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Basic alumina supported one-pot synthesis of structurally diverse pyridine/quinolinine-fused novel diazepanium, diazocanium, imidazodilinium and tetrahydro-pyrimidiniums

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ABSTRACT

Basic alumina supported solvent-free one-pot synthesis of pyridine-fused polycyclic diazepaniums was achieved under microwave irradiation. The process was successfully extended to the synthesis of pyridine-fused bicyclic imidazolidiniums and tetrahydro-pyrimidiniums and also of tri- and tetracyclic diaza-heterocycle-fused quinoliniums. The dual characteristic of basic alumina, a solid support as well as a base, was successfully employed in the current investigation. The method emerged to be an effective route in terms of product yield, reaction time, and ease of purification and most importantly for environment friendly protocols.

Pharmacophores of several bioactive entities are often found to posses seven-membered ring heterocycles. Among them, the azepanes are found in synthetic glycosides and antibacterials,[1] in several antidepressants like, imipramine, clomipramine, desipramine, lofepramine, metapramine, quinupramine, etc. and also in β-*N*-acetylhexosaminidase inhibitors.[2] However, the most important member of this class, which provides the central core motif for quite a lot of scaffolds, is the diazepane ring system, which is found in a number of marketed drugs.[3] Besides these, several receptors,[4,5] inhibitors,[6–9] antagonists,[10] T-type calcium channel blockers,[11] etc. are found to consist of this important heterocycle in their core. Thus, construction and structural modification of this class of compounds has gained a lot of importance in recent times. Although reports regarding the synthesis of diazepanes are available in the literature, the incorporation of this family of compounds into a fused ring system, especially the fusion with nitrogen-heterocycles in a single step, is virtually unexplored.[12]

Besides the diazepaniums, the quinolinium derivatives have also received much attention due to their interesting biological activities.[13] They can selectively block the apamine-sensitive Ca^{+2} activated K^+ channels[14] and inhibit the human choline kinase.[15] Their antiproliferative activity against the HT-29 cell line[15] and high affinity towards DNA[16] has also attracted attention in the recent years. Furthermore, the gifted bioactivities of a variety of heterocyclic ammonium salts[17] like, CFTR activation,[18] DNA-intercalation,[19] antiproliferative activity,[19] antimalarial and antileishmanial activity[20] made them crucial to the biologists for screening against various cell lines, as well as to the organic chemists for the establishment of shorter synthetic routes through the greener modifications of reaction conditions, in a cost-effective manner, from easily available starting materials.

As part of our ongoing research on the establishment of concise synthetic routes to structurally diverse polynuclear N-heteroarocycles through the development of newer environmentally benign technologies, recently we reported a few distinguished methodologies,[21] where microwave irradiation was employed in order to achieve higher energy efficiency and enhancement of both the rate of reaction and the product yield. Our particular interest was on the use of solid supports like silica and alumina, which are basically inorganic oxides and possess excellent ability to adsorb the organic compounds on their surface without absorbing or restricting the transmission of microwave irradiation.[22] Besides this, the homogenous dispersion of active sites, associated selectivity and easy work-up schedule made the solid-supported reactions more advantageous over the conventional solution phase reactions.

Being fascinated by such widespread bioactivities of heterocyclic quaternary ammonium salts, diazepanes and its lower and

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higher-membered ring analogues,[23] we contemplated developing a methodology through an environmentally benign catalytic system and our continuous search enabled us to explore the dual character of basic alumina, a solid support as well as a base. Initially, we succeeded in the synthesis of pyrido-fused diaza heterocycles using basic alumina under microwave irradiation and synthesized several 5–7-membered diaza-heterocycle-fused pyridiniums. The usefulness of basic alumina in pyridine systems prompted us to explore its application further, in the synthesis of 6–8-membered diazaheterocycle-fused tri- and tetracyclic diazaquinoliniums.

In this letter, we wish to disclose a simple, efficient and green protocol for the selective synthesis of pyridine/quinoline-fused polycyclic diazepaniums, imidazolidiniums, tetrahydro-pyrimidiniums and diazocaniums under the basic alumina supported catalytic system.

