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Aqueous N-Heterocyclization of Primary Amines and Hydrazines with Dihalides: Microwave-Assisted Syntheses of *N*-Azacycloalkanes, Isoindole, Pyrazole, Pyrazolidine, and Phthalazine Derivatives

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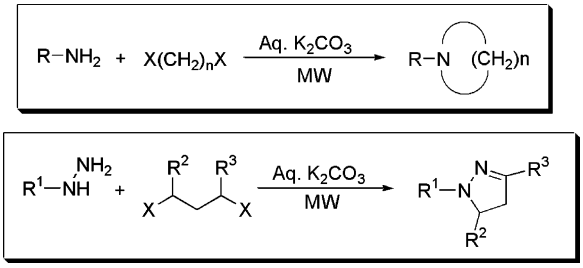

The synthesis of nitrogen-containing heterocycles from alkyl dihalides (ditosylates) and primary amines and hydrazines via a simple and efficient cyclocondensation in an alkaline aqueous medium that occurs under microwave irradiation is described. This improved greener synthetic methodology provides a simple and straightforward one-pot approach to the synthesis of a variety of heterocycles, such as substituted azetidines, pyrrolidines, piperidines, azepanes, N-substituted 2,3-dihydro-1*H*-isoindoles, 4,5-dihydropyrazoles, pyrazolidines, and 1,2-dihydrophthalazines.

Introduction

Heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics, and alkaloids, as well as pharmaceuticals, herbicides, dyes, and many more compounds.[1] The concept of "green chemistry" is now widely adopted to meet the fundamental scientific challenges of protecting the human health and environment while simultaneously achieving commercial viability.[2] The emerging area of green chemistry envisages minimum hazard as the performance criteria while designing new chemical processes. The target is to explore alternative reaction conditions[3] and reaction media to accomplish the desired chemical transformations with minimum byproducts or waste generation, as well as to eliminate the use of conventional organic solvents. The use of alternative energy sources and alternate reaction media such as supercritical fluids, poly(ethylene glycol) (PEG), and room ionic liquids is gaining increasing popularity as well.[4] Organic synthesis in an aqueous medium is a lucrative research area considering its cost, safety, and significance to environmentally benign process

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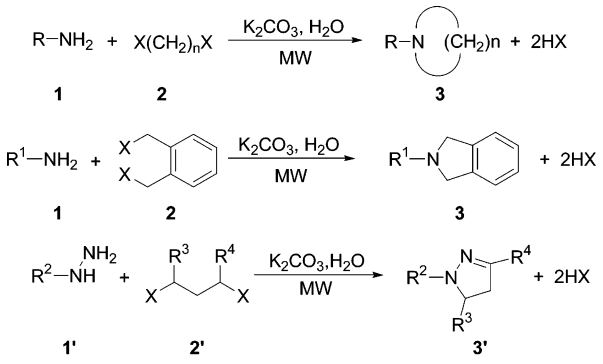
development,[5] and the approach needs to be considered for assembly of heterocyclic compounds.

Organic reactions assisted by microwave (MW) irradiation have attracted considerable attention in the past decade for the efficient and relatively friendlier synthesis of a variety of organic compounds.[6] Use of MW irradiation for the formation of carbon heteroatoms, especially carbon−nitrogen bonds, has been reported.[7] Nitrogen-containing heterocycles are known subunits in many natural products and biologically active pharmaceuticals. Among these, azacycloalkanes, an important class of compounds, are prepared via alkylation of primary amines with glycol disulfonate in refluxed anhydrous dioxane,[8] using complicated multistep reactions,[9] under harsh reaction conditions[10] or via coupling reactions using expensive metal catalysts.[11] The syntheses of dihydroisoindole derivatives include borane−THF reduction of phthalimide,[12] multistep metalation−alkylation of formamidine,[13] reductive amination of phthaldehyde by tetracarbonylhydridoferrate,[14] and catalytic N-heterocyclization using a Cp*Ir complex.[15] The standard preparation of 4,5-dihydropyrazoles involves the cyclocondensation of hydrazine derivatives with α,β-unsaturated carbonyl compounds[16] or the reaction of hydrazine with substituted cyclopropanes,[17] often requiring the use of a crown ether as a phase-transfer catalyst.[18] Pyrazolidines are usually prepared by the condensation reaction of hydrazines with β-diketones or β-ketoesters or alternatively by reacting a protected hydrazine, di-*tert*-butyldihydrazodiformate, with 1,3-dibromopropane in the presence of a phase-transfer catalyst ultimately requiring a sequential deprotection of the Boc group in 4 M HCl.[19] To the best of our knowledge, the direct syntheses of azacycloalkanes, dihydroisoindole derivatives, 4,5-dihydropyrazoles, pyrazolidines, and 1,2-dihydrophthalazines via a single-step one-pot heterocyclization of primary amines or hydrazine derivatives with alkyl dihalides or ditosylates have never been fully explored.

