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Microwave promoted synthesis of cycl[3.2.2]azines in water via a new three-component reaction

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ABSTRACT

A microwave-promoted and base-catalyzed synthesis of cycl[3.2.2]azines is accomplished in water via a three-component reaction (3-CR) of 2-picoline, α-bromoacetophenone and alkyne. The extension of the methodology to the synthesis of steroidal and carbocyclic cycl[3.2.2]azine is also reported.

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The indolizine ring system is an important structural motif frequently found in natural products and has been used as an important skeleton in pharmaceutics because of their interesting and promising biological properties.[1] Synthetic indolizines have found wide-spread application in drug design efforts, biological, and pharmaceutical research.[2] Several reports are available showing the potential of indolizine derivatives as histamine H_3 receptor antagonists,[3] antimicrobacterial agents,[4] leucotriene synthesis inhibitors,[5] calcium entry blockers,[6] and inhibitors of 15-lipooxygenase.[7] The synthesis of indolizine derivatives has been actively investigated and many synthetic strategies for producing indolizine derivatives have been described in the literature.[8] Perhaps the most widely utilized method is the Tschitschibabin indolizine synthesis, in which a quaternary pyridinium halide, resulting from the reaction of a 2-alkyl pyridine and an α-halo carbonyl compound undergoes an intramolecular condensation to the indolizine product.[9] However, in many cases, expensive and toxic metals, extended reaction times, elevated thermal conditions, and environmentally hazardous organic solvents are used.

The application of water as a solvent for performing organic transformations under thermal and microwave heating has received significant interest as a green alternative.[10] Water offers practical advantages over organic solvents as it is readily available, cheap, non-flammable, and environmentally friendly. In addition, the utility of unconventional microwave irradiation has been increasingly recognized in organic synthesis in recent years. Microwave-mediated multi-component reactions (MCRs) constitute a particularly attractive synthetic strategy for rapid and efficient library generation, enhanced reaction rates, cleaner products, and manipulative simplicity. The interest in this area is evidenced by the large number of papers and reviews, which appeared in the literature in the past few years.[11–13]

The cycl[3.2.2.]azine systems, which are tricyclic aromatic heterocycles having nitrogen as the central atom common to the three rings, have attracted lots of attention due to their interesting physical and chemical properties.[14] The most general method for the synthesis of cycl[3.2.2]azine derivative is the (8 + 2)π cycloaddition reaction of indolizines with acetylenes such as DMAD.[15] However, one of the discrepancies of this methodology is that it requires costly and toxic metal catalysts (such as Pd on charcoal) as dehydrogenating agents in organic solvents.[16] Hitherto, no report is available for the synthesis of these cycl[3.2.2]azines using a multi-component reaction and water as the reaction media. Recently, we have reported the synthesis of benzo[*g*]indoles from α-substituted acetophenone and naphthoquinone in the presence of urea under microwave irradiation.[17] In continuation of our interests, herein we report an efficient and facile base-catalyzed preparation of cycl[3.2.2]azines via a three-component reaction between an alkyl pyridine, an α-bromo carbonyl compound, and an alkyne in water. Our synthetic approach, which involves the cycloaddition of in situ generated Tschitschibabin indolizine in aqueous media, turned out to be the first example of a metal-free preparation of cycl[3.2.2]azines.

Typical reaction conditions for the preparation of the cycl[3.2.2]azine system involve the treatment of alkylpyridines (**1a–c**, 0.5 mmol) with α-bromo carbonyl compounds (**2a–f**, 1.2 equiv) and alkynes (**3a–b**, 1.5 equiv) in the presence of a base in a round bottomed flask open to air (Scheme 1). The product 2-phenyl-4,5-dicarbmethoxy-cycl[3.2.2]azine (**4a**) was confirmed by spectroscopic and analytical techniques.[18] The effect of solvents on the rate and yield of the reaction was evaluated using **1a**, **2a**, and **3a** as model substrates in the presence of K_2CO_3 and the results are summarized in Table 1. Different aprotic solvents, such as, CH_2Cl_2, DMF, DMSO, toluene, and CH_3CN and protic solvents, such as MeOH, EtOH, and H_2O were examined. It was observed that protic solvents were significantly preferred over aprotic solvents and that the reaction in water was the fastest.

