Reaction between Guanidine Hydrochloride and Chalcones: An Efficient Solvent-free Synthesis of 2,4,6-Triarylpyridines under Microwave Irradiation

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A series of 2,4,6-triarylpyridines have been synthesized via an efficient solvent-free reaction between guanidine hydrochloride and chalcones under microwave irradiation in excellent yields.

The synthesis, reactions, and biological properties of pyridines constitutes a significant part of modern heterocyclic chemistry.[1] 2,4,6-Triarylpyridines (TAPs)[2] and substituted phenylpyridines[3] are useful intermediates in the synthesis of drugs, herbicides, insecticides, desiccants, and surfactants.[4] Due to their π-stacking ability, these pyridines are used in supramolecular chemistry.[5] Hence their synthesis has received much attention.

TAPs have been synthesized using various methods and procedures. Traditionally, these compounds have been synthesized through the reaction of *N*-phenacylpyridinium salts with α,β-unsaturated ketones in the presence of NH_4OAc.[2,6a] More recently, several new improved methods and procedures have been developed for the synthesis of these pyridines: reaction of *N*-phosphinylethanimines with aldehydes,[6b] reaction of *N*-(diphenylphosphinyl)-1-azaallyl anions with α,β-unsaturated carbonyl compounds,[6c] reaction of in situ generated α,β-unsaturated imines with CH–nucleophiles,[6d] arylation of methylthiopyridines via Ni-induced Grignard reactions,[6e] reaction of phenacylidenedimethylsulfurane with chalcones and NH_4OAc,[6f] pyrolysis of 1-vinyl-1,2-dihydropyridines,[6g] reaction of α-ketoketene dithioacetals with methyl ketones in the presence of NH_4OAc,[6h] addition of lithiated β-enaminophosphonates to chalcones,[6i] reaction of α-benzotriazolyl ketones with α,β-unsaturated ketones and NH_4OAc,[6j] and solvent-free reaction between acetophenones, benzaldehydes, and NH_4OAc in the presence of sodium hydroxide,[6k] or without catalyst under microwave irradiation.[6l] Most of these syntheses of TAPs are multistage, low to moderately yielding laborious processes and involve harsh or environmentally hazardous reaction conditions.

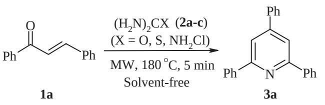
As part of our current studies on the design of efficient methods for the preparation of heterocyclic compounds from readily available starting materials,[7] we have recently described an efficient synthesis of TAPs via a solvent-free reaction between chalcones and NH_4OAc and as most of the earlier syntheses of TAPs, we employed ammonium acetate as the source of pyridine N atom.[8]

There are so many reports concerning the reaction of α,β-unsaturated ketones with urea derivatives producing functionalized pyrimidines.[9] As far as we know there is only one report concerning the reaction of α,β-unsaturated ketones with urea derivatives leading to pyridine derivatives. Recently, Razdan et al. reported a solid-supported synthesis of TAPs from chalcones and urea derivatives using $Bi(NO_3)_3$–Al_2O_3.[10] However, the reaction yields were not very high. Herein we have found that microwave-assisted reaction between chalcones and urea derivatives leads to TAPs. Thus, 1,3-diphenyl-2-propen-1-one, **1a**, and urea derivatives **2a**–**2c** were converted to 2,4,6-triphenylpyridine **3a** under microwave irradiation and solvent-free conditions in 56–96% yields (a cyclization from $[3 + 2 + 1]$ atom fragments: $[C_2C_3C_4 + C_5C_6 + N]$) (Scheme 1).

Therefore, guanidine hydrochloride (**2c**) is the most effective urea derivative for the conversion of chalcones to the corresponding TAPs under microwave irradiation. Thus, a range of symmetrical TAPs **3a**–**3q** were synthesized from the reaction between 1,3-diaryl-2-propen-1-ones, **1a**–**1q**, and guanidine hydrochloride in 90–98% yields (Table 1).[12]

All products were characterized by ^1H and ^{13}C NMR analysis, and their melting points were compared with those of the known compounds reported in the literature.

