Solvent-Free Synthesis of 2,4,6-Triaryl Pyridines

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A modified method to prepare 1,3,5-triarylpyridines by a [3+2+1] ring annulation reaction is described. Three-component condensation of neat reactants when subjected to microwaves afforded the required product in shorter reaction time with higher yield in comparison to conventional methodologies. The microwave accelerated reaction technique without external solvent renders the whole synthesis into a truly ecofriendly protocol.

Key words: Pyridine, Microwaves, Environmentally Benign

Introduction

Industrial chemistry in the new millennium is widely accepting the concept of "green chemistry" to meet the fundamental challenges of environment protection [1]. The emerging area of green chemistry envisages minimum hazard and designing of new chemical processes. One of the thrust areas for achieving this target of environmentally benign synthesis is to explore alternative reaction conditions and reaction media to accomplish the desired transformations with minimised by-products or waste as well as eliminating the use of conventional organic solvents, if possible [2].

Among the important tools, the use of microwave (MW) as an alternative energy source is now becoming an attractive technique [3]. One of the advances in this area where substantial progress has been made is the MW assisted solid support synthesis [4]. It offers the advantages of high product yield and reaction rate enhancement [5]. But the minute observation of this reveals that an appreciable amount of solvent is still required for the adsorption of reactants and elution of product. Another alternative approach which aims at complete elimination of solvent is the "neat reaction" [6] technique in which a mixture of reactants in the absence of solvent is exposed to microwaves. It is associated with the benefits of shorter reaction time, remarkable rate enhancement, high product yield and easier work-up. These no-solvent reactions prove to be advantageous for environmental reasons especially when coupled with microwaves. The solventless approach provides an opportunity to conduct selective organic functional group transformations more efficiently and expeditiously.

The basic skeleton of chalcones that possess α,β-unsaturated carbonyl group is a useful synthon for various heterocyclic compounds of pharmacological importance such as pyrazolines [7], thiophenes [8], *etc*. Further, the importance of pyridine [9 – 11] in pharmaceutical and biological fields is well established. Numerous routes to the pyridine ring are known such as [3+3] pyridine synthesis from iminophosphoranes [12], Chichibabin syntheses [13] which generally results in the formation of mixture of substituted pyridines. Substituted phenacyl isoquinolinium bromide [14] or pyridinium ylide [15] upon reaction with various benzylidene acetophenones also afford 2,4,6-triarylpyridines. The reactants used in the above mentioned methods are not readily available and some require synthesis even at the precursor stage. The synthesis of pyridine ring has been reported widely through conventional heating, however, alternative strategies that are more ecofriendly than traditional ones are being sought due to the increasing concern about the impacts of chemicals on the environment. With a view to explore the studies on reactivity of α-methyl-ketones and benzylidene-acetophenones, significant therapeutic value of pyridines, and the environmentally benign role of solventless synthesis with microwave heating, it was considered worthwhile to explore the synthesis of 2,4,6-triarylprydines by a [3+2+1] ring formation using microwave heating under solvent-free conditions.

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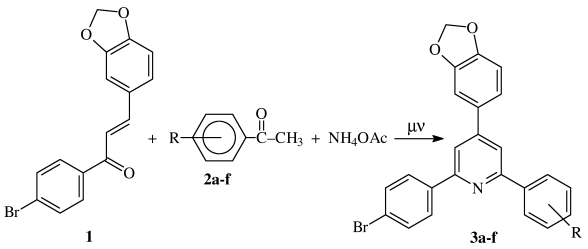

R = H (**a**), 4-Cl (**b**), 4-Br (**c**), 2-CH_3 (**d**), 2-OH (**e**), 4-NH_2 (**f**)

Results and Discussion

The so-called [3+2+1] pyridine ring synthesis utilises the enone functionality as the three-carbon component, differently substituted α-methyl-ketones as the two-carbon component, and ammonium acetate as a one-carbon component and has the potential to meet our goals efficiently. Following the classical procedure [16], 2,4,6-triarylpyridines **3a – f** are obtained in 55 – 65% yield (Table 1) by refluxing enone **1** with different α-methyl-ketones **2** and ammonium acetate as the cyclisation agent in acetic acid under reflux for 10 – 15 h. This procedure employs acetic acid as a corrosive organic reagent, requires long reaction time and gives unsatisfactory yield. Thus, we herein describe the MW accelerated solventless neat synthesis of pyridines **3a – f** with a view to improve the yield and applicability of the desired transformation. In the solventfree technology, appropriate amounts of the neat reactants were mixed and irradiated under microwaves to afford pyridines **3a – f** in 75 – 85% yield in 4 – 8 min (Table 1). This approach eliminates the usage of solid support as well as the solvent from the reaction. These no-solvent conditions prove to be advantageous for environmental reasons and offer the benefits of shorter reaction times and high product yield especially when coupled with microwaves. Further, it is observed that the amount of ammonium acetate required in which ammonium ion acts as the nitrogen source in the case of neat synthesis under microwave is just 1.5 g instead of 3 g as used in the conventional heating procedure. This highlights the role of MW which is attributed to homogenous heating effects [17]. The structures of the resulting pyridines are established on the basic of spectroscopic data and elemental analyses.

