 (d, 1H, J = 7.2 Hz, CH), 7.43 (m, 1H), 7.76 (d, 1H, J = 7.2 Hz, CH), 11.35 (s, 1H, –OH); ^{13}C NMR (150 MHz, DMSO-d_6): δ 25.1 (CH_2), 26.8 (CH), 36.9 (CH_3), 55.3 (CH_3), 85.3 (CH), 110.9 (C), 111.1 (CH), 111.7 (CH), 114.0 (CH), 114.3 (C), 115.1 (CH), 121.3 (CH), 122.1 (CH), 127.7 (C), 130.2 (CH), 135.7 (C), 137.0 (C), 151.2 (C), 155.9 (C), 161.5 (C). ESI-MS: m/z 335 $[M+H]^+$, 357 $[M+Na]^+$, HRMS: calcd for $C_{20}H_{18}N_2O_3Na$; 357.1215; $[M+Na]^+$; found 357.1212; *(b) Spectral data for* **3b**: White crystals (yield: 90%); mp 155–156 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 2.00 (d, 2H, J = 12.6 Hz, CH_2), 2.11 (t, 2H, J = 12.6 Hz, CH_2), 2.50 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 4.13 (bs, 1H, CH), 5.90 (bs, 1H, CH), 6.59 (d, 1H, J = 7.8 Hz, CH), 6.84(d, 1H, J = 8.4 Hz, CH), 7.14 (t, 2H, J = 7.2 Hz, CH), 7.23 (d, 1H, J = 8.4 Hz, CH), 7.43 (m, 1H, CH), 7.76 (d, 1H, J = 7.8 Hz, CH), 11.31 (s, 1H, –OH); ^{13}C NMR (150 MHz, DMSO-d_6): δ 20.1 (CH_3), 25.1 (CH_2), 26.5 (CH), 36.7 (CH_3), 85.1 (CH), 110.5 (CH), 111.1 (C), 111.7 (CH), 114.3 (C), 115.1 (CH), 121.3 (CH), 122.0 (CH), 125.7 (C), 126.4 (C), 127.4 (CH), 128.1 (CH), 130.2 (CH), 137.0 (C), 139.3 (C), 155.6 (C). ESI-MS: m/z 319 $[M+H]^+$, 341 $[M+Na]^+$, HRMS: calcd for $C_{20}H_{18}N_2O_2Na$; 341.1266 $[M+Na]^+$; found 341.1261; *(c) Spectral data for* **3f**: White crystals (yield: 87%); mp 134–135 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.90 (s, 3H, CH_3), 2.11 (dd, 2H, J = 13.2 Hz, CH_2), 2.17 (dd, 2H, J = 13.2 Hz, CH_2), 3.01 (s, 3H, CH_3), 4.10 (t, 1H, J = 3.0 Hz, CH), 6.63 (m, 2H, CH), 7.00 (m, 1H, CH), 7.15 (t, 1H, J = 7.8 Hz, CH), 7.23 (d, 1H, J = 8.4 Hz, CH), 7.27 (m, 1H, CH), 7.44 (m, 1H, CH), 7.81 (m, 1H, CH), 8.31 (s, 1H, CH), 11.33 (s, 1H, –OH); ^{13}C NMR (150 MHz, DMSO-d_6): δ 25.3 (CH_3), 28.4 (CH), 31.5 (CH_3), 33.5 (CH_2), 87.4 (C), 110.1 (C), 111.2 (CH), 114.3(C), 115.0 (CH), 117.0 (CH), 121.3 (CH), 122.0 (CH), 127.0 (CH), 127.1 (CH), 127.3 (C), 130.2 (CH), 137.1 (C), 143.2 (C), 155.4 (C), 162.0 (C). ESI-MS: m/z 319 $[M+H]^+$, 341 $[M+Na]^+$, HRMS: calcd for $C_{20}H_{18}N_2O_2Na$; 341.1266 $[M+Na]^+$; found 341.1259; *(d) Spectral data for* **3i**: Greenish liquid (yield: 88%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (dt, 1H, J_1 = 12.6 Hz, J_2 = 2.4, CH_2), 2.39 (dt, 1H, J = 12.6 Hz, J_2 = 2.4, CH_2), 3.20 (s, 3H, CH_3), 4.08 (bs, 1H, CH), 5.73 (bs, 1H, CH), 6.68 (m, 2H, CH), 7.08 (m, 1H, CH), 7.23 (d, 1H, J = 5.4 Hz, CH), 7.38 (m, 2H, CH), 7.94 (d, 1H, J = 5.7 Hz, CH), 8.47 (d, 1H, J = 5.7 Hz, CH), 9.07 (s, 1H, CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.5 (CH_2), 34.7 (CH), 36.7 (CH_3), 84.1 (CH), 110.5 (CH), 114.8 (CH), 117.8 (CH), 119.1 (CH), 124.5 (C), 126.2 (CH), 126.9 (C), 127.7 (CH), 127.9 (C), 128.1 (CH), 128.2 (C), 142.0 (C), 142.4 (CH), 146.7 (C), 151.7 (CH). ESI-MS: m/z 289 $[M+H]^+$, 311 $[M+Na]^+$, HRMS: calcd for $C_{19}H_{16}N_2ONa$; 311.1160 $[M+Na]^+$; found 311.1157.