Pergamon

Tetrahedron 58 (2002) 1125–1129

TETRAHEDRON

Efficient nucleophilic substitution reactions of quinolyl and isoquinolyl halides with nucleophiles under focused microwave irradiation

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Received 11 September 2001; revised 12 November 2001; accepted 6 December 2001

Abstract—Nucleophilic substitution reactions of 2-chloroquinoline, 3-bromoquinoline and 4-bromoisoquinoline with thiolate, alkoxy ions and aniline were completed within several minutes under microwave irradiation. This method gives the desired products with yields up to 99% in a short reaction time, and is superior to the classical heating process. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Several derivatives of quinolines have been found to possess biological activities.[1] The displacement reactions of the halogen atoms in aryl halides have been studied.[2] The reactions by conventional heating process may encounter difficulty in reaching completion due to several factors which include the ring substituents. Application of microwave irradiation to decrease reaction time has recently received much attention.[3] However, only a few examples of nucleophilic substitution of aromatic halides by using microwave irradiation have been demonstrated.[4] We report herein an extension of this study toward the substitution reactions of heteroaromatic compounds such as 2-chloroquinoline, 3-bromoquinoline and 4-bromoisoquinoline.

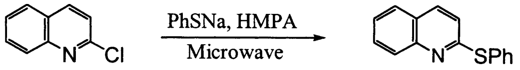
2. Results and discussion

We carried out the substitution reactions of 2-chloroquinoline with sodium thiophenoxide in HMPA by heating in a monomode microwave reactor. The reactions were complete in 35 s to give high yields of 2-phenylthioquinoline after column chromatography (Table 1). On the other hand, the conventional heating method requires 2 days at 100°C.[5]

It appeared that 1.8 equiv. of PhSNa was essential to achieve the optimal yield (99%) by microwave irradiation at 90°C for 35 s (Table 1, entry 2). By comparison, the conventional heating process (Table 1, entry 4) was very inefficient, giving merely 4% of the desired product at the same reaction temperature for the same reaction time. The microwave effect besides giving heating efficacy could be attributable to the high yielding displacement reaction of 2-chloroquinoline.

Because the reaction conditions cause a dramatic effect on the reaction efficiency, we examined the solvent effect in the substitution reactions. The sodium benzenethiolate was used as a model nucleophile in the substitution reaction (Table 2). The experiments indicated that the substitution

Table 1. Reaction of 2-chloroquinoline with sodium thiophenoxide



Entry	Molar proportions of PhSNa	Temperature (°C)	Time (s)	Yield (%)
1	1.5	90	35	83
2	1.8	90	35	99
3	1.8	80	35	95
4	1.8	90	35	4[a]

[a] Heating in an oil bath.

Keywords: nucleophilic substitution reaction.

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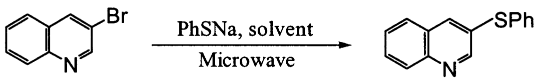
PII: S0040-4020(01)01225-X

Table 2. Solvent effects in the substitution reaction



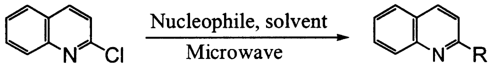
Entry	Solvent	Molar proportions of nucleophile	Temperature (°C)	Time (s)	Yield (%)
1	HMPA	1.8	100	35	99
2	NMP	2.5	120	300	81
3	DMSO	2.5	120	300	78
4	DMF	2.5	120	300	61

reaction could be realized by using NMP (*N*-methylpyrrolidone), DMSO and DMF as the solvent on microwave irradiation. However, HMPA was still the solvent of choice in terms of short reaction times and high yields of the desired product.

When 2 equiv. of PhSNa was used in NMP by microwave irradiation at 120°C for 3 min, 2-chloroquinoline was also converted to 2-phenylthioquinoline in 99% yield (Table 3, entry 1). Under microwave irradiation, 2-chloroquinoline also reacted with MeSNa, EtONa, MeONa and aniline to give the corresponding 2-substituted quinolines (Table 3). In many cases, the substitution reactions in NMP afforded even higher yields than those conducted in HMPA. When 1.2 equiv. of MeONa were used, 2-chloroquinoline was converted to 2-methoxyquinoline in an excellent yield (96%), in HMPA or NMP, within 30 s at a relatively low temperature 70°C (Table 3, entries 6 and 7). However, the yield of 2-methoxyquinoline decreased when greater quantities of MeONa were applied (Table 3, entries 8 and 9). Indeed, 2-hydroxyquinoline instead of 2-methoxyquinoline was formed exclusively when 2-chloroquinoline was treated with 4 equiv. of MeONa at 110°C for 4 min (Table 3, entry 10). These results indicated that 2-methoxyquinoline reacted further to give 2-hydroxyquinoline under microwave irradiation.[6a] An application of this method for the deprotection of methyl ethers might be conceived. The substitution reaction of 2-chloroquinoline with 3 equiv. of aniline required no solvent, and produced 2-(phenylamino)quinoline in 66% yield (Table 3, entry 11).