SCHEME 1. Microwave-Accelerated Synthesis of Nitrogen Heterocycles



R, R^1, R^2 = H, alkyl, aryl; R^3, R^4 = H, alkyl; X = Cl, Br, I, TsO.

In a broad program of developing efficient, selective, and eco-friendly synthetic methods,[20] we started exploring the use of water as reaction media in conjunction with microwave irradiation as a useful, environmentally benign alternative.[21] Initial exploration of the reaction of aniline derivatives with dihalides proved encouraging as it afforded *N*-aryl azacycloalkanes,[21a] and the reaction was also applicable to aliphatic primary amines. The scope of this general reaction was further extended to assemble N-substituted 2,3-dihydro-1*H*-isoindoles in excellent yields and with a great ease of purification. Additionally, the application of this double alkylation approach to hydrazine derivatives generated heterocycles with two heteroatoms such as 4,5-dihydropyrazoles, pyrazolidines, and 1,2-dihydrophthalazines.[21b] Our results on the double alkylation of amines and hydrazine by alkyl dihalides or ditosylates under microwave irradiation in aqueous media in the presence of a mild base, which provides a series of nitrogen-containing heterocycles in a simple and straightforward approach (Scheme 1), are reported here.

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Results and Discussion

1. Choice of Reaction Media. To choose the most appropriate medium in this heterocyclization reaction, the microwave-assisted reaction of aniline and 1,4-dibromobutane was examined under solvent-free condition and using water, poly(ethylene glycol) with an average molecular weight of 300 (PEG 300), acetonitrile, *N*,*N*-dimethylformamide (DMF), and toluene (Table 1). Reaction under solventless conditions, an approach that is gaining popularity as it eliminates the use of volatile organic solvents in synthesis,[22] afforded very low yield (less than 20%) because of the insolubility of the base in the reactants. PEG 300 has proven to be a promising medium as a replacement for the volatile organic solvents,[20f] and although it is more expensive than water, we found that, under microwave irradiation, PEG 300 breaks down to ethylene glycol in the presence of a base. Acetonitrile and DMF are ideal polar aprotic solvents for nucleophilic substitution that enhance the reaction rate of S_N2 reactions.[23] However, volatile acetonitrile gave a poor yield because of its low boiling point, and use of DMF gave rise to side reactions and therefore low product yields (~40%). The reaction in nonpolar toluene was a failure, as the yield was less than 25%. Water is a good absorber for microwave energy[24] and has been successfully employed as a solvent for various organic syntheses; it turned out to be one of the best choices, in view of its relatively environmental-friendly characteristics, as a "cleaner" reaction medium.