Our initial effort was to optimize the reaction condition for the condensation of 2-aminopyridine (**1a**) and 1,4-dibromobutane (**2a**). Attempts using several non-nucleophilic organic bases like, Et_3N, DBU, etc. under the conventional solution-phase methods were frustrating, yielding the product **3a** to the extent of 6–10% (Table 1, entries 1–4). Therefore, the coupling was reinvestigated by replacing the bases by a stronger base NaH. This, however, also failed to show any improvement in the outcome (Table 1, entries 5 and 6) and had to be discarded. We next tested a solid support system to condense **1a** and **2a**. However, with silica as the support and using K_2CO_3 or Cs_2CO_3 as the base, the starting materials were recovered unaltered even after irradiating the reaction mixture (Table 2, entries 1–3) for 20 min at 190 °C (180 W). The yield improved to 19% when silica was replaced by neutral alumina (Table 2, entry 4). We then turned our attention to basic alumina as the solid support and ended up with an improvement in the yield up to 56%, when the model substrates (**1a** and **2a**) were irradiated at 75 °C (180 W) using K_2CO_3 as the base (Table 2, entry 5). To improve the yield further, the reaction temperature was enhanced to 90 °C, leading to maximization of the product yield (92%) in 5 min even in the absence of K_2CO_3 (Table 2, entries 6–8). It is worthy of mention that only 38% of product **3a** was obtained when the condensation of **1a** and **2a** was attempted using an oil bath at 120 °C for 10 h (Table 2, entry 9) under the usual heating procedure, which evidently established the usefulness of microwave irradiation, over the conventional heating.

However, the formation of fused diazepane ring system was not limited only to the bicyclic system; the tricyclic diazepanium was also obtained in high yields by replacing the dihaloalkane **2a** with 1,2-bis-(bromomethyl)benzene **2b** (Table 3, entry 2). The study was then further extended by replacing **2b** with 2,3-bis-bromomethyl-naphthalene **2c**, which was reacted with pyridine-2-amine under the optimal set of reaction conditions and the corresponding tetracyclic diazepanium was successfully isolated in high yield (Table 3, entry 3). The progress of the reactions in all the cases was only upto the diazepanium stage; their oxidation to the corresponding pyridones was never encountered. Thus, complete and selective syntheses of pyridine-fused polycyclic diazepaniums were achieved in this system.

Table 1
Optimization of reaction condition between **1a** and **2a** using solution-phase methods

Entry	Solvent	Base	Time (h)	Temp. (°C)	Yield[a] (%)
1	Et_3N	DCM	10	rt	10
2	Et_3N	DCM	10	40	10
3	DBU	DCM	12	rt	6
4	DBU	DCM	10	80	10
5	NaH	DMSO	12	85	14
6	NaH	DMF	12	85	14

[a] Isolated yield.

Table 2
Optimization of reaction condition between **1a** and **2a** using different solid supports in the reaction[a]

Entry	Solid support-base	Time (min)	Temp. (°C)	Yield[b] (%)
1	Silica gel–K_2CO_3	5	80	NR[c]
2	Silica gel–K_2CO_3	20	190	NR
3	Silica gel–Cs_2CO_3	15	85	NR
4	Neutral alumina–Cs_2CO_3	20	180	19
5	Basic alumina–K_2CO_3	2	75	56
6	Basic alumina	1	90	74
7	Basic alumina	5	90	92[d]
8	Basic alumina	10	120	92
9	Basic alumina	10 h	120	38[e]

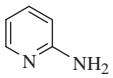
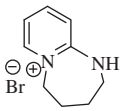
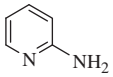
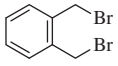
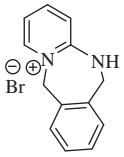
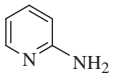
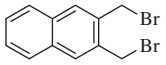
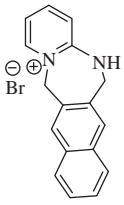
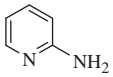
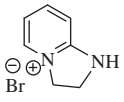
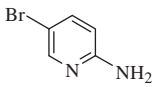
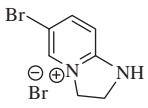
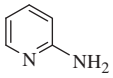
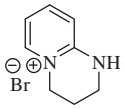
[a] All the solid-supported reactions were performed by using **1a** and **2a** under microwave irradiation at 180 W.
[b] Isolated yield.
[c] NR = No reaction.
[d] Both in absence and presence of K_2CO_3.
[e] In heating condition, using an oil bath.