It is plausible to assume that initially intermolecular condensation of the α,β-unsaturated ketone with an α-methyl-ketone occurs to result in a 1,5-diketone. This, then undergoes ring closure in the presence of ammonium acetate which acts as the nitrogen source as well as the cyclisation agent to afford 2,4,6-trisubstituted pyridines.

Table 1. Comparison of reaction time and yield of compounds **3a – f**.

Compound	R	Method A time (h) / yield (%)	Method B time (min) / yield (%)
3a	H	12/60	5/82
3b	4-Cl	10/58	6/75
3c	4-Br	10/55	5/77
3d	4-CH_3	8/65	4/85
3e	2-OH	15/55	8/78
3f	4-NH_2	12/63	7.5/80

Conclusion

We have described a [3+2+1] pyridine synthesis starting from an enone functionality. A novel, facile and highly efficient MW-accelerated modification of the conventional reaction conditions is introduced that allows the rapid assembly of structurally diverse pyridines. The advantages of this multicomponent ecofriendly condensation reaction includes a simple reaction set up, good product yield, short reaction time and above all, complete elimination of solvent.

Experimental Section

Melting points were determined with a electrothermal melting point apparatus and are uncorrected. Infrared spectra (in KBr) were recorded on a 1710 Perkin Elmer FT infrared spectrophotometer. ^{1}H NMR spectra were recorded on a FT NMR Hitachi R-600 (60 MHz) spectrometer. Elemental analyses were performed on Heraeus CHN-Rapid Analyzer. For microwave irradiation a Kenstar microwave oven, Model no. OM9925E (2450 MHz, 800 W) was used. The purity of compounds was checked on silica gel coated Al plates (Merck).

General procedure for the synthesis of 4-(1,3-benzodioxol-5-yl)-2-(4-bromophenyl)-6-arylpyridines **3a – f**

Method A: Conventional solution phase synthesis

A mixture of 3-(1,3-benzodioxol-5-yl)-1-(4-bromophenyl)-2-propen-1-one **1** (3.32 g, 0.01 mol), α-methyl-ketone **2a – f** (0.01 mol) and ammonium acetate (3.08 g, 0.04 mol) in glacial acetic acid (20 ml) was stirred at reflux temperature for 8 – 12 h. Upon completion of the reaction, the reaction mixture was cooled, concentrated and left overnight at room temperature. Ice-cold water was added and the precipitate was separated, washed with methanol, dried and recrystallised from a suitable solvent to yield pure pyridines **3a – f**.

Method B: Microwave assisted solventless synthesis

A mixture of neat reactants, 3-(1,3-benzodioxol-5-yl)-1-(4-bromophenyl)-2-propen-1-one **1** (3.32 g, 0.01 mol), α-methyl-ketone **2a – f** (0.01 mol) and ammonium acetate (1.54 g, 0.02 mol) was taken in an Erlenmeyer flask and irradiated under microwaves at an interval of 20 sec. The progress of reaction was monitored by TLC examination. Upon completion of the reaction, the mixture was cooled, and methanol was added. During standing at 10 °C, a sticky solid separated which was crystallised from a suitable solvent to afford products **3a – f** in high yield.

3a: M. p. 136 – 138 °C [18] ($CHCl_3$-C_6H_{12}). – IR (KBr pellets): $\nu = 3070$ (C–H), 1599 (C=N), 1543 (C=C) cm^{-1}. – ^1H NMR (60 MHz, $CDCl_3$): $\delta = 5.9$ (s, 2H, OCH_2O), 7.0 (s, 2H, pyridyl), 7.2 – 8.1 (m, 12H, Ar-H).