TABLE 1. Choice of Reaction Media

entry	reaction media	conversion (%)	comments
1	water	89	media of choice
2	none	19	base insoluble in reactants
3	poly(ethylene glycol) (PEG 300)	30	breaks down
4	acetonitrile	32	lower reaction temp
5	*N*,*N*-dimethylformamid (DMF)	45	side reaction
6	toluene	24	base insoluble in toluene

2. Advantage of Using Microwave Heating. The reaction between ethyl 4-aminobenzoate and 1,4-dibromobutane under conventional and MW heating was investigated to demonstrate the specific microwave effect that might be involved in the reaction (Scheme 2). The reaction remained largely incomplete, afforded very low product yields under conventional heating conditions during a short reaction period, and gave rise to undesired byproducts upon prolonged heating. However, the same reaction under microwave irradiation for only 20 min afforded excellent product yields (91%). As can be seen from the results (Table 2), microwave irradiation 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 the transformation of bromides to hydroxides under an alkaline reaction medium, which were both observed in the reactions under conventional heating, could be circumvented, implying the involvement of a specific nonthermal microwave effect which significantly accelerated the reaction.[25]

SCHEME 2. Model Reaction Comparing MW Heating and Conventional Heating

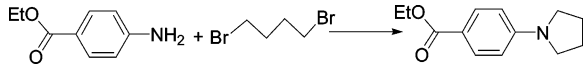

TABLE 2. Reaction Conversion under Conventional Heating (Oil Bath)[a]

entry	reaction time (h)	conversion based on ethyl 4-aminobenzoate (%)[b]
1	0.33	0
2	1.0	26
3	1.5	34
4	3.0	41
5	5.0	56
6	8.0	64 (58)[c]
7	24.0	63 (57)[c]
8	0.33 (MW)[d]	95 (91)[c]

[a] The temperature of the oil bath was 120 °C. [b] Conversions based on quantitative GC-MS analyses. [c] Isolated yields in parentheses. [d] MW power of 80−100 W at 120 °C for 20 min.

3. Microwave-Assisted Synthesis of Azacycloalkanes. The microwave-accelerated heterocyclization reaction was applicable to both aromatic and aliphatic primary amines and dihalides or ditosylates. As exemplified in Table 3, the reactions proceeded smoothly to completion within 20 min and furnished the expected *N*-aryl and *N*-alkyl azacycloalkanes in fair to excellent yields. The scope of this reaction in terms of using substituted anilines, aliphatic primary amines, and functionalized dihalides and ditosylates was examined, and the reaction was found to tolerate various functionalities; acyl (entries 6, 10, and 11), ester (entries 12−15) substituents, and reactive hydroxyl groups (entry 4) were unaffected in the course of the reaction. This feature rendered the reaction even more practically useful to construct the azacycloalkane moiety without tedious functional group protection/deprotection procedures. Shorter reaction times, simpler procedures, higher product yields, tolerance of functional groups, and an aqueous nontoxic reaction medium are distinguished advantages over conventional transitional-metal-catalyzed synthesis of heterocycles.[26]

4. Simple and Efficient Synthesis of 2,3-Dihydro-1*H*-isoindoles. To broaden the scope of this MW-accelerated heterocyclization approach, the assembly of an isoindoline nucleus from reaction of primary amines with α,α-bishalo-*o*-xylenes under aqueous MW irradiation was investigated. The strategy turned out to be practically useful for the syntheses of 2,3-dihydro-1*H*-isoindoles and N-substituted 2,3-dihydro-1*H*-isoindoles. This MW-assisted protocol greatly simplified the workup procedure because the product precipitates out from the aqueous reaction medium, and no flash column chromatography was needed to separate the synthesized product. A simple filtration and washing with cold hexanes afforded analytically pure products. A variety of pharmaceutically significant 2,3-dihydro-1*H*-isoindoles[27] were prepared in good to excellent yields by this novel MW approach (Table 4).