Similar experiments were performed with another two substrates, 3-bromoquinoline and 4-bromoisoquinoline (Tables 4 and 5). The reaction of 3-bromoquinoline with PhSNa in HMPA or NMP under microwave irradiation

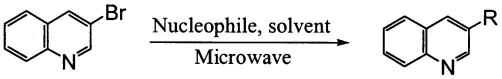
Table 3. Reactions of 2-chloroquinoline with nucleophiles



Entry	Nucleophile	Solvent	Molar proportions of nucleophile	Temperature (°C)	Time (s)	Product, R=	Yield (%)
1	PhSNa	NMP	2.0	120	180	SPh	99
2	MeSNa	HMPA	1.5	70	30	SMe	90
3	MeSNa	NMP	1.8	90	120	SMe	98
4	EtONa	HMPA	4.0	110	360	OEt	70
5	EtONa	NMP	4.0	110	240	OEt	93
6	MeONa	HMPA	1.2	70	30	OMe	96
7	MeONa	NMP	1.2	70	30	OMe	96
8	MeONa	HMPA	1.3	70	30	OMe	81
9	MeONa	HMPA	2.0	70	30	OMe	70
10	MeONa	HMPA	4.0	110	240	OH	99
11	$PhNH_2$	–[a]	3.0	110	360	NHPh	66

[a] No solvent was used.

Table 4. Reactions of 3-bromoquinoline with nucleophiles

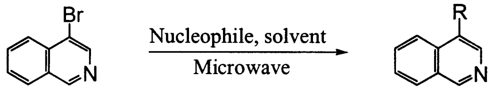


Entry	Nucleophile	Solvent	Molar proportions of nucleophile	Temperature (°C)	Time (s)	Product, R=	Yield (%)
1	PhSNa	HMPA	1.8	100	40	SPh	98
2	PhSNa	HMPA	1.8	100	40	SPh	NR[a]
3	PhSNa	HMPA	1.8	100	40	SPh	98[b]
4	PhSNa	NMP	3.0	120	240	SPh	98
5	MeSNa	HMPA	2.0	90	35	SMe	83
6	MeSNa	NMP	2.0	100	120	SMe	91
7	MeONa	HMPA	1.3	90	35	OMe	72
8	MeONa	NMP	1.3	90	35	OMe	30
9	MeONa	HMPA	1.5	90	35	OMe	64
10	MeONa	HMPA	2.0	90	35	OMe	38
11	MeONa	HMPA	4.0	110	240	OH	63

[a] Heating in an oil bath. NR represents no reaction.

[b] Benzoquinone (10 mol%) was added to the reaction.

Table 5. Reactions of 4-bromoisoquinoline with nucleophiles



Entry	Nucleophile	Solvent	Molar proportions of nucleophiles	Temperature (°C)	Time (s)	Product, R=	Yield (%)
1	PhSNa	HMPA	2.4	110	60	SPh	98
2	PhSNa	HMPA	2.4	110	60	SPh	NR[a]
3	PhSNa	NMP	3.0	120	600	SPh	87
4	MeSNa	HMPA	2.5	100	90	SMe	53
5	MeSNa	NMP	2.5	100	180	SMe	85
6	MeONa	HMPA	1.6	90	35	OMe	56

[a] Heating in an oil bath. NR represents no reaction.

afforded 3-phenylthioquinoline in 98% yield (Table 4, entries 1 and 4). The similar reactions of 4-bromoisoquinoline (Table 5, entries 1 and 3) also gave 4-phenylthioisoquinoline in very high yield (98%). In a sharp contrast, such substitution reactions did not occur by heating at 100–110°C (Table 4, entry 2 and Table 5, entry 2). When 3-bromoquinoline was heated at a higher temperature (165°C) for a prolonged period (7.5 h), 3-phenylthioquinoline was obtained only in a low yield (18%).[6b] The microwave effect in promoting nucleophilic aromatic substitution reactions was remarkable in comparison with heating processes.

3-Bromoquinoline also reacted with MeSNa in HMPA to give 3-methylthioquinoline (83% yield) at 90°C within 35 s (Table 4, entry 5). The yield was increased to 91% in NMP by microwave irradiation at 100°C for 120 s (Table 4, entry 6). Longer microwave irradiation at a higher temperature (up to 110°C) did not further improve the yield. The microwave irradiation of 3-bromoquinoline with 1.3 equiv. of MeONa gave a 72% of 3-methoxyquinoline in HMPA (Table 4, entry 7). The yields of 3-methoxyquinoline deteriorated when 1.5 and 2.0 equiv. of MeONa were used (Table 4, entries 9 and 10). Only 3-hydroxyquinoline was obtained in 63% yield when 4.0 equiv. of MeONa was used (Table 4, entry 11), presumably due to a further cleavage of the methyl ether linkage.

