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Microwave-Promoted and Lewis Acid Catalysed Synthesis of 2,4,6-Triarylpyridines Using Urea as Benign Source of Ammonia

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Abstract: An efficient method for the synthesis of 2,4,6-triarylpyridines via microwave-promoted and $BF_3{\cdot}OEt_2$-catalysed one-pot reaction of ω-pyrrolidinoacetophenone with chalcone is reported. This method illustrates urea as an environmentally benign source of ammonia for the synthesis of 2,4,6-triarylpyridines.

Key words: 2,4,6-triarylpyridine, urea, microwave, Lewis acid

2,4,6-Triarylpyridines are prominent building blocks in supramolecular chemistry[1] and are important because of their biological activities.[2] The quaternary 2,4,6-triarylpyridinium derivatives have significant synthetic applications such as in nucleophilic displacement reaction,[3] C-alkylation of β-diketones,[4] electrophilic amination[5] and azepine synthesis.[6] The facile elimination of pyridinium ions from these stable and sterically hindered compounds have made them useful substrates in organic transformation reactions.[7] The 2,4,6-triarylpyridine nucleus is structurally related to symmetrical triarylthiopyrylium, -selenopyrylium and -telluropyrylium photosensitisers which have been recommended for photodynamic cell-specific cancer therapy.[8]

The synthesis of 2,4,6-triarylpyridines has attracted a great deal of attention from organic chemists. Traditionally, these compounds are synthesised through the reaction of *N*-phenacylpyridinium[9]or *N*-phenacylisoquinolinium salts[10] with α,β-unsaturated ketones in the presence of NH_4OAc. Recently, the synthesis of triarylpyridines has been reported from the dimerisation–heteroannulation reaction of chalcones employing compounds possessing terminal $CONH_2$ functionality catalysed by a $BiNO_3$-derived heterocatalyst.[11] A few more new syntheses have been accomplished by NH_4OAc-promoted reactions, for example, one-pot reaction of acetophenone with benzaldehyde,[12] sodium hydroxide catalysed condensation of heterocyclic aldehydes,[13] Michael addition and solid-phase condensation of chalcones,[14] and reaction of α-benzotriazolyl ketone with 1,5-diketones.[15] The synthesis of 2,4,6-triarylpyridines is also reported from the reaction of *N*-(diphenylphosphenyl)-1-phenylethaneimine with aromatic aldehydes,[16] reaction of α-benzotriazolyl ketone with 1,5-diketones in the presence of NH_4OAc,[16] conversion of 2,4,6-triarylpyrylium salts into 2,4,6-triarylpyridine using aqueous ammonia[17] and addition of lithiated β-enaminophosphonates to chalcones.[18] However, most of these methodologies have the discrepancies of multistage reactions with low to moderately yielding laborious processes and environmentally hazardous or harsh reaction conditions.

The utility of unconventional microwave energy in synthetic organic chemistry is increasingly recognised in recent years.[19] Microwave-promoted solid-phase heterogeneous reactions have turned out as environmentally benign reaction methodologies having greater selectivity, enhanced reaction rates, cleaner products and manipulative simplicity.[20] Microwave-mediated multicomponent reactions constitute a specially attractive synthetic strategy for rapid and efficient library generation due to the fact that products are formed in a single step and the diversity can be achieved simply by varying the reacting components.[21] Recently, we have demonstrated solid-phase synthesis of aza heterocycles using urea as an efficient source of ammonia under microwave irradiation.[22] In continuation of our interests towards development of newer strategy for pyridines,[23] we describe herein a $BF_3{\cdot}OEt_2$-catalysed and solventless one-pot synthesis of 2,4,6-triarylpyridines from the reaction of ω-pyrrolidinoacetophenone with chalcone using urea as an environmentally benign source of ammonia under microwave irradiation.