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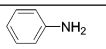
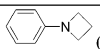
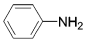
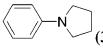
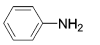
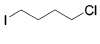
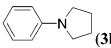
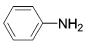
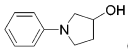
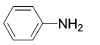
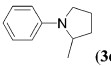
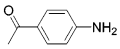
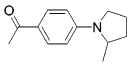
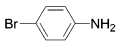
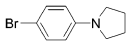
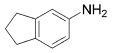
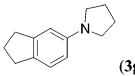
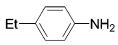
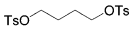
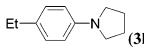
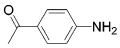
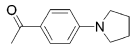
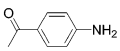
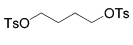
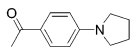
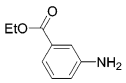
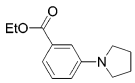
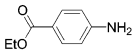
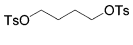
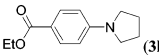
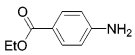
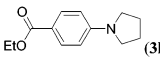
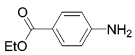
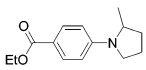
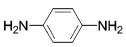
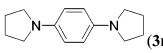
TABLE 3. Microwave-Accelerated Synthesis of Azacycloalkanes[a]

entry	primary amines	dihalides or ditosylates	products[b]	yields (%)[c]
1		Cl $(CH_2)_3$Cl	 **(3a)**	54
2		$Br(CH_2)_4Br$	 **(3b)**	85
3			 **(3b)**	76
4			 **(3c)**	42
5			 **(3d)**	68
6			 **(3e)**	70
7		$Br(CH_2)_4Br$	 **(3f)**	65
8		$Br(CH_2)_4Br$	 **(3g)**	96
9			 **(3h)**	88[d]
10		$Br(CH_2)_4Br$	 **(3i)**	90
11			 **(3i)**	86
12		$Br(CH_2)_4Br$	 **(3j)**	93
13			 **(3k)**	88
14		$Br(CH_2)_4Br$	 **(3k)**	91
15			 **(3l)**	89[d]
16		$Br(CH_2)_4Br$	 **(3m)**	95
17		$Br(CH_2)_5Br$	**(3n)**	96
18		$Br(CH_2)_5Br$	**(3o)**	64
19		$Br(CH_2)_6Br$	**(3p)**	65
20		$Br(CH_2)_6Br$	**(3q)**	87
21		$Br(CH_2)_4Br$	**(3r)**	75
22		$Br(CH_2)_4Br$	**(3s)**	89[d]

[a] All reactions were carried out at 1 mmol scale with a MW power of 80−100 W at 120 °C for 20 min. [b] The NMR spectra of all synthesized azacycloalkanes are in accord with the literature. [c] Isolated yields based on starting amines. [d] Unknown compounds.

5. Syntheses of Pyrazole, Pyrazolidine, and Phthalazine Derivatives. 4,5-Dihydropyrazoles,[28] pyrazolidines,[29] and 1,2-dihydrophthalazines[30] are important classes of heterocycles that are useful as pesticides, anticonvulsants, and potent vasorelaxing agents. The direct syntheses of 4,5-dihydropyrazole, pyrazolidine, and 1,2-dihydrophthalazine derivatives via double alkylation of hydrazine derivatives by alkyl dihalides or ditosylates in aqueous media under microwave irradiation were demonstrated (Scheme 3). The general microwave protocol enabled the synthesis of a wide variety of useful precursors for pharmacologically active heterocycles using water as the reaction medium in the absence of a phase-transfer agent and could be an ideal substitute for hazardous organic solvents. The easy experimental protocol utilizing readily available unprotected hydrazine derivatives and alkyl dihalides/ditosylates are some of the salient features. (Table 5).

TABLE 4. Microwave-Accelerated Synthesis of 2,3-Dihydro-1*H*-isoindoles[a]

entry	primary amines	dihalides or ditosylates	products[b]	yields (%)[c]
1	$NH_3 \cdot H_2O$		**(3aa)**	62
2			**(3ab)**	61
3			**(3ac)**	92
4			**(3ad)**	88[d]
5			**(3ae)**	84[d]
6			**(3af)**	79
7			**(3ac)**	90
8			**(3ag)**	88
9			**(3ah)**	91
10			**(3ai)**	90