After fruitfully constructing these pyridine-fused polycyclic diazepanium derivatives, we focused our attention towards the synthesis of its lower ring homologues under similar reaction conditions. Thus, **2a**, **2b** and **2c** were first replaced with 1,2-dibromoethane (**2d**), which was cyclized with pyridine-2-amines (**1a**, **1b**) and the corresponding dihydroimidazopyridiniums (**3d**, **3e**) were isolated in 70–71% yield (Table 3, entries 4 and 5). Similar reaction of 1,3-dibromopropane (**2e**) with 2-aminopyridine (**1a**), under identical reaction condition successfully yielded the corresponding tetrahydropyridopyrimidiniums (**3f**) in excellent yield (Table 3, entry 6).

After the successful application of basic alumina in the pyridine system we decided to test it in the quinoline family and the study was extended by replacing pyridine-2-amines with quinolin-8-amine (**4**). Reactions with various dibromoalkanes (**2a, 2d, 2e**) under the optimal set of reaction conditions indeed produced the corresponding quinoliniums (**5a–c**) in excellent yields (79–88%). On moving from liquid dibromoalkanes (**2a, 2d, 2e**) to the solid benzylic dibromide **2b**, the method again proved successful and the corresponding tetracyclic dihydrobenzodiazocino-quinolinium bromide **5d** was synthesized in 92% yield (Table 4, entry 4). In all the cases the methodology was able to restrict the reaction up to the quinolinium stage and prevented their oxidation to the corresponding quinolones. Thus, a complete and selective synthesis of diaza-heterocycle-fused quinoliniums was achieved in this basic alumina promoted reaction system, without the formation of quinolones or any other unwanted side products. All the products were characterized by NMR and mass spectral analyses.

The promising performance of basic alumina could be ascribed to the presence of Al–O^- groups on the alumina surface[21b] that play a key role in the annulations of pyridines and quinolines with aliphatic and benzylic dibromides. As depicted in Scheme 1, the dibromide **2b** gets linked to the solid support by forming an intermediate (**II**), through a simple substitution reaction. Subsequent alkylation of the ring nitrogen of pyridine[24] or the amine group of quinoline[25] then extends the linkage to form the intermediates **III** and **IV**, respectively, where the benzene ring acts as the linker between the solid support and the nitrogen heterocycle. The intermediates then lead to the formation of the products (**V** and **VI**), through rapid cyclization and the abstraction of the highly acidic ammonium proton (in case of **III**) by basic alumina. We presume that the key factor responsible for such high catalytic activity of basic alumina is its ability to bring the two reactants at close proximity. The unsurpassed efficiency of basic alumina for effecting such condensation, compared to the other two solid supports, may be attributed to the availability of aluminoxide groups in its surface.

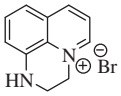
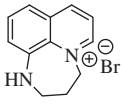
Table 3
Construction of bi-, tri- and tetracyclic 5–7-membered diaza-heterocycle-fused pyridiniums (**3a–f**) from pyridine-2-amine under the optimal set of reaction condition

Entry	Pyridine derivative	Dibromide	Product[a]	Time (min)	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	5	92
2	 **1a**	 **2b**	 **3b**	4	95
3	 **1a**	 **2c**	 **3c**	6	91
4	 **1a**	 **2d**	 **3d**	8	71
5	 **1b**	 **2d**	 **3e**	11	70
6	 **1a**	 **2e**	 **3f**	5	89

[a] All the reactions were performed using basic alumina as solid support under microwave irradiation at 180 W.
[b] Isolated yield.

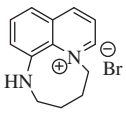
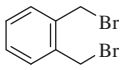
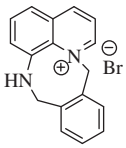
An investigation on the reusability of the solid support was also performed. The results reveal that proper washing with alkaline water, followed by acetone, and subsequent calcination at 150 °C can regenerate the solid support without attenuating its catalytic activity and one can recycle it 3–4 times (Fig. 1).

