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Efficient Nucleophilic Substitution Reaction of Aryl Halides with Amino Acids Under Focused Microwave Irradiation

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Abstract—The nucleophilic substitution reaction of 2,4-dinitrofluorobenzene with amino acids was complete, under microwave iradiation, within 40 s with yields up to 93%, which are far superior to those obtained under conventional heating.

Introduction

Aryl halides are characterized by low reactivity toward nucleophilic reagents like OH^-, OR^-, NH_3, and CN^- that play an important part in the chemistry of aliphatic-halides.[1] Therefore, nucleophilic aromatic substitution is less used in synthesis than either nucleophilic aliphatic substitution or electrophilic aromatic substitution.[2] The reactivity of aryl halides is greatly improved by electron-withdrawing groups such as NO_2, *ortho* and/or *para* to the aryl halides, however, long reaction times or vigorous conditions are required to achieve acceptable yields under conventional heating. The application of microwaves in promoting organic reactions has received intense attention recently.[3] We wanted to determine whether the reaction rate of nucleophilic aromatic substitution can be accelerated under microwave irradiation. We report herein our studies on the microwave-promoted reaction of α-amino acids with 2,4-dinitrohalo-benzenes.

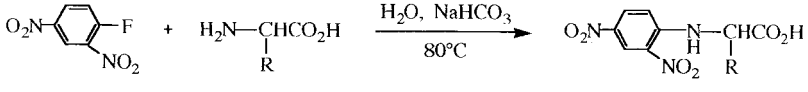
Results and Discussion

2,4-Dinitrofluorobenzene (Sanger's reagent) has been used widely to react with the amino group of amino acids to afford *N*-aryl α-amino acids.[4] The reaction usually requires several hours at room temperature to give a satisfactory yield. In an attempt to develop a more efficient process, glycine was reacted with 2,4-dinitrofluorobenzene in water in a monomode microwave reactor (Synthewave 402) for 20 min at 100°C. Unfortunately, no desired product was detected. We reasoned that the lack of reactivity might be due to the zwitterionic nature of the amino acid. Therefore, two equivalents of sodium bicarbonate were added in order to free the amino group which should increase the nucleophilicity of the reactant. Excellent yields (91–93%) of the *N*-arylated amino acids were produced under microwave irradiation at 80°C in only 35–40 s (Scheme 1). Our results are summarized in Table 1.

To compare the efficacy of microwave irradiation with those of conventional heating, the reaction was heated in an oil bath (95°C bath temperature) for 60 s. No desired product was detected under these conditions. The results suggested that improved yields may be due to microwave effect instead of heating efficiency.[5]

Table 1. Reaction of 2,4-dinitro-1-fluorobenzene and aminoacids

Entry	R	Config	Time (s)	Yield (%)
1	H		35	92
2	Me	*S*	35	93
3	*i*-Pr	*S*	35	92
4	*i*-Bu	*S*	40	91
5	Ph	*R*	35	93
6	$PhCH_2$	*S*	35	93



Scheme 1.

Keywords: microwave irradiation; nucleophilic aromatic substitution.

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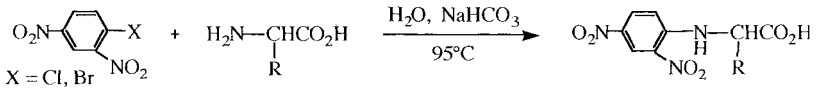

Scheme 2.

Table 2. Reaction of 2,4-dinitro-1-chlorobenzene and aminoacids

Entry	R	Config	Time (min)	Yield (%)
1	H		6	64
2	Me	*S*	7	60
3	*i*-Pr	*S*	8	58
4	*i*-Bu	*S*	9	55
5	Ph	*R*	7	61
6	$PhCH_2$	*S*	7	60

Table 3. Reaction of 2,4-dinitro-1-bromobenzene and aminoacids

Entry	R	Config	Time (min)	Yield (%)
1	H		10	60
2	Me	*S*	11	57
3	*i*-Pr	*S*	13	53
4	*i*-Bu	*S*	15	48
5	Ph	*R*	11	56
6	$PhCH_2$	*S*	11	55

The influence of the halogen on the efficiency of the substitution reaction was investigated by treating 2,4-dinitrochlorobenzene and 2,4-dinitrobromobenzene with amino acids (Scheme 2). Under S_N2 conditions, enhanced reactivity of chloride and bromide over that of the fluoride is expected since they are better leaving groups than the latter. However, our results revealed that longer reaction times were required (up to 26 times) to obtain inferior chemical yields to those of the corresponding fluoride (Tables 2 and 3). The order of the reaction yields (F>Cl>Br) suggested that an S_NAr mechanism is operating in which the rate determining step of the reaction is the attack of the substrate by the nucleophile that is strongly favored by less hindered and more electronegative fluoride.[6] These results are consistent with the literature and that the microwave gives the same effect and conventional heating, i.e. the fluorobenzene reacts more quickly than the chloro- or bromobenzene.