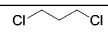
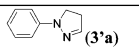
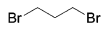
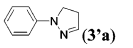
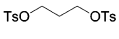
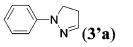
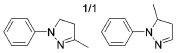
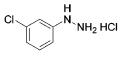
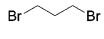
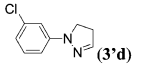
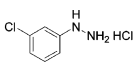
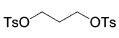
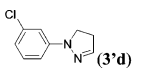
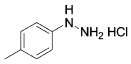
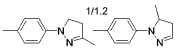
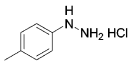
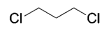
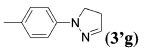
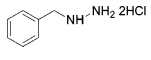
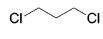
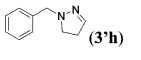
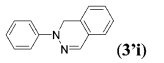
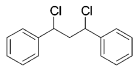
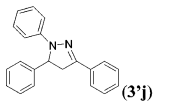
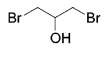
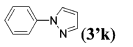
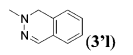
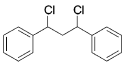
[a] All reactions were carried out at 1 mmol scale with a MW power of 80−100 W at 120 °C for 20 min. [b] The NMR spectra of all synthesized isoindoles are in accord with the literature. [c] Isolated yields based on starting amines. [d] Unknown compounds.

SCHEME 3. Double Alkylation of Hydrazines

6. Mechanistic Postulations. A plausible mechanism for the heterocyclization reaction to form azacycloalkanes is proposed in Scheme 4. 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,

(27) Austin, N. E.; Avenell, K. Y.; Boyfield, I.; Branch, C. L.; Hadley, M. S.; Jeffrey, P.; Johnson, C. N.; Macdonald, G. J.; Nash, D. J.; Riley, G. J.; Smith, A. B.; Stemp, G.; Thewlis, K. M.; Vong, A. K.; Wood, M. D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 685.
(28) Bosum-Dybus, A.; Neh, H. *Liebigs Ann. Chem.* **1991**, 823.
(29) Kornet, M. J.; Garrett, R. J. *J. Pharm. Sci.* **1979**, *68*, 377.
(30) Watanabe, N.; Kabasawa, Y.; Takase, Y.; Matsukura, M.; Miyazaki, K.; Ishihara, H.; Kodama, K.; Adachi, H. *J. Med. Chem.* **1998**, *41*, 3367.

TABLE 5. Aqueous Cyclocondensation of Hydrazines with Dihalides and Ditosylates Using Microwave Irradiation[a]

entry	hydrazine derivatives	dihalides or ditosylates	main products	yields (%)
1			 **(3'a)**	68[b]
2			 **(3'a)**	65[b]
3			 **(3'a)**	70[b]
4			 **(3'b, 3'c)**	65[b, c]
5			 **(3'd)**	64[b]
6			 **(3'd)**	66[b]
7			 **(3'e, 3'f)**	63[b, c]
8			 **(3'g)**	70[b]
9			 **(3'h)**	60[b]
10			 **(3'i)**	89[d]
11			 **(3'j)**	60[b]
12			 **(3'k)**	81[b]
13			 **(3'l)**	85[d]
14	$H_2N-NH_2\ H_2SO_4$		**(3'm)**	74[b]
15			**(3'n)**	80[d]
16			**(3'o)**	60[b]

[a] Reaction was carried out on a 1 mmol scale with a MW power of 70−100 W at 120 °C and a pressure of 40−80 psi for 20 min. [b] Isolated yields based on starting hydrazines. [c] Structure isomer ratio determined by NMR. [d] Yields based on quantitative GC-MS analysis of starting dihalides.

ionic intermediate and the microwave electric field when compared to the less polar ground state. In a very similar manner (Scheme 5), the double alkylation of hydrazine is favored by MW irradiation because the increased polarity of **4′** and **6′** drives the reaction to form 1-phenylpyrazolidine, **7′**. The ease of generation of a carbon−nitrogen double bond to finally afford 1-phenyl-4,5-dihydro-1*H*-pyrazole **3′** was explored in two control experiments by introducing oxygen into the system or, alternatively, by using activated palladium on carbon as a dehydrogenation catalyst. It was found that oxygen in the air plays a critical role in promoting the formation of a C−N double bond instead of a C−N bond in the observed product via a dehydrogenation mechanism, as was the case observed for palladium-catalyzed dehydrogenation processes.