Table 4
Construction of tri-, and tetracyclic diaza-heterocycle-fused quinoliniums (**5a–d**) from quinoline-8-amine under the optimal set of reaction condition

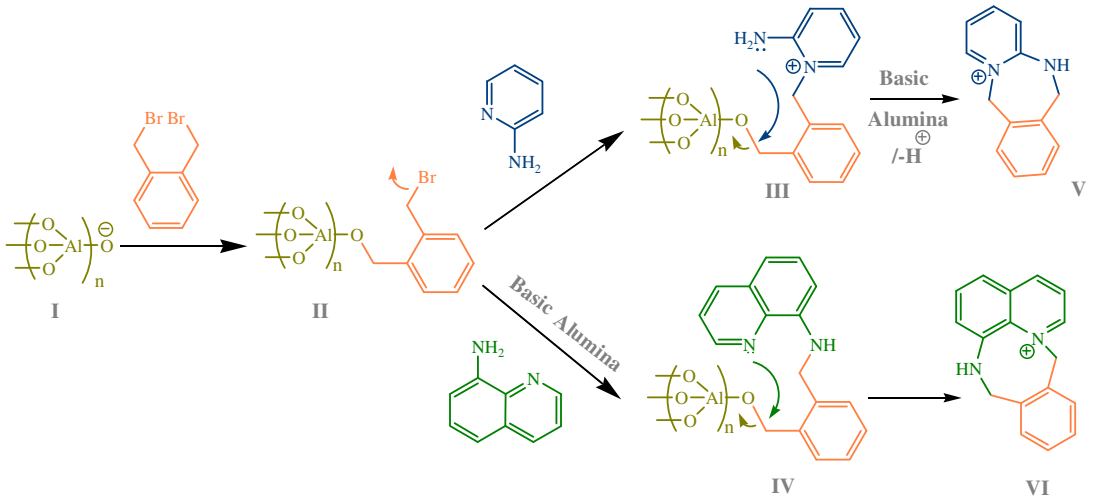
Entry	Quinoline derivative	Dibromide	Product[a]	Time (min)	Yield[b] (%)
1	 **4**	 **2d**	 **5a**	4	88
2	 **4**	 **2e**	 **5b**	7	82

(*continued on next page*)

Table 4 (*continued*)

Entry	Quinoline derivative	Dibromide	Product[a]	Time (min)	Yield[b] (%)
3	 **4**	 **2a**	 **5c**	10	79
4	 **4**	 **2b**	 **5d**	2	92

[a] All the reactions were performed using basic alumina as solid support under microwave irradiation at 180 W.
[b] Isolated yield.



Scheme 1. Plausible mechanistic pathway for the basic alumina supported synthesis of (a) fused pyridiniums (b) fused polycyclic diaza-quinolinium cations.

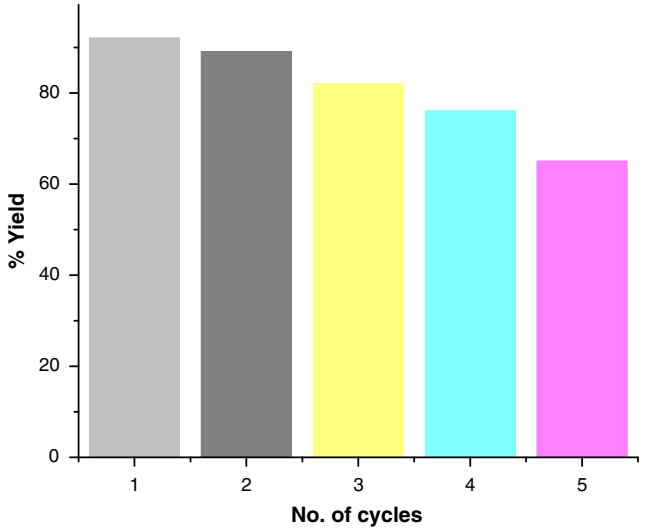


Figure 1. Reusability of the basic alumina tested using **1a** and **2a**. The reactions were performed with **1a** (3.3 mmol) and **2a** (6 mmol), using 400 mg basic alumina at 90 °C for 5 min.

