Pergamon

Tetrahedron 58 (2002) 887–890

TETRAHEDRON

Efficient nucleophilic substitution reactions of pyrimidyl and pyrazyl halides with nucleophiles under focused microwave irradiation

Yie-Jia Cherng*

Department of Medical Technology, Chung-Tai Institute of Health Science and Technology, Taichung 40605, Taiwan, ROC

Received 12 October 2001; accepted 26 November 2001

Abstract—Rapid nucleophilic displacement reactions of 2-chloropyrimidine, 2-bromopyrimidine, 5-bromopyrimidine and chloropyrazine with nucleophiles under microwave irradiation was complete within several minutes with yields up to 99%. The method using microwave irradiation is superior to the classical heating processes.

1. Introduction

Pyrimidines and pyrazines are important heterocyclic compounds. Several derivatives of this class of products are well-known as biologically active compounds: 2-(benzylamino)pyrimidine is an antihistaminic agent,[1] 2-(1*H*-imidazol-1-yl)pyrimidine and 2-(1*H*-pyrazol-1-yl)pyrimidine have antiucler activity,[2] and some pyrazine derivatives have been reported to act as analeptics and antipellagric agents.[3] This class of derivatives are generally prepared by direct displacement reactions of pyrimidyl or pyrazyl halides with nucleophiles via the classical heating processes, which often require long reaction times and result in low yields as that found in most of nucleophilic aromatic substitution reactions. The application of microwaves in promoting organic reactions has received intense attention recently.[4] We have previously developed an auxiliary method with microwave irradiation for acceleration of nucleophilic aromatic substitution reactions.[5] We report herein an extension of this methodology to pyrimidyl and pyrazyl systems.

2. Results and discussion

We first investigated the nucleophilic reactions of 5-bromopyrimidine. When 5-bromopyrimidine was treated with PhSNa or MeSNa under irradiation in a monomode microwave reactor, high yields of 5-phenylthiopyrimidine and 5-methylthiopyrimidine were procured in less than one minute (Table 1). No isomeric 6-phenylthiopyrimidine or 6-methylthiopyrimidine was found in these reactions. Among various solvents, *N*-methylpyrrolidone (NMP) was the solvent of choice for such nucleophilic substitution reactions. The reactions in NMP tended to give higher yields than those conducted in HMPA, DMSO or DMF. However, it is noted in our previous report that the nucleophilic substitution reactions of quinolyl halides are best performed in HMPA. As a comparison (entry 2, Table 1), 5-bromopyrimidine was heated with 2 equiv. of PhSNa at 100°C in NMP in an oil bath for 40 s to give only 7% yield of 5-phenylthiopyrimidine, far less than 96% in microwave irradiation (entry 1, Table 1). As the weaker nucleophile of PhONa was used, the reaction required longer time (100–600 s) and afforded only low yields (20–49%) of the desired product (entries 10–12, Table 1). The reactions with nitrogen-containing nucleophiles (e.g. benzylamine, piperidine) failed to give any appreciable quantities of the desired substitution products.

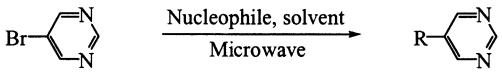
One might expect that 2-bromopyrimidine was more reactive than 5-bromopyrimidine. The results for the nucleophilic substitution reactions of 2-chloropyrimidine and 2-bromopyrimidine were listed in Table 2. The reaction of 2-chloropyrimidine with PhSNa afforded 97% yield of the desired product under microwave irradiation for 30–35 s in either NMP or HMPA (entries 1 and 2, Table 2). The reactions with MeSNa, EtONa, and PhONa also proceeded smoothly under microwave irradiation in NMP, HMPA or DMSO (entries 39, Table 2). Furthermore, the substitution reactions of 2-chloropyrimidine with nitrogen-containing nucleophiles were realized by microwave irradiation without using solvent (entries 10, 11 and 13–15, Table 2). The reactions could be conducted in homogeneous condition when aniline, benzylamine and piperidine were utilized as the nucleophiles, or in solid phase when imidazole, pyrazole and benzotriazole were used as the nucleophiles. The

Keywords: microwave irradiation; nucleophilic substitution; halopyrimidines; chloropyrazine.