When a finely ground mixture of ω-pyrrolidinoacetophenone (**1a**), 1,3-diphenyl-2-propen-1-one (**2a**), urea and $BF_3{\cdot}OEt_2$ was irradiated under microwave in an open vessel in a Prolabo Synthwave 402 microwave reactor[24] for three minutes at atmospheric pressure, it afforded 2,4,6-triphenylpyridine (**3a**) in 90% yield (Table 1). The product **3a** was characterised by comparison of its physical and spectral data.[25] Similarly **1a** reacted with chalcones **2b**–**g** in the presence of urea and $BF_3{\cdot}OEt_2$ to yield 2,4,6-triarylpyridines **3b**–**g** in high yields. The reaction of **1b**,**c** with **2a**–**e** under identical conditions afforded **3h**–**p** in high yields. However, the reaction failed to proceed when thiourea was employed in place of urea under identical conditions. The replacement of the pyrrolidine moiety in **1a** with morpholine or pyridine led to comparatively poor yields of the product **2a**.

In order to study the influence of the Lewis acid on the azacyclisation reaction, we carried out the solid-phase reaction of **1a** and **2a** independently with $SmCl_3$, $ZrCl_4$, $TiCl_4$, $InCl_3$ and $AlCl_3$ and obtained **3a** in 33–51% yields.

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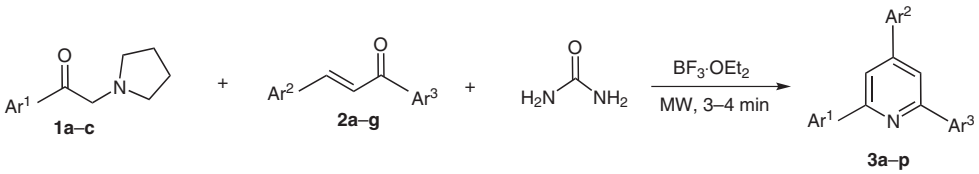
Table 1 Synthesis of Unsymmetrical 2,4,6-Triphenylpyridines **3a–p**[a]