In conclusion, we have unveiled the scope of synthesizing pyridine-fused heteroaromatics from[26,27a] 2-aminopyridines and aliphatic/benzylic dibromides, using basic alumina as a reactive solid support, in solvent-free condition under microwave irradiation. The easy availability and reusability of solid-support, elimination of the use of any base or solvent, cost-effectiveness of the process, operational simplicity, use of environmentally benign techniques and, most importantly, the general applicability of the methodology both for the smaller and larger ring systems and also for the synthesis of tri- and tetracyclic diazaquinoliniums[26,27b] make it a novel green methodology for the synthesis of newer heteroaromatics. The structural similarity of the newly synthesized tri- and tetracyclic diazepaniums with a number of well known antidepressants and also the structural uniqueness of the pyrido-fused bicyclic imidazolidiniums, diazepaniums, and tetrahydro-pyrimidiniums may lead to the identification of newer heteroaromatics having potential biological activity. To the best of our knowledge, this is the first report of basic alumina supported synthesis of pyridine/quinoline-fused diaza-heterocyclic cations.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.134.

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26. *General reaction procedure*: 3.3 mmol 2-aminopyridine derivatives (**1a**, **1b**) or 8-aminoquinoline (**4**) and 6 mmol dibromoalkanes or benzylic dibromides (**2a–e**) were placed in a round bottomed flask (25 ml) and dissolved in minimum amount of chloroform. Basic alumina (0.4 g) was then added to the solution and the organic solvent was then evaporated to dryness under reduced pressure. After fitting the flask with a septum the mixture was subjected to irradiation in a microwave reactor (CEM, Discover, USA) at 90 °C (180 W) for appropriate amount of time (as monitored by TLC). After completion of the reaction the reaction mixture was cooled and methanol was added to it and the slurry was stirred at room temperature for 10 min. The mixture was then vacuum filtered through a sintered glass funnel. The filtrate was then evaporated to dryness under reduced pressure and the residue was purified by flash chromatography to isolate the product. In the recycling experiment the residue obtained after vacuum filtration of the reaction mixture was washed with alkaline water and acetone (2–3 times) and subjected to calcination at 150 °C.
27. (a) *Spectral data for* ***3a***: Brown solid. 92% yield; mp 236–238 °C; R_f (30% ethyl acetate–methanol) 0.35; IR (KBr, ν_{max}): 1290, 1438, 3533 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.90 (2H, m), 2.08 (2H, m), 3.57 (2H, m), 4.50 (2H, m), 6.94 (1H, m), 7.05 (1H, m), 7.87 (1H, m), 8.07 (1H, m); ^{13}CNMR (75 MHz., DMSO-d_6): δ 24.3 (CH_2), 24.6 (CH_2), 43.0 (CH_2), 55.9 (CH_2), 113.9 (CH), 117.2 (CH), 141.4 (CH), 141.9 (CH), 156.6 (C); HRMS (ESI) m/z calcd for $C_9H_{13}N_2$: $[M-Br]^+$ 149.1073; found: 149.1065. (b) *Spectral data for* ***5a***: Brown oil. 88% yield; R_f (30% ethyl acetate–methanol) 0.35; IR (KBr, ν_{max}): 1431, 1500, 3461 cm^{-1}; ^1H NMR (600 MHz., D_2O): δ 3.78 (2H, m), 4.96 (2H, m), 7.32 (1H, m), 7.52 (1H, m), 7.67 (1H, m), 7.89 (1H, m), 8.89 (2H, m); ^{13}C NMR (150 MHz., DMSO-d_6): δ 38.2, (CH_2), 55.4 (CH_2), 116.3 (CH), 117.6 (CH), 121.0 (CH), 126.8 (C), 130.4 (C), 130.5 (CH), 138.3 (C), 145.2 (CH), 146.5 (CH) ; HRMS (ESI) m/z calcd for $C_{11}H_{11}N_2$: $[M-Br]^+$ 171.0917; found: 171.0931.