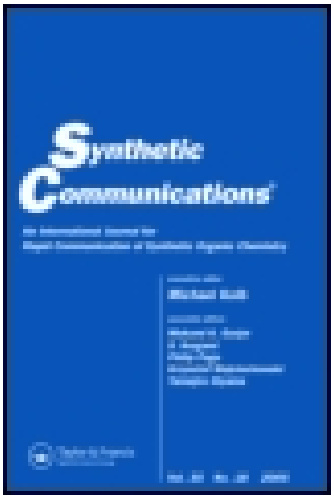


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Facile Synthesis of Triarylpyrimidines with Microwave-Irradiated Reactions of N-Phenacylpyridinium Chloride

Ping Wu [a b], Xi-Mei Cai [a], Qi-Fang Wang [a] & Chao-Guo Yan [a]
[a] College of Chemistry and Chemical Engineering, Yangzhou University, Yangzhou, China
[b] Yangzhou Polytechnic College, Yangzhou, China
Published online: 25 Jul 2007.

To cite this article: Ping Wu, Xi-Mei Cai, Qi-Fang Wang & Chao-Guo Yan (2007) Facile Synthesis of Triarylpyrimidines with Microwave-Irradiated Reactions of N-Phenacylpyridinium Chloride, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:2, 223-229, DOI: 10.1080/00397910601031843

To link to this article: http://dx.doi.org/10.1080/00397910601031843

Synthetic Communications®, 37: 223–229, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910601031843

Facile Synthesis of Triarylpyrimidines with Microwave-Irradiated Reactions of N-Phenacylpyridinium Chloride

Ping Wu
College of Chemistry and Chemical Engineering, Yangzhou University, China and Yangzhou Polytechnic College, Yangzhou, China

Xi-Mei Cai, Qi-Fang Wang, and Chao-Guo Yan
College of Chemistry and Chemical Engineering, Yangzhou University, China

Abstract: In a system of ammonium acetate and acetic acid under microwave irradiation, N-phenacylpyridinium chloride **1** reacted with 2 mol of aromatic aldehydes **2a**–**h** to give 2,4,6-triarylpyrimidine **3a**–**h,** reacted with pyridinecarboxaldehyde **4a**–**c** and acetophenone **5** to yield bipyridine derivatives **6a**–**c**. The structure of the products was characterized with ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopy.

Keywords: aldehyde, condensation, microwave irradiation, pyridine, pyrimidine

INTRODUCTION

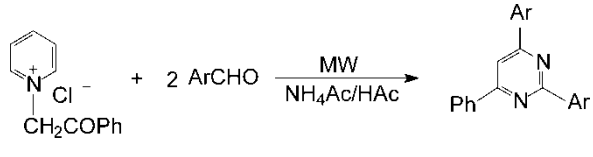
Because of the aromatic character of the pyridine heterocycle, its basicity, and the electron-attracting influence of the nitrogen atom, pyridinium cations can behave as nucleophiles and 1,3-dipoles and show a great variety of synthetic uses such as reactions with alkenes substituted with electron-withdrawing groups.[1] Pyridinium cations with stronger electron-withdrawing carbonyl, cyano, and nitro groups increase the activity of methylene group and have many more versatile applications.[2–4] N-Phenacylpyridinium bromide in

Address correspondence to Chao-Guo Yan, College of Chemistry and Chemical Engineering, Yangzhou University, Yangzhou 225002, China. E-mail: cgyan@yzu.edu.cn

the presence of a base is known to undergo Knoevenagel condensation with aldehydes,[5,6] Michael addition to α,β-unsaturated carbonyl compounds,[7,8] and dipolar cycloaddition with activated alkenes.[9] It was thus worthwhile to investigate new reactions and synthetic applications of this kind of salt with an emphasis on multicomponent reactions (MCRs), which offer significant advantages and are of increasing importance in organic and medical chemistry. Herein we report the reaction results of some one-pot reactions of N-phenacylpyridium chloride with aromatic aldehydes and ketones under microwave irradiation conditions.