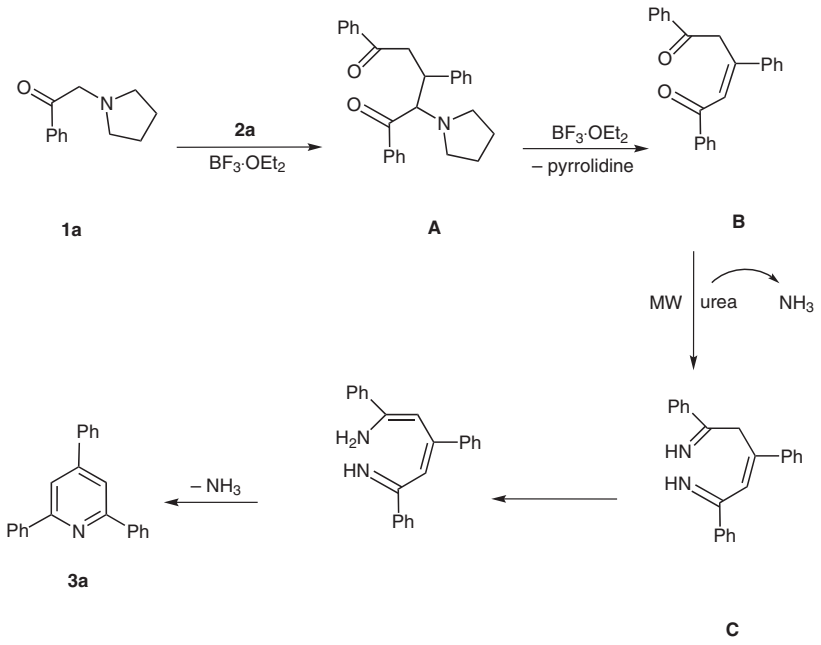
Entry	1	2	Ar^1	Ar^2	Ar^3	Product	Yield[b] (%)	Mp (°C) (Lit.)[c]
1	**1a**	**2a**	Ph	Ph	Ph	**3a**	90	135–36 (134–35)[16]
2	**1a**	**2b**	Ph	Tol	Ph	**3b**	94	123–24 (124.5–25)[16]
3	**1a**	**2c**	Ph	4-ClC_6H_4	Ph	**3c**	88	126–28 (129–30)[16]
4	**1a**	**2d**	Ph	Ph	Tol	**3d**	93	123–24 (124–125)[18]
5	**1a**	**2e**	Ph	Ph	4-ClC_6H_4	**3e**	95	127–28 (125–27)[10a]
6	**1a**	**2f**	Ph	Ph	4-BrC_6H_4	**3f**	87	159–51 (150–52)[15]
7	**1a**	**2g**	Ph	Ph	PMP	**3g**	90	105–06 (105–07)[10a]
8	**1b**	**2a**	4-ClC_6H_4	Ph	Ph	**3h**	88	127–28 (125–27)[10a]
9	**1b**	**2b**	4-ClC_6H_4	Tol	Ph	**3i**	92	154–55 (155–56)[10b]
10	**1b**	**2c**	4-ClC_6H_4	4-ClC_6H_4	Ph	**3j**	90	139–40 (140–42)[15]
11	**1b**	**2d**	4-ClC_6H_4	Ph	Tol	**3k**	87	152–54
12	**1b**	**2e**	4-ClC_6H_4	Ph	4-ClC_6H_4	**3l**	89	176–78 (178–79)[10b]
13	**1c**	**2a**	Tol	Ph	Ph	**3m**	92	123–24 (124–125)[18]
14	**1c**	**2b**	Tol	Tol	Ph	**3n**	91	133–35
15	**1c**	**2c**	Tol	4-ClC_6H_4	Ph	**3o**	88	119–21 (120–22)[15]
16	**1c**	**2d**	Tol	Ph	Tol	**3p**	85	156–57 (157–58)[14]

[a] Conditions: **2** (1 mmol), **1** (1.5 mmol), urea (3.0 mmol), $BF_3{\cdot}OEt_2$ (cat.).
[b] Isolated yields.
[c] Values in parentheses are the melting points reported in the literature.

However, the reactions were found to be sluggish in the absence of Lewis acid and the products were obtained in very poor yields (<10%). When this reaction was carried out under thermal condition, it afforded products **3a–p** in very poor yields.

A plausible mechanism is proposed via $BF_3{\cdot}OEt_2$-catalysed enolate addition of ω-pyrrolidinoacetophenone (**1a**) to chalcone (**2a**) to afford 1,5-dicarbonyl intermediate **A** followed by elimination of pyrrolidine to form intermediate **B** (Scheme 1). Under microwave irradiation urea released ammonia[22] which combined with **B** to facilitate diimine intermediate **C** followed by enolisation and cyclocondensation to afford **3a** with concomitant loss of ammonia. The $BF_3{\cdot}OEt_2$ presumably played a key role by enhancing the electron deficiency on carbonyl carbon of **1a** facilitating Michael addition to afford 1,5-dicarbonyl intermediate **A** and elimination of pyrrolidine from **A** to form intermediate **B**. The isolation of 1,3,5-triphenylpent-2-en-1,5-dione (**B**)[25] from the reaction of **1a** and **2a** without urea under identical condition supported our proposed mechanism.

In conclusion, we have developed a facile and novel strategy for the preparation of 2,4,6-triarylpyridines from $BF_3{\cdot}OEt_2$-catalysed one-pot reaction of ω-pyrrolidinoacetophenone, chalcone and urea under microwave irradiation. We have successfully demonstrated the utility of urea as an environmentally benign source of ammonia for pyridine synthesis under microwave irradiation. The utility of urea as a source of ammonia represents an alternative and novel strategy for pyridine synthesis with respect to hitherto known methodologies using ammonium acetate. The method reported herein describes a new application of ω-pyrrolidinoacetophenone and is expected to be a general route for facile and combinatorial synthesis of a wide range of unsymmetrical 2,4,6-triarylpyridines. Also our strategy provides an efficient methodology for the synthesis of easily inaccessible 1,5-diketones. Further synthetic application of the newly developed methodology is in progress.



