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# An Efficient and Simple Aqueous N-Heterocyclization of Aniline Derivatives: Microwave-Assisted Synthesis of *N*-Aryl Azacycloalkanes

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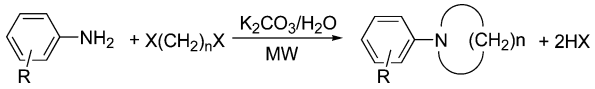
## ABSTRACT




**An efficient and clean synthesis of *N*-aryl azacycloalkanes from alkyl dihalides and aniline derivatives has been achieved using microwave irradiation in an aqueous potassium carbonate medium. The phase separation can simplify the product isolation and reduce usage of volatile organic solvents.**

The concept of "green chemistry" has been widely adopted to meet the fundamental scientific challenges of protecting human health and the environment while simultaneously achieving commercial viability.[1] The emerging area of green chemistry envisages minimum hazard as the performance criteria while designing new chemical processes. One of the thrust areas for achieving this target is to explore alternative reaction conditions and reaction media to accomplish the desired chemical transformations with minimum byproducts and waste generation, as well as eliminating the use of volatile and toxic organic solvents.[2]

Organic reactions accelerated under the influence of microwave (MW) irradiation have attracted considerable attention in the past decade for the efficient and relatively friendlier synthesis of a variety of organic compounds.[3] The use of MW irradiation for the formation of several carbon−heteroatom and carbon−carbon bonds has been successfully demonstrated.[4]

Nitrogen-containing heterocycles are known subunits in many natural products and biologically active pharmaceuticals.[5] They are prepared via alkylation of primary amines with glycol disulfonate in refluxed anhydrous dioxane,[6] using complicated multistep reactions,[7] under harsh reaction conditions,[8] or via coupling reactions using expensive metal catalysts.[9] Developing efficient, selective and eco-friendly synthetic methods for applications in complex organic

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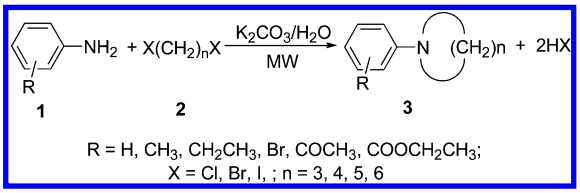
preparations is the ultimate goal of several research groups, including ours.[10] Among alternative, friendlier solvents, water is very benign[11] and has been utilized in combination with microwave irradiation[12] wherein activation of reactions can be achieved. We wish to report here that the double alkylation of aniline derivatives by alkyl dihalides occurs in mildly basic aqueous media upon microwave irradiation and affords a series of *N*-aryl azacycloalkanes in a simple and straightforward manner (Scheme 1). Although theoretically feasible, this simple approach has not been explored previously.

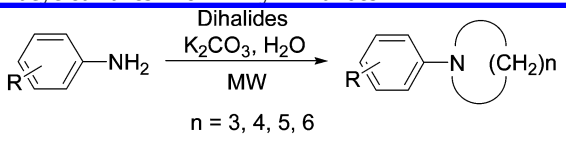
**Scheme 1.** Microwave-Accelerated Synthesis of Azacycloalkanes

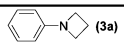
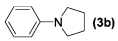
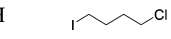
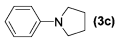
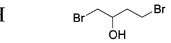
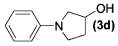
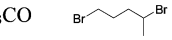
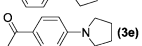
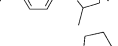
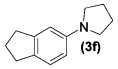
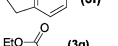
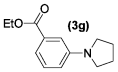
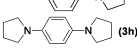
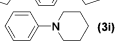



The reaction between ethyl 4-aminobenzoate and 1,4-dibromobutane under conventional and MW heating conditions was investigated to demonstrate the specific microwave effect. We found that under conventional heating conditions, the reaction did not proceed within 20 min and gave rise to a moderate yield (58%) within 8 h of reaction time. However, the same reaction under microwave irradiation for only 20 min afforded excellent product yield (91%). Microwave-assisted reaction exhibited several advantages over the conventional heating by not only significantly reducing the reaction time but also by improving the reaction yield dramatically and, in the process, eliminating the side reactions. Thus, the hydrolysis of esters to carboxylic acid and alcohol and transformation of bromides to hydroxides in an alkaline reaction medium,[13] which were both observed in the separate controlled experiments, could be avoided, thus implying the involvement of a specific nonthermal microwave effect.

This microwave-accelerated double-alkylation reaction was applicable to a variety of aniline derivatives and dihalides to furnish *N*-aryl azacycloalkanes in good to excellent yields expeditiously within 20 min under microwave irradiation (Table 1).[14] The reaction was general in nature and applicable

**Table 1.** Microwave-Accelerated Synthesis of *N*-Aryl Azacycloalkanes[a] from Alkyl Dihalides




| *entry* | *R* = | *dihalides* | *products*[b] | *yields (%)*[c] |
|---|---|---|---|---|
| 1 | 4-H | Cl(CH$_2$)$_3$Cl |  (3a) | 54 |
| 2 | 4-H | Br(CH$_2$)$_4$Br |  (3b) | 89 |
| 3 | 4-H |  |  (3c) | 76 |
| 4 | 4-H |  |  (3d) | 42 |
| 5 | 4-CH$_3$CO |  |  (3e) | 70 |
| 6 | 3,4-(CH$_2$)$_3$ | Br(CH$_2$)$_4$Br |  (3f) | 96 |
| 7 | 3-EtOCO | Br(CH$_2$)$_4$Br |  (3g) | 93 |
| 8 | 4-NH$_2$ | Br(CH$_2$)$_4$Br |  (3h) | 95 |
| 9 | 4-H | Br(CH$_2$)$_5$Br |  (3i) | 96 |
| 10 | 4-Br | Br(CH$_2$)$_6$Br |  (3j) | 65 |
| 11 | 4-CH$_3$CH$_2$ | Br(CH$_2$)$_6$Br |  (3k) | 87 |