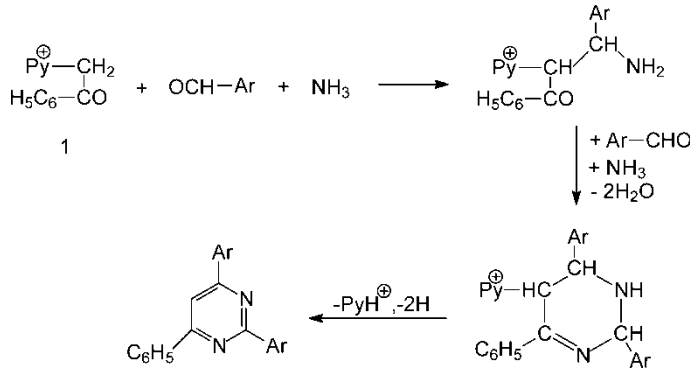
RESULTS AND DISCUSSION

N-Phenacylpyridinium chloride **1** was easily prepared by refluxing the benzene solution of phenacyl chloride and pyridine for 2 h. Early in 1963, F. Kronke et al. reported one example of the reaction of N-phenacylpyridinium bromide with p-nitrobenzaldehyde to give 2,4-bis-(p-nitrophenyl)-6-phenylpyrimidine.[10] But until now, there have been no other reports about this kind of reaction. The first microwave-irradiation reaction we tested is the reaction of N-phenacylpyridinium chloride **1** with 2 mol of aromatic aldehydes **2a**–**g** in a mixture of ammonium acetate and acetic acid (Scheme 1). After irradiating 2–4 min, 2,4,6-triarylpyrimidine **3a**–**i** were synthesized in satisfactory yields (54–82%). Under microwave irradiation, all aromatic aldehydes even bearing electron-donating methyl and methoxy groups form pyrimidine smoothly. When 3- or 4-pyridinecarboaldehyde was used in the reaction, the 2,4-pyrdinyl groups were introduced on the pyrimidine, which shows this reaction procedure has wide scope and is a facile synthetic route to pyrimidine compared with the other method.[11] Evidently the reaction mechanism was as follows (Scheme 2): N-phenacylpyridinium chloride reacts with 1 mol of aldehyde and ammonia via a Mannich-type reaction to give substituted aminopropiophenone, which then reacts with the ammonia and second molecular aldehyde and cyclizes to form a tetrahydropyrimidine ring. The latter pyrolyzes smoothly to give triarylpyrimidine.



1 **2a-h** **3a-h**

Scheme 1. Ar = Ph, p-ClC_6H_4, p-$CH_3OC_6H_4$, m-$NO_2C_6H_4$, p-$NO_2C_6H_4$, p-$CH_3C_6H_4$, 3-py, 4-py.



Scheme 2.

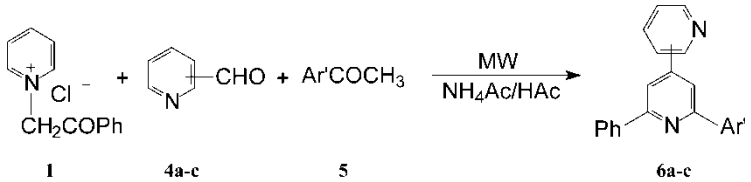
The analytical data of **3a**–**h** is listed in Table 1. In ^{1}H NMR spectroscopy, 5-H of pyrimidine usually appears as one singlet peak at 7.90 ppm. The proton signals of the triaryl group show a couple of splitting peaks of 8.50–7.50 ppm with o-H at the lower field and m-, p-H at the higher field. But it is very difficulty to elucidate each peak because there are three aryl groups with few differences. In ^{13}C spectra, C-2 of pyrimidine shows one peak at about 160 ppm, and other aromatic carbons show a couple of peaks at 100–140 ppm. These peaks overlap very heavily, and they are not listed in Table 1.