We examined the substitution reaction of 3-bromoquinoline with PhSNa in the presence of benzoquinone as a radical scavenger (Table 4, entry 3). This experiment also provided a high yield (98%) of 3-phenylthioquinoline without the inhibition of benzoquinone. Involvement of an $S_{RN}1$ mechanism was thus excluded. As the substitution reactions of 3-bromoquinoline and 4-bromoisoquinoline were regiospecific, the elimination–addition mechanism via quinoline or isoquinoline intermediates was unlikely. Thus, the substitution reactions under microwave irradiation probably proceeded via an ionic S_NAr mechanism.[7]

3. Conclusion

According to our present study, microwave irradiation did exert a beneficial effect to accelerate the nucleophilic substitution reactions of heteroaromatic halides.[8] For example, the substitution reaction of 3-bromoquinoline with PhSNa by heating at 165°C for 7.5 h gave a low yield (18%) of 3-phenylthioquinoline,[6b] whereas the reaction was promoted significantly by microwave irradiation at 100°C for 40 s to give a very high yield (98%) of the desired product (Table 4, entry 1). Our results also indicated that the relative aptitude for the nucleophilic substitution reactions appeared to be 2-chloroquinoline>3-bromoquinoline>4-bromoisoquinoline. For example, the substitution reaction of 2-chloroquinoline with MeSNa occurred at 70°C in 30 s (Table 3, entry 2), the reaction of 3-bromoquinoline occurred at 90°C in 35 s (Table 4, entry 5), and the corresponding reaction of 4-bromoisoquinoline occurred at 100°C in 90 s (Table 5, entry 4). NMP was found to be an appropriate solvent to replace HMPA in the aromatic nucleophilic substitution reactions under microwave irradiation. Such substitution reactions of quinolyl and isoquinolyl halides probably proceed via an S_NAr mechanism.

4. Experimental

^{1}H NMR spectra were measured in deuterochloroform solutions on a Varian Mercury 400 spectrometer using Me_4Si as the internal standard. Reactions were monitored by analytical thin-layer chromatography using silica gel 60 F-254 (0.2 mm layer thickness). Flash chromatography was carried out by utilizing silica gel 60 (70–230 mesh ASTM). The Synthewave 402™ monomode microwave reactor was purchased from Prolabo Company.

4.1. General procedure for reaction of hetaryl halides with nucleophile

In a quartz reaction vessel (12 mL) were placed heteroaromatic halide (0.3 mmol) and nucleophile in an appropriate solvent (1 mL). The reaction vessel was then placed into the cavity of a focused monomode microwave reactor (Synthewave 402), and irradiated for the period indicated in the tables. The reaction temperature was maintained by modulating the power level of the reactor. The crude reaction mixture was then absorbed directly onto silica gel, and purified using silica gel chromatography by elution with a mixture of hexane and ethyl acetate.

4.1.1. 2-Phenylthioquinoline.[5b] White solid, mp=46–47°C (lit[5b] mp=48–49°C). ^{1}H NMR (400 MHz) δ 7.96 (d,

J=8.4 Hz, 1H), 7.89 (d, J=8.4 Hz, 1H), 7.71–7.64 (m, 1H), 7.47–7.43 (m, 4H), 6.98 (dd, J=8.4, 1.2 Hz, 1H).

4.1.2. 2-Methylthioquinoline.[9] Yellow oil, ^{1}H NMR (400 MHz) δ 7.97 (d, J=8.2 Hz, 1H), 7.88 (d, J=8.8 Hz, 1H), 7.71 (d, J=8.2 Hz, 1H), 7.67–7.63 (m, 1H), 7.44–7.41 (m, 1H), 7.31 (d, J=8.8 Hz, 1H), 2.71 (s, 3H).

4.1.3. 2-Ethoxyquinoline.[10] Colorless oil, ^{1}H NMR (400 MHz) δ 7.97 (d, J=8.6 Hz, 1H), 7.83 (d, J=8.8 Hz, 1H), 7.70 (d, J=8.0 Hz, 1H), 7.61–7.59 (m, 1H), 7.38–7.34 (m, 1H), 6.88 (d, J=8.8 Hz, 1H), 4.54 (q, J=7.2 Hz, 2H), 1.45 (t, J=7.2 Hz, 3H).