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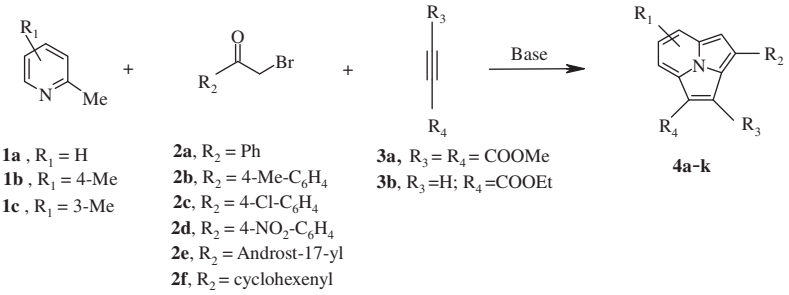
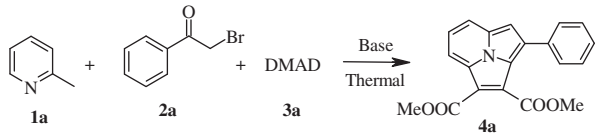


Scheme 1.

Table 1
Effect of solvents on the formation of **4a**[a]



Solvent	% Yield[b]			
	1 h	2 h	8 h	24 h
CH_2Cl_2	0	0	0	0
DMF	0	5	8	8
DMSO	0	0	0	0
Toluene	0	0	0	0
CH_3CN	2	4	4	8
MeOH	10	20	25	35
EtOH	8	15	26	40
H_2O	70	78	84	80

[a] Reactions were carried out at 100 °C using 0.5 mmol of 2-picoline (**1a**) with phenacylbromide (**2a**, 1.2 equiv), DMAD (**3a**, 1.5 equiv) and K_2CO_3 (1.5 mmol).
[b] Yields are based on HPLC analysis compared to an analytical sample.

The versatility of the reaction was then evaluated in aqueous medium under microwave irradiation using various 2-alkyl pyridines, acyl bromides, and alkynes with modification at the pyridyl ring, aromatic moiety of acetophenone and alkyne substituents (Table 2). Hence, substrates with alkylpyridines (**1a–c**), substituted acetophenones (**2a–d**) and alkynes (**3a–b**) afforded cycl[3.2.2]azine products (**4a–i**) within 2–5 min in 20–92% yield.[18,19] It was observed that substrates bearing an electron releasing group at the *para* position of the aromatic ring (**2b**) facilitated the enhancement in yields of the products (entries 2 and 6), whereas electron deficient **2d** gave lower yields (entries 4 and 8). The three-component reactions (3-CRs) in water were found sluggish when carried out under thermal conditions (1–24 h) in comparison to microwave heating wherein the reactions were very rapid (2–5 min).

In the light of the operational simplicity and mild condition of our cycl[3.2.2]azine synthesis, we intended to expand the described protocol to the preparation of steroidal and non-steroidal derivatives. Reaction of **1a** with 21-bromo-pregn-5,16-dieno-3-acetate (**2e**) and **3a** under identical conditions afforded **4j** in 78% yield (Table 2, entry 10). Similarly α-bromoacetyl-1-cyclohexene

Table 2
Synthesis of cycl[3.2.2]azines **4a–k** in aqueous medium[a]