SCHEME 4. Possible Reaction Pathway Favored by MW Irradiation

SCHEME 5. Proposed Mechanism for Cyclocondensation Reactions

It is noteworthy to mention that these reactions are not homogeneous, single-phase reaction systems, as neither reactant is soluble in an 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 similar to that of ultrasound irradiation.[31] 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 by tedious column chromatography, distillation, or extraction processes, thus reducing the use of volatile organic solvents for extraction or column chromatography. In most of the reactions discussed herein, we observed the completion of reactions simply indicated by phase transition of lower-layered reactants to upper-layered products. As exemplified by the reaction of aniline with 1,4-dibromobutane, a distinct phase separation was exhibited (Figure 1) wherein the lower 1,4-dibromobutane and the aniline layer transitioned to the upper layer of 1-phenylpyrrolidine as the reaction proceeded to completion.

Conclusion

In conclusion, an efficient synthesis of azacycloalkanes, isoindolidines, pyrazole, pyrazolidine, and phthalazine derivatives, important classes of building blocks in natural products and pharmaceuticals, was accomplished via double N-alkylation

(31) Varma, R. S.; Naicker, K. P.; Kumar, D. *J. Mol. Catal. A: Chem.* **1999**, *149*, 153.

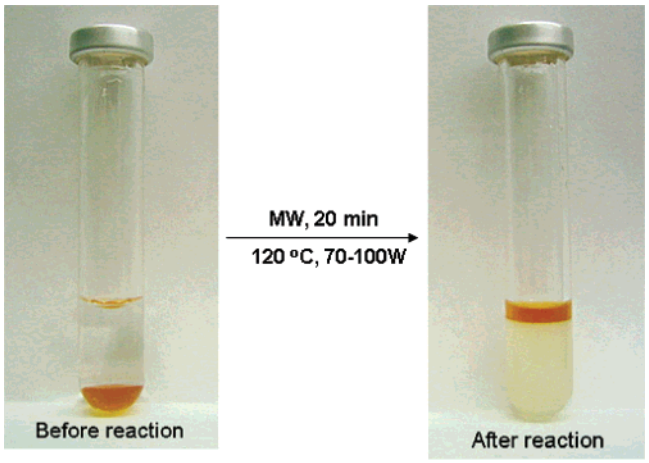


FIGURE 1. Favorable transition of the product to the upper layer.

of primary amines and hydrazine derivatives assisted by microwave irradiation in an aqueous medium. This MW-accelerated general approach shortened the reaction time significantly and utilized readily available amines and hydrazines with alkyl dihalides or ditosylates to assemble two C−N bonds in a simple S_N2-like sequential heterocyclization experimental protocol which has never been fully realized under conventional reaction conditions. Obtaining good to excellent product yields, avoiding multistep reactions and functional group protection/deprotection sequences to construct useful heterocycles, and eliminating the use of expensive phase transfer- and transition-metal catalysts are some of the salient features of this approach.

Experimental Section

Synthesis of Azacycloalkanes. Aniline (1.0 mmol, 0.093 g), 1.1 mmol 1,4-dibromobutane (0.237 g), and 1.1 mmol potassium carbonate (0.162 g) in 2 mL of distilled water were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The reaction tube was placed in a focused microwave synthesis system and operated at 120 ± 5 °C using a power of 70−100 W and a pressure of 40−80 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 using hexane/ethyl acetate (90:10) as eluent afforded the product, 1-phenylpyrrolidine, in 89% yield. Satisfactory ^{1}H and ^{13}C NMR data are consistent with those found in the literature.