[a] All reactions were carried out at 1 mmol scale, microwave power = 80−100 W, and $T$ = 120 °C for 20 min. [b] NMR spectra of all synthesized *N*-aryl azacycloalkane products are in accord with the literature. [c] Isolated yields based on starting aniline derivatives.

to alkyl chlorides, bromides, and iodides. A detailed examination of this reaction revealed that the mild reaction conditions tolerated a variety of functional groups such as hydroxyls, carbonyls, and esters (entries 4, 5, and 7 in Table 1) in the presence of a mild base, potassium carbonate $K_2CO_3$. This advantageous attribute renders the reaction useful to build the *N*-aryl cycloalkane moiety without tedious functional group protection/deprotection sequences.

The experimental observations are consistent with the mechanistic postulation wherein the polar transition state of the reaction is favored by microwave irradiation with respect to the dielectric polarization nature of microwave energy transfer.[15] As proposed in Scheme 2, the charge developed in intermediates **4** and **7** induces a specific microwave enhancement, thus lowering the activation energy due to a greater stabilization of the transition state **6** by the dipole−dipole interaction between the more polar, ionic intermediate and the microwave electric field when compared to the less polar ground state.[16]

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(13) March, J. *Advanced Organic Chemistry*; John Wiley & Sons: New York, 1992; pp 375−386.

(14) In a representative reaction, 1.0 mmol of aniline derivatives, 1.1 mmol of dihalides, and 1.1 mmol of potassium carbonate in 2 mL of distilled water were placed in a 10 mL crimp-sealed, thick-walled reaction tube equipped with a pressure sensor and a magnetic stirrer. The reaction tube was placed in the microwave cavity (CEM Discover Focused Microwave Synthesis System with a built-in infrared temperature sensor), operated at 120 ± 5 °C, 80−100 W, and a pressure of 65−70 psi for 20 min. After completion of the reaction, the organic portion was extracted into ethyl acetate. Removal of the solvent under reduced pressure and flash column chromatography furnished the desired product.

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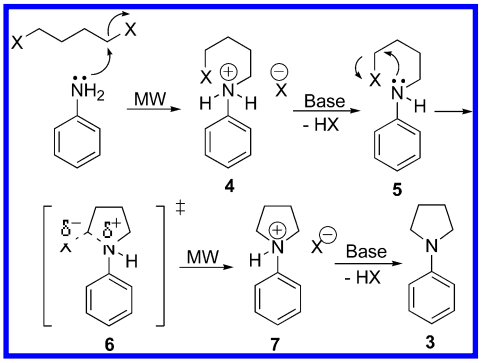
**Scheme 2.** Possible Reaction Pathway




It is noteworthy that this reaction is not a homogeneous single-phase reaction system, as neither reactant was soluble in aqueous alkaline reaction medium. We postulate that selective absorption of microwaves by polar molecules and intermediates in a multiphase system could substitute as a phase transfer catalyst without using any phase transfer reagent, thereby providing the observed acceleration.[17]

In large-scale experiments, the phase separation of the desired product in either solid or liquid form from the aqueous media can facilitate product purification by simple filtration or decantation instead of tedious column chromatography, distillation, or extraction processes and reduces the usage of volatile organic solvent required for extraction or column chromatography. A distinct phase separation is exhibited in Figure 1 wherein the lower 1,4-dibromobutane and aniline layer transition to the upper layer of 1-phenylpyrrolidine as the reaction proceeds to completion.

In brief, an efficient synthesis of *N*-aryl azacycloalkanes, an important class of building blocks in natural products and pharmaceuticals, has been discovered via double N-alkylation of aniline derivatives accelerated under microwave irradiation conditions in an aqueous medium. The method shortens the reaction time significantly and utilizes readily available aniline and alkyl dihalide derivatives to assemble two C−N bonds in a simple $S_N2$-like sequential heterocyclization protocol that has never been fully realized under conventional reaction conditions. The protocol circumvents the difficulty associated with running multistep reactions to assemble *N*-aryl azacycloalkanes and avoids the use of expensive metal catalysts in building aryl C−N bonds. Further, reactive functional groups such as carbonyl, ester, and hydroxyl groups, etc., remain unaffected under these mild reaction conditions.

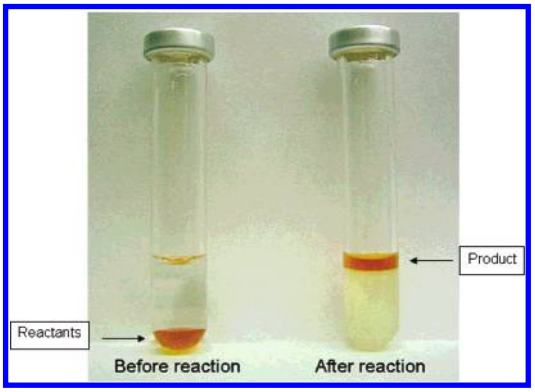



**Figure 1.** Favorable transition of product to the upper layer.

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**Supporting Information Available:** NMR, MS, HRMS, and procedures for the synthsis of compounds **3a**−**k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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