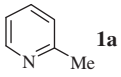
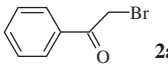
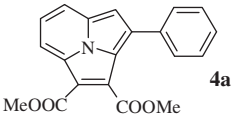
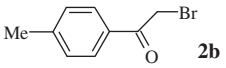
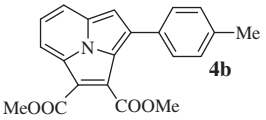
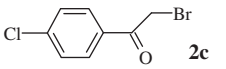
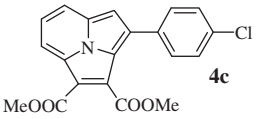
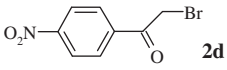
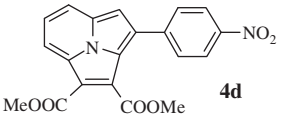
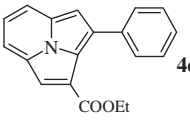
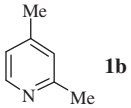
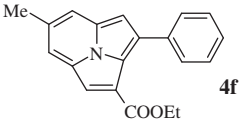
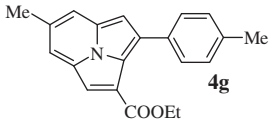
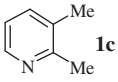
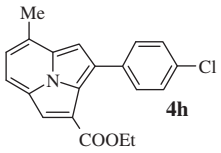
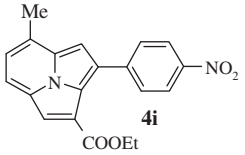
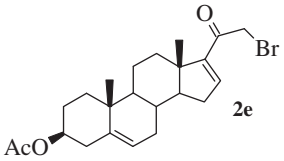
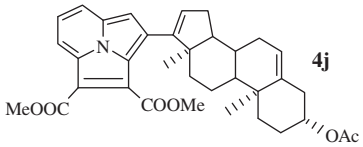
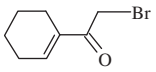
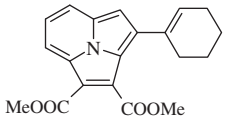
Entry	Alkylpyridine	Acylbromide	Alkyne	Product[b]	Yield[c]
1	 **1a**	 **2a**	DMAD **3a**	 **4a**	90
2	**1a**	 **2b**	**3a**	 **4b**	92
3	**1a**	 **2c**	**3a**	 **4c**	60
4	**1a**	 **2d**	**3a**	 **4d**	20
5	**1a**	**2a**	Ethyl propiolate **3b**	 **4e**	78
6	 **1b**	**2a**	**3b**	 **4f**	80

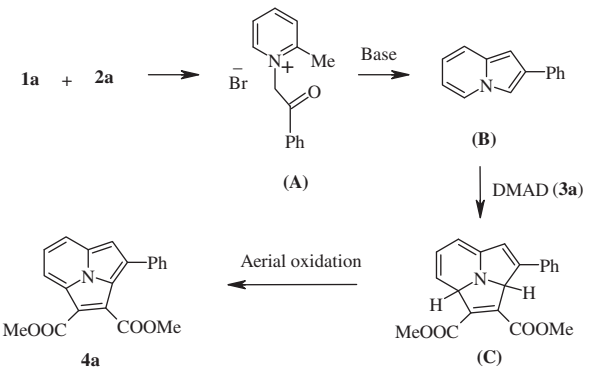
Table 2 (*continued*)

Entry	Alkylpyridine	Acylbromide	Alkyne	Product[b]	Yield[c]
7	**1b**	**2b**	**3b**	 **4g**	74
8	 **1c**	**2c**	**3b**	 **4h**	65
9	**1c**	**2d**	**3b**	 **4i**	22
10	**1a**	 **2e**	**3a**	 **4j**	78
11	**1a**	 **2f**	**3a**	 **4k**	74

[a] Conditions: **1** (1 mmol), **2** (1.2 mmol), **3** (1.5 mmol), K_2CO_3 (1.5 mmol), water (10 ml).
[b] Reactions were carried out under microwave irradiation for 2–5 min at 100 °C.
[c] Isolated yields.

(**2f**) reacted with **1a** and **3b** to yield **4k** in good yield (74%, Table 2, entry 11).

A plausible mechanism is proposed for the formation of **4a** from the water mediated three-component reaction (Scheme 2). The quaternary salt (**A**), obtained from the reaction of 2-picoline (**1a**) with α-bromoacetophenone (**2a**) initially undergoes cyclodehydration in the presence of base to afford the Tschitschibabin indolizine (**B**), which then undergoes [3 + 2]cycloaddition with DMAD (**3a**) to form dihydrocycl[3.2.2]azine (**C**). Finally, the oxidation of the latter to **4a** is rapidly accomplished under microwave irradiation in the presence of air to form the stable 10π aromatic system. As a support of this hypothesis, we carried the reaction sequentially in order to isolate the various intermediates. Hence, 2-picoline (**1a**) and phenacyl bromide (**2a**) were first reacted under basic condition to afford Tschitschibabin indolizine (**B**).[20] The latter was then subjected to DMAD (**3a**) in water under microwave irradiation to rapidly trigger the cycloaddition and the concomitant aerial oxidation