* Tel.: +886-4-22391647; fax: +886-4-22393305;
e-mail: yjcherng@chtai.ctc.edu.tw

0040–4020/02/$ - see front matter
PII: S0040-4020(01)01182-6

Table 1. Reactions of 5-bromopyrimidine with nucleophiles



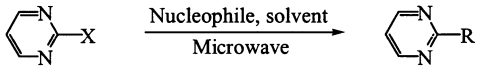
Entry	Nucleophile	Solvent	Molar proportions of nucleophile	Temp (°C)	Time (s)	Product, R=	Yield (%)
1	PhSNa	NMP	2.0	100	40	SPh	96
2	PhSNa	NMP	2.0	100	40	SPh	7[a]
3	PhSNa	NMP	2.0	90	40	SPh	86
4	PhSNa	HMPA	2.0	90	40	SPh	82
5	PhSNa	DMSO	2.0	90	40	SPh	82
6	PhSNa	DMF	2.0	90	40	SPh	76
7	MeSNa	NMP	1.8	100	60	SMe	88
8	MeSNa	HMPA	1.8	100	60	SMe	77
9	MeSNa	DMSO	1.8	100	60	SMe	70
10	PhONa	NMP	2.5	110	600	OPh	23
11	PhONa	HMPA	1.5	110	150	OPh	49
12	PhONa	DMSO	1.5	110	100	OPh	20

[a] Heating in oil bath.

substitution reaction of 2-chloropyrimidine with piperidine occurred readily without using heating or microwave irradiation.

The nucleophilic substitution reactions of 2-bromopyrimidine were similarly carried out (entries 16–27, Table 2). Of the two 2-halogenopyrimidines studied, 2-chloropyrimidine was more reactive towards the alkoxide nucleophiles (EtONa and PhONa) than 2-bromopyrimidine (compared entries 5 with 18, and entries 7 with 19 in Table 2). However, 2-bromopyrimidine was more reactive toward amine nucleophiles (aniline, benzylamine, piperidine, imidazole, pyrazole and benzotriazole) than 2-chloropyrimidine (compared entries 21 with 10, 22 with 11, 24 with 13, 26 with 14, and 27 with 15 in Table 2). To account for the sharp contrast reactivities of 2-halopyrimidines, the

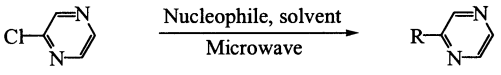
Table 2. Reactions of 2-halopyrimidines with nucleophiles



Entry	X	Nucleophile	Solvent	Molar proportions of nucleophile	Temperature (°C)	Time (s)	Product, R=	Yield (%)
1	Cl	PhSNa	NMP	2.0	85	35	SPh	97
2	Cl	PhSNa	HMPA	2.0	85	30	SPh	97
3	Cl	MeSNa	NMP	1.5	70	35	SMe	90
4	Cl	MeSNa	HMPA	1.5	70	30	SMe	73
5	Cl	EtONa	NMP	1.8	90	40	OEt	82
6	Cl	EtONa	HMPA	1.5	90	35	OEt	69
7	Cl	PhONa	NMP	1.5	100	40	OPh	73
8	Cl	PhONa	HMPA	1.5	100	35	OPh	83
9	Cl	PhONa	DMSO	1.5	100	40	OPh	88
10	Cl	NH_2Ph	[a]	3.0	120	840	NHPh	40
11	Cl	NH_2CH_2Ph	[a]	4.0	100	360	$NHCH_2Ph$	91
12	Cl	Piperidine	[a]	4.0	25	[b]	Piperidyl	96
13	Cl	Imidazole	[a]	3.0	120	1020	Imidazolyl	62
14	Cl	Pyrazole	[a]	3.0	110	1200	Pyrazolyl	67
15	Cl	Benzotriazole	[a]	1.0	120	870	Benzotriazol-1-yl	76
16	Br	PhSNa	NMP	2.0	85	35	SPh	95
17	Br	MeSNa	NMP	1.7	95	50	SMe	74
18	Br	EtONa	NMP	3.0	100	60	OEt	34
19	Br	PhONa	NMP	2.0	110	50	OPh	54
20	Br	PhONa	DMSO	1.5	110	60	OPh	66
21	Br	$PhNH_2$	[a]	4.0	110	180	NHPh	55
22	Br	$PhCH_2NH_2$	[a]	4.0	100	90	$NHCH_2Ph$	97
23	Br	Piperidine	[a]	4.0	25	[b]	Piperidyl	96
24	Br	Imidazole	[a]	3.0	110	900	Imidazolyl	88
25	Br	Imidazole	NMP	3.0	110	900	Imidazolyl	39
26	Br	Pyrazole	[a]	3.0	110	600	Pyrazolyl	75
27	Br	Benzotriazole	[a]	1.0	90	120	Benzotriazol-1-yl	76

[a] No solvent was used.
[b] The reaction occurred without microwave irradiation.