With the initial success of this reaction, we set out to determine the scope and variability of the procedure. It is generally recognized that chalcone was easily formed from the condensation of aromatic aldehydes with acetophenone under mild basic conditions, and in fact there are several reports[12] about the aldol condensation under microwave conditions. We realized that aromatic aldehydes could react with acetophenone to give chalcone in situ in the previously described microwave-irradiation procedure. Equivalent molar ratios of 2-, 3-, or 4-pyridinecarboaldehyde **5a**–**c** and p-chloroacetophenone **5** were used to react with N-phenacylpyridinium chloride **1** in a mixture of ammonium acetate and acetic acid (Scheme 3). Under microwave irradiation the five-component mixture reacted smoothly to give 2,4,6-triarylpyridine **6a**–**c** in high yields (84–92%). Here the formation of 2,4,6-triarylpyridine is a typical multicomponent domino reaction. The reaction proceeds via pyridinecarboaldehyde, reacted first with acetophenone to form α,β-unsaturated ketone, which in turn reacted with N-phenacylpyridinium chloride to give 1,5-diketone derivatives, then cyclized with ammonium, and finally eliminated pyridine cation to form the triarylpyridines (Scheme 4). This method allows freely selective introduction of variously substituted aryl groups into the 2-, 4-, and 6-position of pyridine and also provides one practical synthetic routes for bipyridine derivatives with two aryl groups on one pyridine ring. In ^{1}H NMR, the proton signals of 3,5-H in triarylpyridine usually show one peak at about 7.90 ppm.

Table 1. Physical data of 2,4,6-triarylpyrimidines **3a–g** and bipyridines **6a–c**

Entry	Ar	Yield (%)	Mp (°C)	^{1}H NMR ($CDCl_3$ ppm)	IR (KBr Disk, cm^{-1})
3a	Ph	54	148.5	8.74 (d, $J = 6.6$ Hz, 1H, PhH), 8.30 (d, $J = 6.0$ Hz, 2H, PhH) 8.21 (d, $J = 7.2$ Hz, 2H, PhH), 7.90 (s, 1H, 5-PyH) 7.75 (d, $J = 7.2$ Hz, 1H, PhH), 7.56 (m, 8H, PhH) 7.46 (d, $J = 7.2$ Hz, 1H, PhH)	2924(w), 2854(w), 1569(s) 1526(s), 1494(m), 1396(m) 1361(m), 1174(m), 1072(w) 1027(w), 866(w), 749(s)
3b	p-ClC_6H_4	71	188.2	8.64 (d, $J = 8.4$ Hz, 2H, ArH), 8.25 (d, $J = 7.2$ Hz, 2H, ArH) 8.21 (d, 2H, $J = 8.4$ Hz, ArH), 7.96 (s, 1H, 5-PyH) 7.56 (s, 3H, PhH), 7.53 (d, $J = 8.4$ Hz, 2H, ArH) 7.50 (d, J = 8.4 Hz, 2H, PhH)	2924(s), 2854(m), 1591(m) 1526(vs), 1490 (s), 1385(m) 1361(m), 1093(m), 768(m)
3c	p-$CH_3OC_6H_4$	65	147–148	8.15–8.18 (m, 4H, ArH), 7.769 (s, 2H) 7.66 (d, $J = 6.0$ Hz, 2H), 7.51–7.45 (m, 4H) 7.03 (d, $J = 6.0$ Hz, 2H), 3.88 (s, 3H, OCH_3)	2922(w), 2856(w), 1607(vs) 1518(s), 1357 (m), 1182(m) 1064(w), 953(w), 813(m)
3d	m-$NO_2C_6H_4$	82	206.5	9.52 (s, 1H), 9.06 (m, 2H), 8.70 (d, $J = 7.2$ Hz, 1H) 8.43 (d, $J = 7.8$ Hz, 1H), 8.40 (d, $J = 7.8$ Hz, 1H) 8.33 (s, 2H), 8.15 (s, 1H), 7.81 (t, $J = 7.2$ Hz, 1H) 7.75 (t, $J = 7.2$ Hz, 1H), 7.62 (s, 3H, PhH)	3092(w), 2860(w), 1579(m) 1530(vs), 1351(vs), 1089(w) 878(w), 730(m), 685(m)
3e	p-$NO_2C_6H_4$	78	230	8.90 (d, $J = 7.8$ Hz, 2H, ArH), 8.46 (d, $J = 7.8$ Hz, 4H, ArH) 8.41 (d, $J = 7.8$ Hz, 2H, ArH), 8.32 (s, 2H, PhH) 8.17 (s, 1H, 5-PyH), 7.62 (s, 3H, PhH)	2925(w), 2853(w), 1572(s) 1532(s), 1344(vs), 1108(w) 1012(w), 858(m), 743(m)