Scheme 2.

to afford **4a** in good yield (88%).[21] It was interesting to note that the three-component reaction in water required no metal catalyst for the oxidation of **C** to stable aromatic **4a** in contrast to reactions carried in organic solvents. All of our efforts to isolate dihydrocycl[3.2.2]azine (**C**) when performing the three-component reaction under anaerobic condition failed as it solely led to **4a**. Moreover, the metal-free two-component reaction of **B** with **3a** in refluxing toluene failed in our hands.[16a,16b]

In conclusion, we have developed an efficient and fast reaction for the synthesis of cycl[3.2.2]azines using water as a reaction medium under microwave irradiation. The reaction proceeds via the initial formation of the corresponding Tschitschibabin indolizine, followed by a [3 + 2]cycloaddition with an alkyne with concomitant aerial oxidation. We have further shown that this reaction can be applied to the synthesis of cycl[3.2.2]azine starting from steroidal and carbocyclic acyl bromides. Our procedure in aqueous medium is environmental friendly and devoid of organic solvents and metal catalysts.

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18. *Typical procedure for the preparation of cycl[3.2.2]azine* (**4a**): (a) *Thermal condition*: To a mixture of 2-picoline (0.12 ml, 1 mmol), α-bromoacetophenone (240 mg, 1.2 mmol) and DMAD (0.18 ml, 1.5 mmol) in water (10 ml) was added K_2CO_3 (207 mg, 1.5 mmol) and the mixture was heated to 100 °C. The reaction was monitored by TLC and on completion of the reaction after 1 h, the reaction mixture was cooled and extracted with CH_2Cl_2 (3 × 20 ml). The organic portion was washed with water, dried over anhydrous Na_2SO_4 and the solvent was removed to obtain a crude product. Preparative TLC separation using EtOAc/hexane (10:90) as eluant afforded 2-phenyl-4,5-dicarbmethoxy-cycl[3.2.2]azine **4a** in 70% yield. (b) *Microwave condition*: A mixture of 2-picoline (0.12 ml, 1 mmol), α-bromoacetophenone (240 mg, 1.2 mmol), DMAD (0.18 ml, 1.5 mmol) and K_2CO_3 (207 mg, 1.5 mmol) was taken in water (10 ml) and the mixture was irradiated in an open vessel of Synthwave 402 Prolabo focused microwave reactor at 100 °C and power at 60% (maximum output 300 W). The reaction was monitored by TLC and upon completion of reaction after 2 min, the reaction mixture was cooled and extracted with CH_2Cl_2 (3 × 20 ml). The organic portion was washed with water, dried over anhydrous Na_2SO_4, and the solvent removed to obtain a crude product. Preparative TLC separation using EtOAc/hexane (10:90) as eluant afforded **4a** in 90% yield.
