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A Novel Microwave-Mediated One-Pot Synthesis of Indolizines via a Three-Component Reaction

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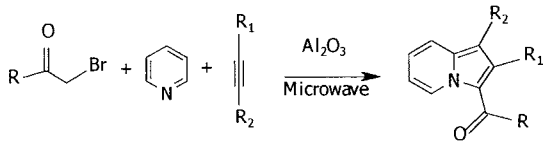
ABSTRACT



The microwave-mediated three-component reaction of acyl bromide, pyridine, and acetylene is catalyzed by basic alumina to give corresponding indolizines in excellent yields in a one-pot reaction.

The design of multicomponent reactions (MCR) is an important field of research from the point of view of combinatorial chemistry.[1] Being a one-pot reaction, generally multicomponent reactions afford good yields and are fundamentally different from two-component reactions in several aspects.[2] Although the first MCR dates back to the Strecker synthesis[3] of α-amino acid in 1850, the MCR strategy has been utilized successfully in Robinson's synthesis of alkaloid tropinone[4] and Hantsch's synthesis of 1,4-dihydropyridines.[5] Consequently, in the past decade there has been tremendous development in three- and four-component reactions involving Passerini-,[6] Ugi-,[7] and Mannich-type reactions[8] which led to the renaissance of MCRs. Unfortunately, despite the enormous scope of MCR, only the 3-CRs with isocyanide have been developed into popular organic reactions. Nevertheless, great efforts have been and still are being made to find and develop new MCRs.[9]

The indolizines constitute the core structure of many naturally occurring alkaloids, viz., (−)-slaframine,[10] (−)-dendroprimine,[11] indalozin 167B,[12] and coniceine.[13] The synthesis of biologically active indolizines[14] continues to attract the attention[15] of organic chemists. The indolizines

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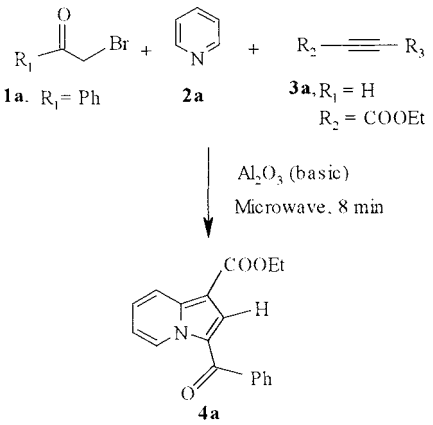
are most commonly synthesized by sequential *N*-quarternization and intramolecular cyclocondensation reactions[16] or the cycloaddition reaction[17] of *N*-acyl/alkyl pyridinium salts. This reaction, however, suffers from the disadvantage of the handling problem of the pyridinium salt due to its hygroscopic nature. Another stereoselective route is based on the iron-catalyzed cyclization of *N*-substituted pyrrolotrienes.[18] A similar strategy was reported for the synthesis of indolizines via intramolecular 1,5-dipolar cyclization of 2-vinyl pyridinium ylide in the presence of tetrakis[pyrido]cobalt(II)-dichromate.[19] A new pathway to chiral indolozines was accomplished from proline via the Pauson Khand reaction[20] involving an intramolecular cyclization reaction. These strategies, however, involved multistep synthesis employing two-component reactions and do not represent the goal of an ideal synthesis.[21]

The microwave-promoted solid-phase heterogeneous reaction is well-known[22] as an environmentally benign reaction methodology that usually provides improved selectivity, enhanced reaction rates, cleaner products, and manipulative simplicity. We recently reported our efforts[23] for fast and facile reaction strategies that involve microwave energy as an unconventional energy source in a two-component reaction. The objective of the present study was to establish the viability of a three-component reaction (3-CR) involving a 1,3-dipolar cycloaddition reaction between an in situ generated dipole (α-bromoacetophenone and pyridine) and acetylene using microwave energy. If successful, such a strategy would provide access to fast one-pot synthesis of cycloadducts which otherwise are accessible only through multistep synthesis. The first successful examples of the application of this approach are described herein (Scheme 1).

Scheme 1



It was reasoned that basic alumina can be used as a basic catalyst under microwave energy for in situ dipole generation from the *N*-acyl pyridinium salt, which could participate in a [3+2] intramolecular cycloaddition reaction with acetylene dienophiles. Thus, when a three-component mixture of phenacyl bromide (**1a**, 1 mmol), pyridine (**2a**, 1.2 equiv), and ethyl propiolate (**3a**, 1.2 equiv) was thoroughly mixed in basic alumina (1 g) and irradiated in a Synthewave 402 Prolabo focused microwave unit at a frequency of 2450 MHz and 80% power for 8 min, the reaction product 3-benzoyl-1-carbethoxy-indolizine (**4a**)[24] was obtained in 92% yield (Table 1, entry 1). The product exhibited a characteristic[19] doublet proton signal at δ 9.96 (J = 7.11 Hz) for the C-5 proton of indolizine. The 3-CR when conducted without basic alumina resulted in the dramatic decrease in the yield (entry 2). Similarly, the reaction carried out in dry pyridine without basic alumina led to poor yield of **4a** (entry 3). However, when the reaction was conducted in dry pyridine with alumina as catalyst, the cycloaddition reaction afforded good yield of the indolizine (entry 4). We attempted a similar reaction with basic alumina in organic solvents, but the results were less satisfactory (entries 5, 6, and 7). However, a combination of the organic solvent, triethylamine, and alumina under microwave irradiation afforded good results (entries 8, 9, and 10).