Table 3. Reactions of 2-chloropyrazine with nucleophiles



Entry	Nucleophile	Solvent	Molar proportions of nucleophiles	Temperature (°C)	Time (s)	Product, R=	Yield (%)
1	PhSNa	NMP	2.0	80	35	SPh	96
2	MeSNa	NMP	1.7	80	50	SMe	88
3	EtONa	NMP	1.8	90	45	OEt	68
4	PhONa	NMP	2.0	100	50	OPh	69
5	PhONa	HMPA	2.0	100	40	OPh	54
6	PhONa	DMSO	2.0	100	50	OPh	62
7	Piperidine	[a]	8	110	900	Piperidyl	88

[a] No solvent was used.

rate-determining steps might vary in the S_NAr mechanisms when different nucelophiles were employed. A charge-controlled reaction might predominate in the reactions with charge localized anionic nucelophiles RO. The chlorine atom with high electronegativity would induce a highly electrophilic center at C-2,[6] and thus facilitate the substitution reaction with RO. As to aminations with non-ionic nucleophiles, the bond-breaking process of CX appeared to be involved in the rate-determining step. The substrate with more labile CBr bond would undergo the substitution reaction with amines more rapidly.

Under microwave irradiation, chloropyrazine also reacted with the nucleophiles of PhSNa, MeSNa, EtONa and PhONa in NMP to afford 69–96% yields of the substituted pyrazines (Table 3). The reactions could also be conducted in HMPA or DMSO, albeit in lower yields (entries 5 and 6, Table 3). Chloropyrazine was less reactive than 2-chloropyrimidine toward nitrogen-containing nucleophiles. Only the reaction with piperidine gave the desired substitution product in a good yield of 88% (entry 7, Table 3).

3. Conclusion

Our present study indicated that chloro- and bromopyrimidines and chloropyrazine are sufficiently reactive under microwave irradiation. An efficient method for the synthesis of ethers, thioethers and amines of pyrimidines and pyrazines is thus devised. Of paramount importance, the nucleophilic substitution reactions with imidazole, pyrazole and benzotriazole were achieved in solid phase by microwave irradiation. This finding is significant as it is an environmental benign process. From a comparison of the results listed in Tables 1–3, one can deduce the relative aptitude for the nucleophilic substitution reactions: 2-halopyrimidine>chloropyrazine~5-bromopyrimidine. In general, microwave irradiation surpasses the conventional heating process in the nucleophilic aromatic substitution reactions to enhance the yield and reaction rate.

4. Experimental

^{1}H NMR spectra were measured in deuteriochloroform 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 Co.

4.1. General procedure for reaction of heteroaromatic halides with nucleophile

In a quartz reaction vessel (12 mL) was placed a heteroaromatic halide (0.3 mmol) and a 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 listed in the tables. The reaction temperature was kept by modulating the power level of the reactor. The crude reaction mixture was then absorbed directly onto silica gel, and purified by silica gel chromatography eluting with a mixture of hexane and ethyl acetate.

4.1.1. 5-Phenylthiopyrimidine.[7] Yellow oil, ^{1}H NMR (400 MHz) δ 9.03 (s, 1H), 8.59 (s, 2H), 7.46–7.37 (m, 5H).

4.1.2. 5-Methylthiopyrimidine.[8] Yellow oil, ^{1}H NMR (400 MHz) δ 9.00 (s, 1H), 8.62 (s, 2H), 2.55 (s, 3H).

4.1.3. 5-Phenoxypyrimidine. Yellow oil, ^{1}H NMR (400 MHz) δ 8.98 (s, 1H), 8.49 (s, 2H), 7.44–7.06 (m, 5H); ^{13}C NMR (100 MHz) δ 155.12, 153.02, 152.34, 146.85, 130.30, 125.02, 119.10; IR ($CHCl_3$): 2956, 2924, 2853, 1498, 1407, 1256 cm^{-1}; MS *m/e* 172 (M^+), 77; HRMS *m/e* calcd for $C_{10}H_8N_2O$ 172.0637, found 172.0631.

4.1.4. 2-Phenylthiopyrimidine.[7] Colorless oil, ^{1}H NMR (400 MHz) δ 8.49 (d, J=4.8 Hz, 2H), 7.65–7.63 (m, 2H), 7.46–7.63 (m, 3H), 6.97 (t, J=4.8 Hz, 1H).

4.1.5. 2-Methylthiopyrimidine.[9] Colorless oil, ^{1}H NMR (400 MHz) δ 8.53 (d, J=4.8 Hz, 2H), 6.70 (t, J=4.8 Hz, 1H). 2.57 (s, 3H).

