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Tetrahedron Letters 44 (2003) 255–257

TETRAHEDRON LETTERS

Microwave enhanced solvent-free synthesis of a library of quinoline derivatives

Suk Jin Song,[a] Seong Jin Cho,[a] Dong Kyu Park,[a] Tae Woo Kwon[a,*] and Samson A. Jenekhe[b]

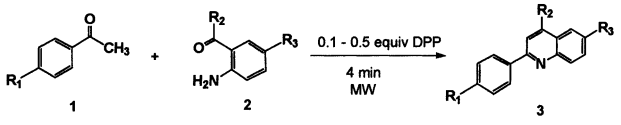
[a]*College of Science, Kyungsung University, Busan 608-736, South Korea*
[b]*Department of Chemical Engineering, University of Washington, Seattle, WA 98195-1750, USA*

Received 16 October 2002; revised 7 November 2002; accepted 8 November 2002

Abstract—A minilibrary of 12 quinoline derivatives was synthesized in the presence of 0.1–0.5 equiv. of diphenylphosphate without any solvents. Each compound was obtained with high yield in 4 min of microwave irradiation.

Quinolines are well known not only for their significant biological activities[1] but also for their formation of conjugated molecules and polymers that combine enhanced electronic, optoelectronic, or nonlinear optical properties with excellent mechanical properties.[2,3] Diblock and triblock copolymers incorporating polyquinoline blocks have been found to undergo hierarchical self-assembly into a variety of nanostructures and mesostructures with electronic and photonic functions.[4] Previously we reported a variety of polyquinolines prepared from 2-aminoacetophenones and benzophenones.[2,3] To carry out the synthesis of quinoline molecules and polymers, it was usually required to heat the reaction mixture for several or even more than 24 hours in the presence of 5–10 equiv. of an acidic catalyst such as diphenylphosphate (DPP) and in highly toxic *m*-cresol solvent.[2,3a,b]

Recently, much attention has focused on microwave-assisted organic reactions in the absence of solvent.[5] Often, thermal demanding reactions take hours in solution, and may require repetitive treatments with excess reagents to drive them to completion. However, with microwave irradiation these same reactions may be completed in minutes.[5,6]



Herein we report the Friedlander[7] coupling condensation reactions between various acetophenones (**1**; R_1 = H, *n*-hexyl, Br and NH_2) and 2-aminoacetophenone (**2**; $R_2 = CH_3$, $R_3 = H$) or benzophenone (**2**; $R_2 = Ph$, $R_3 = H$ or Br) under microwave irradiation.

We first examined the reaction time and temperature effects when 1.0 equiv. of DPP was used under microwave irradiation. As time increased, the reaction temperature also increased and the maximum yield (78%) was obtained after 4 min at 110°C as shown in Table 1, entry 4. The temperature was one of the important factors that improved the yields but a longer time and a higher temperature did not increase the yield (Table 1, entry 5).

Table 1. Optimization of the reaction time in the synthesis of 2,4-DPQ (**3**; R_1, R_2 and $R_3 = H$) under microwave irradiation or conventional heating in a thermostated oil bath (scale = 3 mmol, ratio of **1**:**2**:DPP = 1:1:1)

Entry	Time (min)	Temp. (°C)[a]	Yield (%)	
			Microwave[b]	Conventional
1	1	52	34	–
2	2	87	69	–
3	3	104	72	–
4	4	108	78	24[c]
5	6	112	77	–

[a] Temperature of reaction mixture was recorded after the microwave irradiation at the given reaction time.
[b] The reactions were carried out in a 2450 MHz commercial microwave oven (Sam Sung, Model # RE-555 TCW).
[c] Oil bath temperature = 108°C.

* Corresponding author. Tel.: +82-51-620-4637; fax: +82-51-627-4115; e-mail: twkwon@star.kyungsung.ac.kr

0040-4039/03/$ - see front matter
PII: S0040-4039(02)02499-1

Table 2. Optimization of the DPP equivalents and reaction time in the synthesis of 2,4-DPQ (**3**; R_1, R_2 and R_3=H) under microwave irradiation (scale=3 mmol, ratio of **1**:**2**=1 equiv.:1 equiv.)