3f	p-$CH_3C_6H_4$	80	166–168	8.64 (d, $J = 7.8$ Hz, 2H, ArH), 8.31 (d, $J = 7.2$ Hz, 2H, ArH) 8.22 (d, $J = 7.8$ Hz, 2H, ArH), 7.99 (s, 1H, 5-PyH) 7.59-7.56(m, 3H, ArH), 7.39–7.36 (m, 4H, ArH) 2.48 (s, 6H, CH_3)	3027(w), 2915(w), 1571(s) 1524(vs), 1444(w), 1358(s) 1239(w), 1178(m), 1110(w) 1024(w), 824(m), 764(s)
3g	3-py	61	226	9.90 (s, 1H, PyH), 9.47 (s, 1H, PyH) 8.95 (d, $J = 7.8$ Hz, 1H, PyH), 8.79 (m, 2H, PyH) 8.60 (d, $J = 7.8$ Hz, 1H, PyH), 8.30 (s, 2H, PyH) 8.09 (s, 1H, 5-PyH), 7.59 (s, 3H, PhH), 7.53–7.49 (m, 2H, PhH)	3064(w), 2924(w), 2854(w) 1590(vs), 1528(s), 1483(w) 1253(w), 1193(w), 765(m)
3h	4-py	74	>250	8.87 (d, $J = 11.4$ Hz, 4H, PyH), 8.57 (s, 2H, PyH) 8.31 (s, 2H, PyH), 8.21–8.16 (m, 1H, PyH) 8.15 (d, 2H, PhH), 7.61 (s, 3H, PhH)	3032(w), 2923(w), 2854(w) 1583(vs), 1557(m), 1525(m) 1367(m), 1062(w), 765(m)
6a	2-Py	88	160	8.80 (d, $J = 3.6$ Hz, 1H, PyH), 8.29 (s, 2H, 3,5-PyH) 8.23 (d, $J = 7.2$ Hz, 4H), 7.92 (d, $J = 7.8$ Hz, 1H) 7.86 (t, $J = 7.8$ Hz, 1H), 7.52 (t, $J = 7.8$ Hz, 2H) 7.474 (m, 3H), 7.381 (t, $J = 3.6$ Hz, 1H)	3089(w), 3061(w), 2926(w) 2855(w), 1604(s), 1550(s) 1495(m), 1472(m), 1385(m) 1093(m), 1013(m), 837(m)
6b	3-Py	92	144	9.02 (s, 1H), 8.75 (s, 1H), 8.18–8.16 (m, 4H) 8.084 (s, 1H), 7.890 (s, 1H), 7.849 (s, 1H) 7.60-7.50 (m, 6H)	3039(w), 2925(w), 1545(s) 1486(m), 1427 (m), 1384(s) 1091(m), 1014(m), 831(m)
6c	4-Py	84	201	8.79 (s, 2H), 8.18 (d, $J = 7.2$ Hz, 2H) 8.16 (d, $J = 7.2$ Hz, 2H), 7.90 (s, 1H) 7.86 (s, 1H), 7.66 (s, 2H), 7.54–7.49(m, 5H, PhH)	3036(w), 2923(w), 1590(vs) 1536(s), 1493(s), 1400(m) 1086(m), 1012(m), 778(s)



6a-c = 2-Py, 3-py, 4-py, Ar'= p-ClC$_6$H$_4$

Scheme 3.