Table 1. Microwave-Promoted Three-Component Reaction[a] According to Scheme 1 Catalyzed by Alumina[b]

entry	catalyst	yield[c] of **4a** (%)
1	Al_2O_3	92
2	Nil	12
3	pyridine[d]	48
4	pyridine/Al_2O_3	78
5	toluene/Al_2O_3	68
6	THF/Al_2O_3	60
7	DMF/Al_2O_3	75
8	toluene/Et_3N/Al_2O_3	80
9	THF/Et_3N/Al_2O_3	76
10	DMF/Et_3N/Al_2O_3	82

[a] Reactions were carried using 1 mmol of phenacyl bromide, 1.2 equiv of pyridine, 1.2 equiv of ethyl propiolate, and 1 g of basic alumina. [b] Basic alumina was activated at 450 °C for 12 h. [c] Isolated yields. [d] An excess of pyridine was used without alumina.

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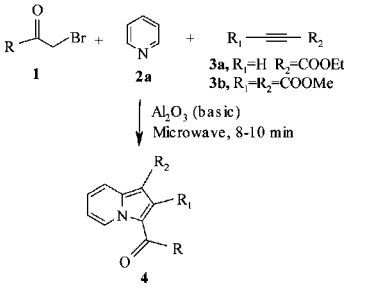
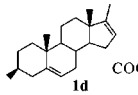
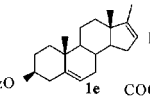
The 3-CR of acylhalides (**1a**−**e**), pyridine (**2a**), and acetylenes (**3a**,**b**) was carried out under similar microwave reaction conditions in the presence of basic alumina catalyst as in entry 1 of Table 1 to afford **4b**−**j** in excellent yields (Table 2). However, when the same reactions were carried out in toluene as in entry 4 in Table 1, yields of the products **4b**−**j** were decreased. The advantage of the solid-phase reaction is that the reaction products were easily separated from alumina by extraction with dichloromethane or ethyl acetate. The cycloaddition reaction of acetylenes with in situ generated 1,3-dipoles from pyridinium salts proceeded smoothly irrespective of whether the substitutent is aroyl, cinnamoyl, or steroidal in nature.

Table 2. Microwave-Mediated Three-Component Reaction of Acyl Halide **1**, Pyridine **2a**, and Acetylene **3** Catalyzed by Alumina



Entry	R		Product R_1	R_2		Yield[a] (%) Solid[b]	Solvent[c]
1	Ph	**1a**	COOMe	COOMe	**4b**	94	71
2	*p*-Tolyl	**1b**	H	COOEt	**4c**	93	65
3	*p*-Tolyl	**1b**	COOMe	COOMe	**4d**	91	62
4	Styryl	**1c**	H	COOEt	**4e**	90	66
5	Styryl	**1c**	COOMe	COOMe	**4f**	87	60
6		**1d**	H	COOEt	**4g**	94	70
7	AcO		COOMe	COOMe	**4h**	93	67
8		**1e**	H	COOEt	**4i**	92	64
9	BzO		COOMe	COOMe	**4j**	90	62

[a] Yields refer to pure isolated yields. [b] Solid-phase reaction without solvent. [c] Reaction carried out in dry toluene.

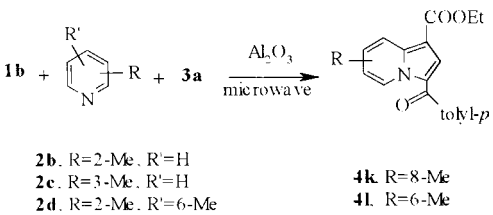
For comparison, when a three-component reaction was carried out thermally in refluxing toluene (10 mL) with phenacyl bromide (**1a**, 1 mmol), pyridine (**2a**, 1.2 equiv), ethyl propiolate **(3a**, 1.4 equiv), and Et_3N (0.1 equiv) for 6 h, it afforded the indolizine product **4a** in 60% yield (Table 3, entry 1). The change of the solvent to THF or acetonitrile did not improve the reaction rate or yield (entries 2 and 3). However, when the reaction was carried out with pyridine as solvent for 6 h, the product **4a** was obtained in good yield (entry 4). A thin layer chromatrography (TLC) monitoring and workup of the reaction mixture after 2 h showed partial conversion (35%) of the product. The thermal reaction of **1a**, **2a**, and **3a** in other organic solvents in combination with basic alumina did not improve the yield of **4a** (entries 5, 6, and 7), whereas 3-CR of **1a**, **2a**, and **3a** in pyridine/alumina (basic) for 6 h under identical conditions afforded **4a** in high yield (entry 8).