4.1.6. 2-Ethoxypyrimidine.[10] Colorless oil, ^{1}H NMR (400 MHz) δ 8.51 (d, J=4.8 Hz, 2H), 6.92 (t, J=4.8 Hz, 1H). 4.43 (q, J=7.2 Hz, 2H), 1.44 (t, J=7.2 Hz, 3H).

4.1.7. 2-Phenoxypyrimidine.[11] Colorless needles, mp 86–88°C (lit. mp 89–91°C); ^{1}H NMR (400 MHz) δ 8.57 (d, J=4.8 Hz, 2H), 7.46–7.42 (m, 2H), 7.46–7.42 (m, 3H), 7.04 (t, J=4.8 Hz, 1H).

4.1.8. 2-Anilinopyrimidine.[12] Colorless needles, mp 110–112°C (lit. mp 112.5–113°C); ^{1}H NMR (400 MHz) δ 8.43 (d, J=4.8 Hz, 2H), 7.63–7.61 (m, 2H), 7.37–7.26 (m, 3H), 7.08–7.04 (m, 1H), 6.72 (t, J=4.8 Hz, 1H).

4.1.9. 2-(Benzylamino)pyrimidline.[1] White solid, mp 75–76°C (lit. mp 75–80°C); ^{1}H NMR (400 MHz) δ 8.32 (d, J=4.8 Hz, 2H), 7.36–7.26 (m, 5H), 6.59 (t, J=4.8 Hz, 1H), 5.69 (b, –NH), 4.66 (d, J=6.0 Hz, 2H).

4.1.10. 2-Piperidylpyrimidine.[13] Colorless oil, ^{1}H NMR (400 MHz) δ 8.29 (d, J=4.8 Hz, 2H), 6.42 (t, J=4.8 Hz, 1H), 3.78 (t, J=5.6 Hz, 4H), 1.70–1.58 (m, 6H).

4.1.11. 2-(1*H*-Imidizol-1-yl)pyrimidine.[2] Colorless crystals, mp 118–120°C (lit. mp 115–116°C); ^{1}H NMR (400 MHz) δ 8.70 (d, J=4.8 Hz, 2H), 8.63 (b, 1H), 7.90 (d, J=1.0 Hz, 1H), 7.22 (t, J=4.8 Hz, 1H), 7.17 (d, J=1.0 Hz, 1H).

4.1.12. 2-(1*H*-Pyrazol-1-yl)pyrimidine.[2] White needles, mp 72–73°C (lit. mp 73.5–74°C); ^{1}H NMR (400 MHz) δ 8.70 (d, J=4.8 Hz, 2H), 8.63 (b, 1H), 7.90 (d, J=1.0 Hz, 1H), 7.22 (t, J=4.8 Hz, 1H), 7.17 (d, J=1.0 Hz, 1H).

4.1.13. 2-(Benzotriazol-1-yl)pyrimidine.[14] White solid, mp 160–162°C (lit. mp 164–165°C); ^{1}H NMR (400 MHz) δ 8.96 (d, J=4.8 Hz, 2H), 8.61 (d, J=8.4 Hz, 1H), 8.18 (d, J=8.4 Hz, 1H), 7.66 (m, 1H), 7.50 (m, 1H), 7.39 (t, J=4.8 Hz, 1H).

4.1.14. Phenylthiopyrazine.[15] Colorless oil, ^{1}H NMR (400 MHz) δ 8.35 (dd, J=2.8, 1.6 Hz, 1H), 8.24 (d, J=2.8 Hz, 1H), 8.20 (d, J=1.6 Hz, 1H), 7.60–7.63 (m, 2H), 7.44–7.48 (m, 3H).

4.1.15. Methylthiopyrazine.[16] Colorless needles, mp 41–43°C (lit. mp 42–46°C); ^{1}H NMR (400 MHz) δ 8.47 (d, J=1.2 Hz, 1H), 8.38 (dd, J=2.8, 1.6 Hz, 1H), 8.20 (t, J=2.8 Hz, 1H), 2.57 (s, 3H).

4.1.16. Ethoxypyrazine.[3] Colorless oil, ^{1}H NMR (400 MHz) δ 8.21 (s, 1H), 8.10 (d, J=2.4 Hz, 1H), 8. 07 (d, J=2.4 Hz, 1H) 4.39 (q, J=7.2 Hz, 2H), 1.43 (t, J=7.2 Hz, 3H).