2-Phenyl-4,5-dicarbmethoxy-cycl[3.2.2]azine **4a**: yellow needles, mp 139–42 °C (dec); R_f = 0.5 (EtOAc/Hexane = 10:90); IR ($CHCl_3$) cm^{-1}: ν 2924, 2853, 1716, 1705, 1617, 1487, 1256, 1209, 1169, 1117, 1067, 772; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.93–8.42 (4H, m), 7.43–7.52 (5H, m), 4.02 (3H, s), 3.96 (3H, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.7, 164.3, 137.4, 134.1, 132.3, 129.6, 129.1, 128.8, 128.5, 125.6, 125.1, 122.6, 119.8, 116.4, 114.3, 112.2, 111.6, 100.4, 52.9, 51.8; EI mass m/z = 333 [M$^+$]. *2-Phenyl-4-carbethoxy-cycl[3.2.2]azine* **4e**: yellow needles, mp 112–15 °C (dec); R_f = 0.55 (EtOAc/Hexane = 10:90): IR ($CHCl_3$) cm^{-1}: ν 2924, 1698, 1610, 1505, 1256, 1176, 1097, 772; ^{1}HNMR ($CDCl_3$, 300 MHz) δ 8.37 (1H, d, J = 4.7 Hz), 8.33 (1H, s), 8.05 (1H, d, J = 4.7 Hz), 7.90 (1H, d, J = 4.6 Hz), 7.85 (3H, m), 7.51 (1H, s), 7.54 (1H, t, J = 4.6 Hz), 7.41 (1H, t, J = 4.5 Hz), 4.50 (2H, q, J = 4.3 Hz), 1.51 (3H, t, J = 4.3 Hz); ^{13}CNMR $CDCl_3$, 75 MHz): δ 165.2, 135.7, 134.1, 132.0, 129.9 (2C), 129.1, 128.5, 127.6 (2C), 124.4, 119.6, 114.7 (2C), 114.5, 113.1, 109.1, 60.2, 14.6; EI mass m/z 289 [M+]. 2-(3′-Acetoxy-5′,16′-dieno-androst-17-yl)-4,5-carbmethoxy-cycl[3.2.2]azine **4j**: light yellow crystal, mp 203–05 °C (dec); R_f = 0.50 (EtOAc/Hexane = 10:90): IR ($CHCl_3$) cm^{-1}: ν 2930, 1710, 1702, 1613, 1510, 1260, 1090, 770; ^{1}HNMR ($CDCl_3$, 300 MHz) δ 8.28 (1H, d, J = 4.8 Hz), 8.17(1H, m), 8.02 (1H, d, J = 4.8 Hz), 7.51 (1H, s), 6.50 (1H, br s), 5.62 (1H, br s), 4.70 (1H, m), 4.10 (3H, s), 4.01 (3H, s), 2.35–1.20 (17H, m), 2.10 (3H, s), 1.20 (3H, s), 1.03 (3H, s); ^{13}CNMR $CDCl_3$, 75 MHz): δ 165.8, 164.9, 163.6, 153.4, 139.2, 139.0, 138.5, 127.8, 126.3 (2C), 125.6, 124.8, 122.4 (2C), 118.2, 113.3, 104.4, 72.5, 58.9, 55.1, 49.2, 46.8, 37.1, 35.8, 33.2, 31.7, 30.5, 29.1, 28.7, 26.4, 19.4, 18.6, 15.4, 15.3, 15.2; EI mass m/z 569 [M$^+$].
19. The regioselectivity of the products **4e**–**i** were in compliance with the reported frontier orbital treatment of 1,3-dipolar cycloaddition reactions: Houk, K. N.; Sims, J.; Watts, C. R.; Luscos, L. J. *J. Am. Chem. Soc.* **1973**, *95*, 7301.
20. *Preparation of Tschitschibabin 2-phenyl-indolizine* (**B**): A mixture of 2-picoline (0.12 ml, 0.1 mmol), α-bromoacetophenone (240 ml, 1.2 mmol), and K_2CO_3 (207 mg, 1.5 mmol) was taken in water (10 ml) and irradiated in an open vessel of Synthwave 402 Prolabo focused microwave reactor at 100 °C and power at 60% (Maximum output 300 W). On completion of reaction after 1 min, the reaction mixture was cooled and extracted with CH_2Cl_2 (3 × 20 ml). The organic portion was washed with water, dried over anhydrous Na_2SO_4, and the solvent removed to obtain a crude product, which on purification afforded **B** in 93% yield. mp 188–90 °C; R_f = 0.6 (EtOAc/Hexane = 05:95): IR ($CHCl_3$) cm^{-1}: ν 2920, 1633, 1604, 1452, 1384, 1297, 1252, 781, 755; ^{1}HNMR ($CDCl_3$, 300 MHz) δ 7.88 (1H, d, J = 6.8 Hz), 7.65 (1H, d, J = 7.6 Hz), 7.56 (1H, s), 7.32 (3H, m), 7.25 (2H, J = 6.9 Hz), 6.69 (1H, s), 6.66 (1H, m), 6.44 (1H, m); ^{13}CNMR $CDCl_3$, 75 MHz): δ 135.0, 13.3, 129.1 (2C), 128.5, 226.2, 125.9, 125.6, 124.8, 118.7, 117.1, 110.2, 108.9, 96.3; ESI mass m/z 193 [M$^+$].
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