Entry	DPP (equiv.)	Time (min)	Yield (%)	
			Microwave	Conventional
1	0	4	15	2[a]
2	0.1	4	73	–
3	0.3	4	75	–
4	0.5	4	78	15[a]
5	1.0	4	78	24[a]
6	5.0	2	77	–
7	5.0	4	62	–
8	5.0	330	–	70[b]

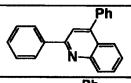
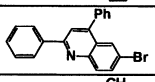
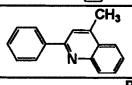
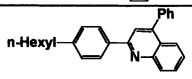
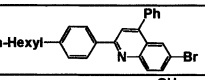
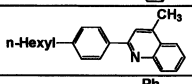
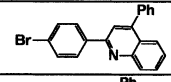
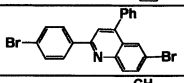
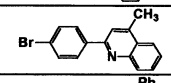
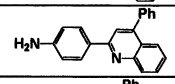
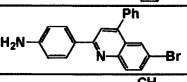
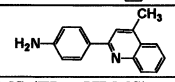
[a] Oil bath temperature=108°C.
[b] Oil bath temperature=136°C.

In order to evaluate the influence of DPP, the reactions were carried out using different DPP equivalents. It should be pointed out that cyclization is enhanced by DPP as shown in Table 2. In the absence of DPP, microwave irradiation effect was not observed in the synthesis of DPQ at 108°C (Table 2, entry 1). However, when 0.1 equiv. of DPP was added, the yield was significantly increased up to 73% (Table 2, entry 2). DPP in excess of 0.5 equiv. did not help to increase the yield (Table 2, entries 6 and 7).

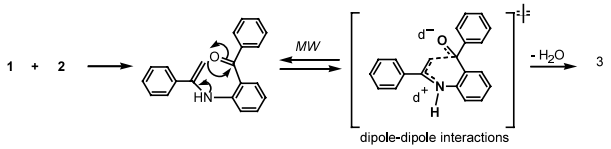
To check the possibility of intervention of specific (non purely thermal) microwave effects, the reaction has also been examined using a pre-heated oil-bath for the same duration and at the same final temperature as measured at the end of exposure during the microwave-assisted synthesis. It was found that reaction proceeded slowly with 15–24% yield in 4 min (Table 2, entries 4 and 5) whereas 70% of DPQ was obtained after 330 min under conventional heating at 136°C (Table 2, entry 8).

It is well established that microwave-reactants interactions are increased with the polarity of the material.[8] Therefore microwave effects can be easily understood by considering the possible microwave activation effects by dipole–dipole interactions according to mechanistic considerations and to an increase of the polarity of the system during the progress of the reaction.[9]

Table 3. Solvent-free quinoline library synthesis of **3** under microwave irradiation (scale=3 mmol, equivalent ratio of **1**:**2**:**DPP**=1:1:0.5, 4 min)

entry	R_1	R_2	R_3	product[a]	
				Structure	yield (%)
1	H	Ph	H		78
2	H	Ph	Br		73
3	H	CH_3	H		76
4	$CH_3(CH_2)_4CH_2$	Ph	H		62
5	$CH_3(CH_2)_4CH_2$	Ph	Br		75
6	$CH_3(CH_2)_4CH_2$	CH_3	H		63
7	Br	Ph	H		80
8	Br	Ph	Br		85
9	Br	CH_3	H		50
10	NH_2	Ph	H		80
11	NH_2	Ph	Br		61
12	NH_2	CH_3	H		53

*The products were characterized by comparison of their melting points, ^1H, ^{13}C NMR, MS (EI or HRMS) and TLC with those of the authentic samples.



To investigate further the scope and limitations of the above optimal condition, a minilibrary of quinoline derivatives was synthesized. Long chain alkyl, bromo, and amino substituted acetophenones with 2-amino aceto- or benzophenones were subjected to the above optimal reaction conditions. The results are summarized in Table 3. It is noteworthy that under the same reaction conditions, bromo (Table 3, entries 7–9) or basic amino (Table 3, entries 10 and 11) functionality remained intact and aqueous work-up was not required.[3]

In summary, microwave-assisted solvent-free (under conditions of so-called 'Green Chemistry') reactions were employed to synthesize quinoline derivatives. The method not only offers substantial improvement in yield over conventional heating methods but also eliminates the use of hazardous solvents and excess expensive acidic catalyst. Advantages of this method include the fact that it is environmentally benign, an economical procedure, has a short reaction time and the simplicity of the performance with non-aqueous work-up.