4.1.4. 2-Methoxyquinoline.[10] Colorless oil, ^{1}H NMR (400 MHz) δ 7.98 (d, J=8.8 Hz, 1H), 7.88 (d, J=8.4 Hz, 1H), 7.72 (d, J=8.0 Hz, 1H), 7.64–7.61 (m, 1H), 7.40–7.38 (m, 1H), 6.91 (d, J=8.8 Hz, 1H), 4.09 (s, 3H).

4.1.5. 2-Hydroxyquinoline.[11] White solid, mp=198–199°C (lit[11] mp=199°C). ^{1}H NMR (400 MHz) δ 7.85 (d, J=9.2 Hz, 1H), 7.58 (d, J=8.0 Hz, 1H), 7.54 (d, J=8.4 Hz, 1H), 7.52–7.46 (m, 1H), 7.26–7.22 (m, 1H), 6.75 (d, J=9.2 Hz, 1H), 2.14 (br, –OH).

4.1.6. 2-(Phenylamino)quinoline.[12] Colorless crystals, mp=101–102°C (lit[12] mp=103–104°C). ^{1}H NMR (400 MHz) δ 7.94 (d, J=9.0 Hz, 1H), 7.79 (d, J=8.4 Hz, 1H), 7.67–7.55 (m, 4H), 7.40–7.29 (m, 3H), 7.12 (t, J=7.4 Hz, 1H), 7.00 (d, J=8.4, 1.2 Hz, 1H).

4.1.7. 3-Phenylthioquinoline.[6b] White solid, mp=79–80°C (lit[6b] mp=78.5–80.5°C). ^{1}H NMR (400 MHz) δ 8.82 (d, J=2.4 Hz, 1H), 8.11–8.09 (m, 2H), 7.73–7.68 (m, 2H), 7.57–7.54 (m, 1H), 7.42–7.31 (m, 5H), 6.98 (dd, J=8.4, 1.2 Hz, 1H).

4.1.8. 3-Methylthioquinoline.[13] Yellow oil, ^{1}H NMR (400 MHz) δ 8.81 (d, J=2.2 Hz, 1H), 8.08 (d, J=8.4 Hz, 1H), 7.91 (d, J=2.2 Hz, 1H), 7.74 (d, J=8.4 Hz, 1H), 7.67–7.63 (m, 1H), 7.56–7.53 (m, 1H), 2.61 (s, 3H).

4.1.9. 3-Methoxyquinoline.[14] Colorless oil, ^{1}H NMR (400 MHz) δ 8.68 (d, J=2.8 Hz, 1H), 8.06 (d, J=8.4 Hz, 1H), 7.74 (d, J=8.0 Hz, 1H), 7.59–7.39 (m, 2H), 7.40 (d, J=2.8 Hz, 1H), 3.96 (s, 3H).

4.1.10. 3-Hdroxyquinoline.[15] Colorless crystals, mp=198–199°C (lit[15] mp=198°C). ^{1}H NMR (400 MHz) δ 8.90 (s, 1H), 8.15 (d, J=8.4 Hz, 1H), 7.75 (d, J=8.0 Hz, 1H), 7.73 (s, 1H), 7.63–7.54 (m, 2H), 3.31 (br, –OH).

4.1.11. 4-Phenylthioisoquinoline.[2a] White solid, mp=57–58°C (lit[2a] mp=60–61°C). ^{1}H NMR (400 MHz) δ 9.24 (s, 1H), 8.63 (s, 1H), 8.28 (d, J=8.0 Hz, 1H), 8.03 d, J=8.0 Hz, 1H), 7.77–7.73 (m, 1H), 7.68–7.66 (m, 1H), 7.26–7.19 (m, 5H).

4.1.12. 4-Methylthioisoquinoline.[2a] Colorless crystals, mp=61–62°C (lit[2a] mp=65–66°C). ^{1}H NMR (400 MHz) δ 9.09 (s, 1H), 8.43 (s, 1H), 8.23 (d, J=8.4 Hz, 1H), 8.00 (d, J=8.4 Hz, 1H), 7.81–7.77 (m, 1H), 7.69–7.26 (m, 1H), 2.62 (s, 3H).

4.1.13. 4-Methoxyisoquinoline.[6a] Colorless crystals, mp=68–69°C (lit[6a] mp=71–75°C). ^{1}H NMR (400 MHz) δ 8.91 (s, 1H), 8.21 (d, J=8.4 Hz, 1H), 8.08 (s, 1H), 7.95 (d, J=8.0 Hz, 1H), 7.73–7.69 (m, 1H), 7.66–7.26 (m, 1H), 4.08 (s, 3H).

Acknowledgements

We thank the financial support of the Chung-Tai Institute of Health Science and Technology, and the facility support of the Department of Chemistry, National Chung-Hsing University.

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