4.1.17. Phenoxypyrazine.[17] Colorless needles, mp 50–51°C (lit. mp 50–52°C); ^{1}H NMR (400 MHz) δ 8.43 (d, J=1.2 Hz, 1H), 8.27 (d, J=2.8 Hz, 1H), 8.12 (dd, J=2.8, 1.2 Hz, 1H), 7.46–7.16 (m, 5H).

4.1.18. Piperidylpyrazine.[18] Yellow solid, mp 34–35°C (lit. mp 36–37°C); ^{1}H NMR (400 MHz) δ 8.13 (d, J=1.2 Hz, 1H), 8.04 (dd, J=2.4, 1.2 Hz, 1H), 7.77 (d, J=1.2 Hz, 1H), 3.59–3.57 (m, 4H), 1.70–1.63 (m, 6H).

Acknowledgements

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

References

1. MatsuKawa, T.; Shirakawa, K.; Kawasaki, H. *J. Pharm. Soc. Jpn* **1951**, *46*, 895.
2. Ikeda, M.; Maruyama, K.; Nobuhara, Y.; Yamada, T.; Ukabe, S. *Chem. Pharm. Bull.* **1996**, *44*, 1700.
3. Erickson, A. E.; Spoerri, P. E. *J. Am. Chem. Soc.* **1946**, *68*, 400.
4. (a) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe', D. *Synthesis* **1998**, 1213. (b) Strauss, C. R. *Aust. J. Chem.* **1999**, *52*, 83. (c) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665. (d) Sridor, V. *Curr. Sci.* **1998**, *74*, 446. (e) Mingos, D. M. P. *Res. Chem. Intermed.* **1994**, *20*, 85. (f) Majetich, G.; Hick, R. *Phys. Chem.* **1995**, *45*, 567. (g) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (h) Morcuende, A.; Ors, M.; Valverde, S.; Herradon, B. *J. Org. Chem.* **1996**, *61*, 5264. (i) Chen, S. T.; Tseng, P. H.; Yu, H. M.; Wu, C. Y.; Hsiao, K. F.; Wu, S. H.; Wang, K. T. *J. Chin. Chem. Soc.* **1997**, *44*, 169. (j) Gelopujic, M.; Guibejampel, E.; Loupy, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2777. (k) Diazotir, A.; Prieto, P.; Loupy, A.; Abenhaim, D. *Tetrahedron Lett.* **1996**, *37*, 1695. (l) Giguere, R. J.; Namen, A. M.; Lopez, B. O.; Arepally, A.; Ramos, D. E.; Majetich, G.; Defauw, J. *Tetrahedron Lett.* **1987**, *28*, 6553. (m) Gedye, R.; Smith, F.; Westaway, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279. (n) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945.
5. Cherng, Y.-J. *Tetrahedron* **2000**, *56*, 8287.
6. (a) Miller, J. *Nuccleophilic Substitution*; Elsevier: Amsterdam, 1968. (b) Klopman, G. *J. Am. Chem. Soc.* **1968**, *90*, 223. (c) Loupy, A.; Philippon, N.; Pigeon, P.; Galons, H. *Heterocycles* **1991**, *32*, 1947.
7. Chen, J.; Crisp, G. T. *Synth. Commun.* **1992**, *22*, 683.
8. Maggiali, C.; Morini, G.; Mossini, F.; Barocelli, E.; Impicciatore, M. *Farmaco. Ed. Sci.* **1988**, *43*, 277.
9. Albert, A.; Barlin, G. B. *J. Chem. Soc.* **1962**, 3129.
10. Crestini, C.; Enrico, M.; Raffaele, S.; Rosario, N. *Tetrahedron* **1994**, *50*, 3259.
11. Ohta, B.; Kawasaki, H. *J. Pharm. Soc. Jpn* **1951**, *46*, 1420.
12. Takeuchi, H.; Watanabe, K. *J. Phys. Org. Chem.* **1998**, *11*, 478.
13. Chapman, N. B.; Rees, C. W. *J. Chem. Soc.* **1954**, 1190.
14. Katritzky, A. R.; Ignatchenko, A. V.; Lang, H. *Heterocycles* **1995**, *41*, 131.
15. Anne, L.; Alain, T.; Nelly, P.; Guy, Q. *Tetrahedron* **2000**, *56*, 3709.
16. Lee, D. H.; Kim, D. H. *Xenobiotica* **2000**, *29*, 909.
17. Kushner, S.; Dalalian, H.; Sanjurjo, J. L.; Bach, F. L.; Safir, S. R.; Smith, V. K.; Williams, J. H. *J. Am. Chem. Soc.* **1952**, *74*, 3617.
18. Klein, B.; O'Donnell, E.; Auerbach, J. *J. Org. Chem.* **1967**, *32*, 2412.