1-(4-Ethylphenyl)pyrrolidine (3h). The reaction of 4-ethylaniline (1.0 mmol, 0.121 g) and 1,4-butanediol ditosylate (1.1 mmol, 0.418 g) was carried out as described earlier and produced 0.154 g (88%) of 1-(4-ethylphenyl)pyrrolidine as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ ppm 7.04 (dd, 2H, J = 8.4, 4.1 Hz), 6.51 (d, 2H, J = 8.5, 4.2 Hz), 3.23 (t, 4H, J = 6.6 Hz), 2.50 (q, 2H, J = 7.5 Hz), 1.94 (t, 4H, J = 6.6 Hz), 1.18 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$/TMS) δ ppm 146.4, 131.3, 128.6, 111.9, 47.9, 28.0, 25.5, 16.2; MS (EI) *m*/*z* (relative intensity, %) 175 (M, 53), 174 (M^+, 30), 160 (100), 119 (11), 118 (9), 91 (6), 77 (5); HR-MS (ESI) calcd $(M + H)^+$ for $C_{12}H_{17}N$ 176.1439 ($C_{12}H_{18}N^+$), found $(M + H)^+$ 176.1433.

4-(2-Methylpyrrolidinyl)benzoic Acid Ethyl Ester (3l). The reaction of 4-aminobenzoic acid ethyl ester (1.0 mmol, 0.165 g) and 1,4-dibromopentane (1.1 mmol, 0.253 g) was carried out as described earlier and produced 0.207 g (89%) of 4-(2-methylpyrrolidinyl)benzoic acid ethyl ester as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ ppm 7.91 (d, 2H, J = 8.5 Hz), 6.52 (d, 2H, J = 8.4 Hz), 4.32 (q, 2H, J = 7.2 Hz), 3.96 (q, 1H, J = 6.4 Hz), 3.46 (m, 1H), 3.24 (m, 1H), 2.05 (m, 3H), 1.80 (m, 1H), 1.36 (q, 3H, J = 7.0 Hz), 1.18 (d, 3H, J = 6.5 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$/TMS) δ ppm 167.2, 150.2, 131.0, 116.5, 110.8, 60.0, 53.7, 47.9, 32.9, 23.1, 18.9, 14.5; MS (EI) *m*/*z* (relative intensity, %) 233 (M, 29), 219 (16), 218 (100), 190 (36), 188 (19), 145 (7); HR-MS (ESI) calcd $(M + H)^+$ for $C_{14}H_{19}NO_2$ 234.1494 ($C_{14}H_{20}NO_2^+$), found $(M + H)^+$ 234.1508.

1-Benzylpyrrolidine (3s). The reaction of benzylamine (1.0 mmol, 0.106 g) and 1,4-dibromobutane (1.1 mmol, 0.231 g) was carried out as described earlier and produced 0.143 g (89%) of 1-benzylpyrrolidine as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ ppm 7.24 (m, 5H), 3.53 (s, 2H), 2.42 (m, 4H), 1.70 (m, 4H, J = 4.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$/TMS) δ ppm 139.4, 128.9, 128.2, 126.9, 60.8, 54.2, 23.5; MS (EI) *m*/*z* (relative intensity, %) 161 (M, 69), 160 (M^+, 96), 91 (100), 84 (56), 70 (34), 42 (19); HR-MS (ESI) calcd $(M + H)^+$ for $C_{11}H_{15}N$ 162.1283 ($C_{11}H_{16}N^+$), found $(M + H)^+$ 162.1286.

Synthesis of 2,3-Dihydro-1*H*-isoindoles. Aniline (1.0 mmol, 0.093 g), 1.1 mmol 1,2-bisbromomethylbenzene (0.270 g), and 1.1 mmol potassium carbonate (0.162 g) in 2 mL of distilled water were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The reaction tube was placed in a focused microwave synthesis system and operated at 120 ± 5 °C using a power of 80−100 W and a pressure of 40−80 psi for 20 min. After completion of the reaction, the solid product was separated from the aqueous phase, filtered, and washed with cold hexanes three times. This afforded the off-white, solid, analytically pure 2-phenyl-2,3-dihydro-1*H*-isoindole in 92% yield. Satisfactory ^{1}H and ^{13}C NMR data was obtained and was consistent with those found in the literature.