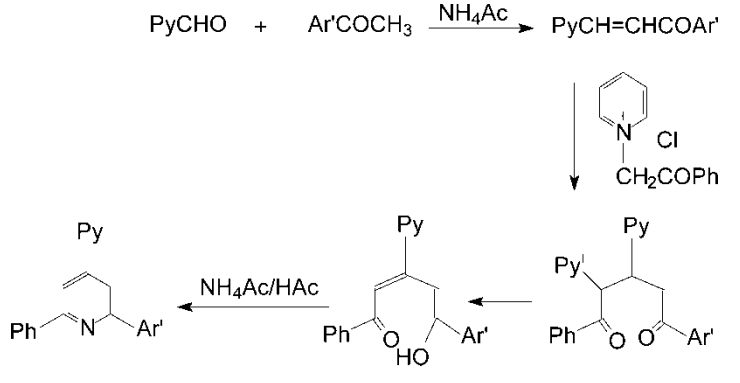
EXPERIMENTAL

General Procedure for the Preparation of Pyrimidine 3a–h

To a 50-mL of flask, N-phenacylpyridinium chloride (1.0 mmol, 0.225 g), aromatic aldehyde (2.2 mmol), ammonium acetate (3.0 g), and acetic aid (2.0 mL) were added. The mixture was put in the microwave (Lin-Jiang microwave reactor LWMC-201, Nanjing) and heated for about 2–4 min (130 W). After cooling, the reaction mixture was diluted with 50 mL of water, and the resulting precipitate was collected with filtration. The crude product was recrystallizated with ethanol to give the pure solid sample **3a–h** for analysis with FeLiegen high pressure liquid chromatography/mass spectrometer (HPLC/MS), ^{1}H NMR, and IR.

General Procedure for the Preparation of Bipyridines 6a–c

To a 50-mL flask, N-phenacylpyridinium chloride (1.2 mmol, 0.280 g), pyridinecarbaldehyde (1.0 mmol), p-chloroacetophenone (1.0 mmol), ammonium acetate (3.0 g), and acetic aid (2.0 mL) were added. The mixture



Scheme 4.

was put in the microwave (Lin-Jiang microwave reactor LWMC-201, Nanjing) and heated for about 2–4 min (130 W). After cooling, the reaction mixture was diluted with 50 mL of water, and the resulting precipitate was collected with filtration. The crude product was recrystallizated with ethanol to give the pure solid sample **6a–c** for analysis with HPLC/MS, ^{1}H NMR, and IR.

REFERENCES

1. Kowalkowska, A.; Sucholbiak, D.; Jonczyk, A. Generation and reactions of ammonium ylide in basic two-phase systems. *Eur. J. Org. Chem.* **2005**, 925.
2. Risitano, F.; Grassi, G.; Foti, F.; Bilardo, C. Pyridinium N-ylides and arylmethylene azol-5-ones: Reaction cascade leading to an unusual spiroiosxazolineone ring. *Tetrahedron* **2000**, *56*, 9674.
3. Vo, N. H.; Eyermann, C. J.; Hodge, C. N. Transformations of resin-bound pyridinium ylides, I: A stereoselective synthesis of 2,2,3-trisubstituted cyclopropanecarboxylates. *Tetrahedron Lett.* **1997**, *38*, 7951.
4. Papageorgiou, C. D.; Ley, S. V.; Graut, M. J. Organic-catalyst-mediated cyclopropanation reaction. *Angew. Chem. Int. Ed.* **2003**, *42*, 828.
5. Krohnke, F. New methods of preparative organic chemistry: Syntheses using pyridinium salts. *Angew. Chem. Int. Ed.* **1963**, *2* (5), 225.
6. Krohnke, F.; Zecher, W. Synthesis using the Michael addition of pyridium salts. *Angew. Chem. Int. Ed.* **1962**, *1* (12), 626.
7. Ghosh, C. K.; Sahana, S. Benzopyrans: Part 34—reactions of 3-substituted 1-benzopyran-4-ones with N-phenacylpyridinium bromide. *Ind. J. Chem.* **1996**, *35B*, 203.
8. Brahambhatt, D. I.; Raolji, G. B.; Pandya, S. U.; Pandya, U. R. A facile synthesis of some 3-(2-pyridyl)-coumarins. *Ind. J. Chem.* **1999**, *38B*, 212.
9. Katritsky, A.; Grzeskowiak, N.; Alvarez-Builla, J. Preparation of tetrahydroindolizines from pyrinium and isoquinolinium ylides. *J. Chem. Soc. Perkin Trans. 1* **1981**, 1180.
10. Krohnke, F.; Schmidt, E.; Zecher, W. *Neue Pyrimidin-Synthesen, Chem. Ber.* **1963**, 1163.
11. Müller, T. J.; Braun, R.; Ansorge, M. A novel three-component one-pot pyrimidine synthesis based upon a coupling-isomerization sequence. *Org. Lett.* **2000**, *2* (13), 1967.
12. Varma, R. S.; Dahiya, R.; Kumar, S. Microwave-assisted Henry reaction: Solventless synthesis of conjugated nitroalkenes. *Tetrahedron Lett.* **1997**, *38*, 5131.