Typical microwave procedure for 2,4-diphenylquinoline (Table 3, entry 1). Acetophenone (0.36, 3.0 mmol), 2-aminobenzophenone (0.59 g, 3.0 mmol) and 0.5 equiv. of DPP (0.38 g, 1.50 mmol, purchased from Aldrich) were mixed in the absence of any organic solvent and then submitted for 4 min to microwave irradiation inside a domestic microwave oven (Sam Sung, RE-555 TCW). After the reaction, the product was purified by column chromatography (20% ethyl acetate/80% hexane, v/v, $R_f = 0.64$) to give 2,4-diphenylquinoline (0.66 g, 2.34 mmol, 78%) as a colorless solid. mp = 112–113°C (lit.[10] = 112°C).

Acknowledgements

This work was supported by grant from the Basic Research Program of the Korea Science and Engineering Foundation (KOSEF R01-2000-000-00039-0). Work at the University of Washington was supported by the US Office of Naval Research. We thank Professor André Loupy (Université Paris-Sud, France) and Dr. X. X. Kong (the University of Washington, USA) for helpful discussion.

References

1. (a) Burkhaller, J. H.; Edgerton, W. H. *J. Am. Chem. Soc.* **1951**, *73*, 4837; (b) Ibrahim, A.; Rahman, A.; Abdu, E.; Etity, B. A. *Collect Czech. Chem. Commun.* **1991**, *56*, 1749; (c) Kidwai, M.; Bhushan, K. R.; Sapra, P.; Saxena, R. K.; Gupta, R. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 139.
2. (a) Stille, J. K. *Macromolecules* **1981**, *14*, 870; (b) Agrawal, A. K.; Jenekhe, S. A. *Macromolecules* **1991**, *24*, 6806; (c) Agrawal, A. K.; Jenekhe, S. A. *Chem. Mater.* **1992**, *4*, 95; (d) Agrawal, A. K.; Jenekhe, S. A. *Macromolecules* **1993**, *26*, 895; (e) Agrawal, A. K.; Jenekhe, S. A. *Chem. Mater.* **1993**, *5*, 633; (f) Jenekhe, S. A.; Lu, L.; Alam, M. M. *Macromolecules* **2001**, *34*, 7315; (g) Agrawal, A. K.; Jenekhe, S. A.; Vanherzeele, H.; Meth, J. S. *J. Phys. Chem.* **1992**, *96*, 2837.
3. (a) Jegou, G.; Jenekhe, S. A. *Macromolecules* **2001**, *34*, 7926; (b) Lu, L.; Jenekhe, S. A. *Macromolecules* **2001**, *34*, 6249; (c) Agrawal, A. K.; Jenekhe, S. A. *Chem. Mater.* **1996**, *8*, 579; (d) Jenekhe, S. A.; Zhang, X.; Chen, X. L.; Choong, V. E.; Gao, Y.; Hsieh, B. R. *Chem. Mater.* **1997**, *9*, 409; (e) Zhang, X.; Shetty, A. S.; Jenekhe, S. A. *Macromolecules* **1999**, *32*, 7422; (f) Zhang, X.; Shetty, A. S.; Jenekhe, S. A. *Macromolecules* **2000**, *33*, 2069.
4. (a) Jenekhe, S. A.; Chen, X. L. *Science* **1998**, *279*, 1903; (b) Jenekhe, S. A.; Chen, X. L. *Science* **1999**, *283*, 372.
5. (a) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213; (b) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199; (c) Lindstroem, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225; (d) Varma, R. S. *Green Chem.* **1999**, 43; (e) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213; (f) Elander, N.; Jones, J. R.; Lu, S.-Y.; Stone-Elander, S. *Chem. Soc. Rev.* **2000**, *29*, 239; (g) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95; (h) Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624.
6. (a) Kim, J. K.; Kwon, P. S.; Kwon, T. W.; Chung, S. K.; Lee, J. W. *Synth. Commun.* **1996**, *26*, 535; (b) Kim, S. Y.; Kwon, P. S.; Kwon, T. W.; Chung, S. K.; Chang, Y. T. *Synth. Commun.* **1997**, *27*, 533; (c) Kwon, P. S.; Kim, Y. S.; Kang, C. J.; Kwon, T. W.; Chung, S. K.; Chang, Y. T. *Synth. Commun.* **1997**, *27*, 4091.
7. (a) Cheng, C.-C.; Yan, S.-J. *Org. React.* **1982**, *28*, 37; (b) Thummel, R. P. *Synlett* **1992**, 1.
8. Gedye, R. N.; Smith, F. E.; Westaway, K. C. *Can. J. Chem.* **1998**, *66*, 17.
9. (a) Loupy, A.; Perreux, L.; Liagre, M.; Burle, K.; Moneuse, M. *Pure Appl. Chem.* **2001**, *73*, 161; (b) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199.
10. Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 804.