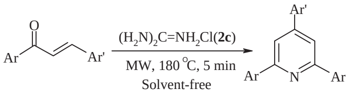
The mechanism of the reaction may be rationalized as involving condensation and the Michael addition of guanidine with chalcone leading to condensed product **4** and 1:1 adduct,



X = O, 56%; S, 64%; NH_2Cl, 96%

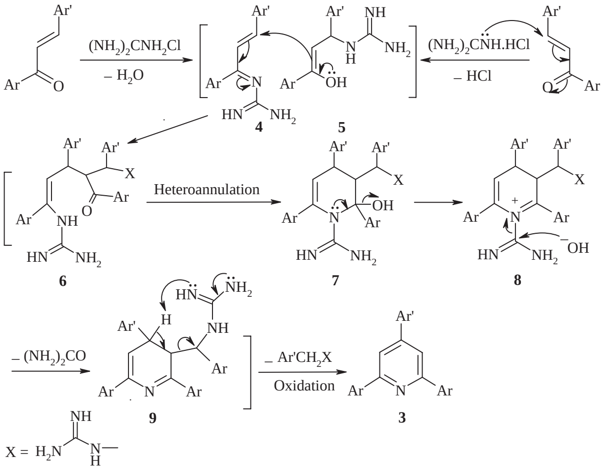
Scheme 1.

Table 1. Solvent-free microwave-assisted synthesis of 2,4,6-triarylpyridines



3	Ar	Ar′	% Yield[a]	mp/°C (Lit.)
a	C_6H_5	C_6H_5	96	134–135 (137–138)[2]
b	$4\text{-}CH_3C_6H_4$	C_6H_5	95	157–158 (159–160)[11a]
c	C_6H_5	$4\text{-}CH_3C_6H_4$	94	123–124 (124.5–125)[6b]
d	$4\text{-}CH_3C_6H_4$	$4\text{-}CH_3C_6H_4$	94	178–179 (178–180)[11b]
e	C_6H_5	$4\text{-}CH_3OC_6H_4$	95	100–103 (99–100)[11a]
f	$4\text{-}CH_3C_6H_4$	$4\text{-}CH_3OC_6H_4$	96	155–157 (156.8–157.9)[6l]
g	C_6H_5	$4\text{-}(CH_3)_2NC_6H_4$	93	139–140 (142–143)[6b]
h	C_6H_5	$4\text{-}O_2NC_6H_4$	90	195–197 (202–203)[6b]
i	C_6H_5	$4\text{-}ClC_6H_4$	98	125–127 (129–130)[6b]
j	C_6H_5	$2\text{-}ClC_6H_4$	95	113–114 (114–115)[6b]
k	$4\text{-}CH_3C_6H_4$	$4\text{-}ClC_6H_4$	96	199–201 (200.6–202)[6l]
l	$4\text{-}CH_3OC_6H_4$	$4\text{-}ClC_6H_4$	98	115–116 (113.8–115)[6l]
m	$4\text{-}CH_3OC_6H_4$	$4\text{-}CH_3OC_6H_4$	95	135–136 (136–137)[6l]
n	$4\text{-}CH_3OC_6H_4$	$4\text{-}BrC_6H_4$	97	164 (163.9–165)[6l]
o	C_6H_5	4-Pyridyl	96	187–190
p	C_6H_5	2-Furyl	90	168–170
q	C_6H_5	2-Thienyl	92	162–163 (165–166)[6b]

[a]Isolated yields.



Scheme 2.

5, respectively, followed by the Michael addition of the enolized adduct **5** to **4** from β carbon atom to form δ-aminoketone intermediate **6**, which on heteroannulation may lead to formation of tetrahydropyridine intermediate **7**. Removal of a molecule of urea may form dihydropyridine intermediate **9** through dihydropyridinium hydroxide intermediate **8**. Then oxidative aromatization via disproportionation and removal of the benzyl side chain would yield TAP **3**. This oxidative dealkylation has been previously observed.[13] Similar reaction mechanisms have been proposed for the reaction between *N*-(diphenylphosphinyl)-1-ethanimine and aromatic aldehydes,[6b] by Kiselyov for the reaction between azadienes and CH–nucleophiles[6d] and by Razdan et al. for the $Bi(NO_3)_3$–Al_2O_3 promoted reaction between benzylideneacetophenones and urea derivatives.[10] GC-Mass analysis of the reaction mixture of **1a** revealed presence of $C_6H_5CH_2X$ by-product, which increased possibility of the proposed mechanism (Scheme 2).

In conclusion, we have developed a microwave-assisted facile and efficient method for the preparation of 2,4,6-triarylpyridines of potential synthetic and chemical interest. Solvent-free conditions, excellent yields, a simplified purification process, and short reaction times are the main advantages of the presented method.

This research was supported by the Research Council of the University of Tehran as a research project (No. 6102036/1/03).

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12 General procedure for the preparation of compounds **3**: A mixture of **1** (2 mmol) and guanidine hydrochloride (0.24 g, 2.5 mmol) ground using a mortar and pestle. Then the mixture was irradiated in a microwave oven (ETHOS 1600, Milestone with a power of 600 W) at 180 °C for 5 min. Then the reaction mixture cooled to room temperature and the crude solid obtained washed with water and recrystallized from absolute ethanol.

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