3b: M. p. 235 – 238 °C [14] ($CHCl_3$-MeOH). – IR (KBr pellets): $\nu = 3060$ (C–H), 1598 (C=N), 1543 (C=C) cm^{-1}. – ^1H NMR (60 MHz, $CDCl_3$): $\delta = 6.0$ (s, 2H, OCH_2O), 7.1 (s, 2H, pyridyl), 7.4 – 8.3 (m, 11H, Ar-H).

3c: M. p. 193 – 195 °C [15] ($CHCl_3$-MeOH). – IR (KBr pellets): $\nu = 3065$ (C–H), 1598 (C=N), 1542 (C=C) cm^{-1}. – ^1H NMR (60 MHz, $CDCl_3$): $\delta = 6.0$ (s, 2H, OCH_2O), 7.0 (s, 2H, pyridyl), 7.3 – 8.3 (m, 11H, Ar-H).

3d: M. p. 160 – 162 °C [16] ($CHCl_3$-EtOH). – IR (KBr pellets): $\nu = 3068$ (C–H), 1599 (C=N), 1543 (C=C) cm^{-1}. – ^1H NMR (60 MHz, $CDCl_3$): $\delta = 2.4$ (s, 3H, CH_3), 6.0 (s, 2H, OCH_2O), 6.9 (s, 2H, pyridyl), 7.2 – 8.1 (m, 11H, Ar-H).

3e: M. p. 122 – 124 °C ($CHCl_3$-EtOH). – IR (KBr pellets): $\nu = 3425$ (OH), 3062 (C–H), 1598 (C=N), 1544 (C=C) cm^{-1}. – ^1H NMR (60 MHz, $CDCl_3$): $\delta = 5.8$ (s, 1H, OH), 6.0 (s, 2H, OCH_2O), 6.8 (s, 2H, pyridyl), 7.1 – 8.1 (m, 11H, Ar-H).

3f: M. p. 190 – 192 °C ($CHCl_3$-C_6H_{12}). – IR (KBr pellets): $\nu = 3143$ (NH_2), 3071 (C–H), 1599 (C=N), 1543 (C=C) cm^{-1}. – ^1H NMR (60 MHz, $CDCl_3$): $\delta = 5.9$ (s, 2H, OCH_2O), 4.2 (brs, 2H, NH_2), 6.8 (s, 2H, pyridyl), 7.0 – 8.1 (m, 11H, Ar-H).

[1] W. Xie, Y. Jin, P. G. Wang, Chemtech. **292**, 23 (1999).
[2] D. C. Dittmer, Chem. and Ind. 779 (1997).
[3] R. S. Varma, Green Chem. **1**, 43 (1999).
[4] M. Kidwai, S. Rastogi, R. Venkataramanan, Bull. Chem. Soc. Jpn. **761**, 203 (2003).
[5] M. Kidwai, P. Sapra, K. R. Bhushan, P. Misra, Synthesis **10**, 1509 (2001).
[6] M. Kidwai, S. Saxena, R. Mohan, R. Venkataramanan, J. Chem. Soc. Perkin Trans. I, 1845 (2002).
[7] M. D. Ankhiwala, M. V. Hathi, J. Indian Chem. Soc. **71**, 587 (1994).
[8] A. M. Van Leusen, J. W. Terpestra, Tetrahedron Lett. **22**, 5097 (1981).
[9] H. Shirai, K. Hanabusa, Y. Takahashi, F. Mizobe, K. Hanada, Jap. Pat. 93126541 (1993); Chem. Abstr. **122**, 178410 (1995).
[10] J. H. Archibald, G. Bradley, A. Opalko, T. J. Ward, J. C. White, C. Ennis, N. B. Shepperson, J. Med. Chem. **33**, 646 (1990).
[11] C. E. Sunkel, M. F. de Casa-Juana, L. Santos, M. M. Gomez, M. Villarroya, M. A. Gonzalez-Morales, J. G. Priego, M. P. Ortega, J. Med. Chem. **33**, 3205 (1990).
[12] T. Kobayashi, M. Nitta, Chem. Lett. 1549 (1986).
[13] R. L. Frank, R. P. Seven, J. Am. Chem. Soc. **71**, 2629 (1949).
[14] R. S. Tewari, A. K. Dubey, Indian J. Chem. **19B**, 153 (1980).
[15] P. S. Kendurkar, R. S. Tewari, Z. Naturforsch **29b**, 552 (1974).
[16] A. R. Katritzky, A. A. A. Abdel-Fattah, D. O. Tymoshenko, S. A. Essawy, Synthesis **12**, 2114 (1999).
[17] D. Stuerga, P. Gaillard, Tetrahedron **52**, 5505 (1996).