2-(4-Ethylphenyl)-2,3-dihydro-1*H*-isoindole (3ad). The reaction of 4-ethylaniline (1.0 mmol, 0.121 g) and 1,2-bischloromethylbenzene (1.1 mmol, 0.195 g) was carried out as described earlier and produced 0.196 g (88%) of 2-(4-ethylphenyl)-2,3-dihydro-1*H*-isoindole as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ ppm 7.29 (m, 4H), 7.14 (d, 2H, J = 8.4 Hz), 6.62 (d, 2H, J = 8.5 Hz), 4.61 (s, 4H), 2.57 (q, 2H, J = 7.8 Hz), 1.22 (t, 3H, J = 7.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$/TMS) δ ppm 145.4, 138.2, 132.0, 128.8, 127.1, 122.6, 111.7, 54.0, 28.0, 16.1; MS (EI) *m*/*z* (relative intensity, %) 223 (M, 71), 222 (M^+, 100), 208 (33), 206 (11), 193 (4), 165 (4), 104 (6), 90 (5), 77 (4); HR-MS (ESI) calcd $(M + H)^+$ for $C_{16}H_{17}N$ 224.1439 ($C_{16}H_{18}N^+$), found $(M + H)^+$ 224.1440.

2-Indan-5-yl-2,3-dihydro-1*H*-isoindole (3ae). The reaction of indanyl-5-amine (1.0 mmol, 0.133 g) and 2-bischloromethylbenzene (1.1 mmol, 0.195 g) was carried out as described earlier and produced 0.197 g (84%) of 2-indan-5-yl-2,3-dihydro-1*H*-isoindole as a light-yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ ppm 7.29 (m, 4H), 7.14 (m, 1H), 6.54 (s, 2H), 6.49 (t, J = 8.2 Hz), 4.63 (s, 4H), 2.86 (t, 4H, J = 9.8 Hz), 2.04 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$/TMS) δ ppm 146.2, 145.6, 138.1, 132.2, 127.1, 124.9, 122.5, 110.1, 108.0, 54.3, 33.4, 31.9, 25.8; MS (EI) *m*/*z* (relative intensity, %) 235 (M, 61), 234 (M^+, 100), 233 (14), 115 (9), 104 (4), 91 (4); HR-MS (ESI) calcd $(M + H)^+$ for $C_{17}H_{17}N$ 236.1439 ($C_{17}H_{18}N^+$), found $(M + H)^+$ 236.1436.

Syntheses of 4,5-Dihydropyrazole, Pyrazolidine, and 1,2-Dihydrophthalazine Derivatives. 1,2-Diethylhydrazine dihydrochloride (1 mmol, 0.161 g), 1,2-bischloromethylbenzene (1 mmol, 0.175 g), 2 M sodium hydroxide (1 mL), and potassium carbonate (1 mmol, 0.138 g) in water (1 mL) were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The reaction tube was placed inside the cavity of a focused microwave synthesis system and operated at 120 ± 5 °C (temperature monitored by a built-in infrared sensor) using a power of 70−100 W and a pressure of 40−80 psi for 20 min. After completion of the reaction, the biphasic system was allowed to stir in the air for 6 h, and the product was extracted into ethyl acetate. The removal of the solvent under reduced pressure (rotary evaporator) and flash column chromatography using hexane/ethyl acetate

(9:1) as eluent afforded the product, 2,3-diethyl-1,2,3,4-tetrahydrophthalazine (0.114 g, 60% yield).

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Supporting Information Available: Experimental procedures, NMR spectrum, and HR-MS data for compounds **3h**, **3l**, **3s**, **3ad**, and **3ae**. This material is available free of charge via the Internet at http://pubs.acs.org.

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