Scheme 1 Proposed mechanism for 2,4,6-triphenylpyridine synthesis

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(24) Microwave experiments were conducted in open reaction vessels of a Synthwave 402 reactor manufactured by M/s Prolabo, 54 rue Roger Salengro, Cedex, France. The temperature of the reaction mixture was set at 140 °C and measured by a computer controlled sensor using 80% power (maximum output 300 Watts) with an operating frequency of 2.45 GHz. The reaction time specified is the total irradiation time. The hold time at final temperature is 25% of the total time.

(25) **Spectral and Analytical Data of Selected Compounds**:
Compound B: mp 97–99 °C; R_f = 0.7 (EtOAc–hexane, 10:90). IR (KBr): 3059, 3028, 2922, 1686, 1653, 1606, 1448, 1217, 1180, 1010, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, 2 H, *J* = 7.4 Hz), 7.92 (d, 2 H, *J* = 7.4 Hz), 7.88 (d, 2 H, *J* = 8.0 Hz), 7.18–7.54 (m, 6 H), 5.25 (s, 1 H), 4.84 (s, 2 H), 2.40 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.0, 190.5, 152.7, 152.0, 143.3, 141.7, 136.9, 136.2, 134.2, 132.9, 132.4, 129.1, 129.0, 128.5 (2 × C), 128.4, 128.3, 128.2, 128.2, 128.0, 126.5, 123.3, 42.7, 21.4. MS (ESI): *m*/*z* = 341 [M^+ + 1].
Compound 3a: mp 135–36 °C; R_f = 0.8 (EtOAc–hexane, 10:90). IR (KBr): 3035, 2924, 1595, 1550, 1495, 1449, 1180, 756 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.21 (m, 4 H), 7.89 (s, 2 H), 7.75 (d, 2 H, *J* = 7.0), 7.03–7.53 (m, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2 (2 × C), 149.9, 139.3 (2 × C), 138.8, 128.9 (2 × C), 128.8, 128.7 (3 × C), 128.4 (3 × C), 126.9 (3 × C), 126.9 (3 × C), 116.9 (2 × C). MS (ESI): *m*/*z* = 308 [M^+ + 1].
Compound 3k: mp 152–54 °C; R_f = 0.8 (EtOAc–hexane, 10:90). IR (KBr): 3056, 2922, 1596, 1544, 1492, 1184 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–8.14 (m, 13 H), 7.82 (s, 2 H), 2.42 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.3, 157.1, 155.8, 150.0, 149.7, 138.9, 138.7, 137.8, 136.6, 136.3, 134.8, 129.2, 129.1, 128.9, 128.8, 128.6, 128.1, 126.9, 126.7 (2 × C), 125.6, 116.8, 116.3, 21.1. MS (ESI): *m*/*z* = 356 [M^+ + 1].
Compound 3n: mp 133–35 °C; R_f = 0.7 (EtOAc–hexane, 10:90). IR (KBr): 3034, 2924, 1597, 1546, 1496, 1417, 1185 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.20 (m, 4 H), 7.87 (s, 2 H), 7.64 (d, 2 H, *J* = 5.8 Hz), 7.14–7.51 (m, 7 H), 2.42 (s, 3 H), 1.34 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2 (2 × C), 139.4 (2 × C), 129.6 (3 × C), 128.7 (3 × C), 128.4 (3 × C), 126.9 (4 × C), 126.7 (4 × C), 116.6 (2 × C), 29.5, 21.0. MS (ESI): *m*/*z* = 336 [M^+ + 1].