Table 3. Three-Component Reaction of **1a**, **2**, and **3a** under Thermal Condition

entry	solvent	base	yield of **4a** (%)
1	toluene	Et_3N	60
2	THF	Et_3N	55
3	CH_3CN	Et_3N	50
4	pyridine	Et_3N	80
5	toluene	Al_2O_3	45
6	THF	Al_2O_3	42
7	CH_3CN	Al_2O_3	35
8	pyridine	Al_2O_3	88

To broaden the scope of the 3-CR reaction, the alumina-catalyzed solid-phase reaction of **1b**, 2-picoline (**2b**), and **3a** was carried under microwave irradiation as in entry 1 of Table 1 to afford 1-carbethoxy-3-(4′-tolyl)-5-methylindolizine (**4k**) in 88% yield (Scheme 2). A similar reaction with 3-picoline (**2c**) resulted in 1-carbethoxy-3-(4′-tolyl)-6-methyl indolizine (**4l**) in 91% yield. However, an attempt to carry 3-CR with **1b**, 2,6-lutidine (**2d**), and **3a** under identical conditions failed.

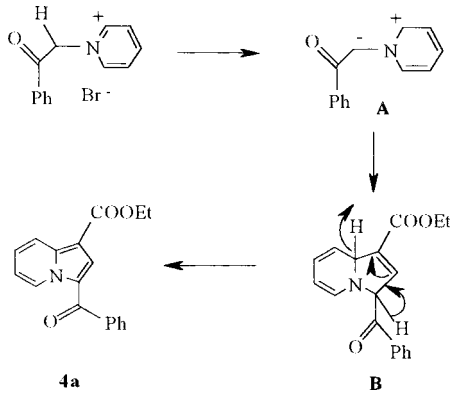
Scheme 2



(24) Illustrative procedure for the preparation of 3-benzoyl-1-carbethoxy-indolizine **4a**: Phenacyl bromide (0.20 g, 1 mmol), pyridine (0.12 mL, 1.5 equiv), and ethylpropiolate (0.15 mL, 1.5 equiv) were intimately mixed with activated basic alumina (1 g) and irradiated for 8 min in a Synthewave 402 Prolabo focused microwave at power 80% and temperature limitation of 250 °C. The reaction mixture turned deep brown. After cooling to room temperature, the mixture was eluted with methanol/chloroform (5/95), washed with water (3 × 50 mL), and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed (silica gel, ethyl acetate/hexane = 10/90) to give a crude solid. The crude product was recrystallized from *n*-hexane to give 0.27 g (92%) of 3-benzoyl-1-carbethoxy-indolizine (**4a**) as white crystals, mp 76.5−77 °C; R_f 0.6 (ethyl acetate/hexane = 10/90); *m*/*z* (ESI) 316 (M^+ + 23); IR (KBr) ν_{max} 2976, 1696, 1617, 1523 cm^{-1}; ^1H NMR (δ in $CDCl_3$) δ 9.96 (d, 1H, J = 7.11 Hz, C-5), 8.40 (d, 1H, J = 8.94 Hz, C-8), 7.81(s, 1H, C-2), 7.85−7.09 (m, 7H, Ph, C-6, C-7), 4.41 (q, 2H, J = 7.11 Hz, $-OCH_2-$), 1.42 (t, 3H, J = 7.10 Hz, ester Me); ^{13}C NMR (δ in $CDCl_3$) δ 184.69, 163.20, 138.98, 130.61, 128.32, 128.17, 128.09 (2C), 127.53 (3C), 126.86, 121.60, 118.60, 114.44, 105.37, 59.26, 13.68. Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.53; H, 5.19; N, 4.67.

It is proposed that the *N*-alkylpyridinium salt, generated in situ from condensation of phenacyl bromide and pyridine, is converted into the 1,3-dipole species (**A**)[17b,25] under the influence of base and cycloadds to ethyl propiolate to form an unstable intermediate (**B**), which instantly facilitates aromatization to afford **4a** comprising a 10-π electron system (Scheme 3).

Scheme 3



The usefulness of this methodology lies in the fact that the three-component reactions are carried out rapidly under microwave-promoted environmentally benign, solvent-less conditions to give 2-acyl indolizines (entries **4a**−**l**) in excellent yields. The catalytic effect of basic alumina was found more prominent in solid-phase 3-CRs than liquid-phase 3-CRs (Table 2). Moreover, the reaction is compatible with substitutents such as aroyl, cinnamoyl, or steroid-20-one groups and substituted pyridines. In conclusion, the methodology reported herein denotes a new class of 3-CR, which is expected to be a general route for the facile, one-pot combinatorial synthesis of a wide range of indolizines.

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Supporting Information Available: Characterization data for all new compounds including ^{1}H and ^{13}C NMR spectra for **4a**, **4c**, **4e**, and **4g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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