The yields of the reaction decrease slightly as the steric bulkness of the side chain on the amino acid increases from alanine, valine to leucine (Table 1, entries 2–4). This steric effect is more profound with the less reactive chloride and the bromide (entries 2–4 of Tables 2 and 3) presumably as a result of decreasing electronegtivities and increasing steric demands of the halides.

These results are consistent with the literature and that the microwaves give the same effect as conventional heating, i.e. the fluorobenzene reacts more quickly than the bromo or chlorobenzene.

Conclusion

We have established an extremely efficient substitution reaction of an aryl fluoride by a nitrogen nucleophile under microwave irradiation to achieve high yields in very short reaction time. Furthermore, our reaction conditions only required water as the solvent which is more environmentally friendly.

Experimental

Melting points are uncorrected. Infrared spectra were taken in KBr solid. ^1H NMR (Me_4Si as internal standard) and ^{13}C NMR (CD_3COCD_3 at 205.4 ppm as internal standard) spectra were measured in deuteroacetone solutions on a Varian Mercury 400. Reactions were monitored by analytical thin-layer chromatography using silica gel 60 F-254, layer thickness 0.2 mm. Flash chromatography was carried out utilizing silica gel 60, 70–230 mesh ASTM. The Synthewave 402™ monomode microwave reactor was purchased from Prolabo Co.

General procedure for reaction of amino acid and 2,4-dinitrohalobenzene

To a quartz reaction vessel (12 mL) was added a solution of amino acid (0.3 mmol) and sodium bicarbonate (0.6 mmol, 2 equiv.) in H_2O (2 mL) followed by 2,4-dinitrohalobenzene (0.3 mmol). 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 desired product precipitates after the addition of 2N HCl (1 mL) to the reaction mixture. The yellow *N*-arylated amino acid, collected via filtration and washed with water (1 mL×2), required no further purification to pass elemental analysis. Then was purified by recrystallization.

***N*(2,4-Dinitrophenyl)-(*s*)-glycine.** Solid; mp 201–202°C; IR (KBr) 3355 (NH), 3106 (OH), 1716 (C=O), 1523, 1342 cm^{-1}; ^1H NMR (400 MHz) 9.01 (d, J=2.8 Hz, 1H), 8.33 (dd, J=9.6, 2.8 Hz, 1H), 7.20 (d, J=9.6 Hz, 1H), 4.46 (m, 2H); ^{13}C NMR (100 MHz) 170.09, 148.55, 137.00, 131.42, 130.62, 124.05, 116.19, 45.13; MS *m/z* (rel intensity) 241 (27, M^+), 196 (100); Anal. calcd for $C_8H_7N_3O_6$: C, 39.84; H, 3.93; N, 17.42. Found: C, 39.20; H, 3.61; N, 17.48.

***N*(2,4-Dinitrophenyl)-(*s*)-alanine.** Solid; mp 173–174°C; $[\alpha]_D^{25}=-14.1$ (c=1.0, acetone); IR (KBr) 3350 (NH), 3114 (OH), 1715 (C=O), 1504, 1361 cm^{-1}; ^1H NMR (400 MHz) 9.01 (d, J=2.8 Hz, 1H), 8.34 (dd, J=9.6, 2.8 Hz, 1H),7.26 (d, J=9.6 Hz, 1H), 4.78 (m, 1H); 1.66 (d, J=7.2 Hz, 3H), ^{13}C NMR (100 MHz) 173.1, 147.89, 137.04, 131.64, 130.85, 124.33, 116.06, 52.05, 18.60; MS *m/z* (rel intensity) 255 (16, M^+), 210 (100); Anal. calcd for $C_9H_9N_3O_6$: C, 42.36; H, 3.55; N, 16.47. Found: C, 42.45; H, 3.11; N, 16.93.

***N*(2,4-Dinitrophenyl)-(*s*)-valine.** Solid; mp 127–128°C; $[\alpha]_D^{25}=-61.8$ (c=1.2, acetone); IR (KBr) 3336 (NH), 3110 (OH), 1747 (C═O), 1523, 1340 cm^{-1}; ^1H NMR (400 MHz) 9.02 (d, J=2.8 Hz, 1H), 8.32 (dd, J=9.6, 2.8 Hz, 1H), 7.27 (d, J=9.6 Hz, 1H), 4.61 (dd, J=8.0, 4.4 Hz, 1H), 2.44 (m, 1H), 1.16 (d, J=6.8 Hz, 3H), 1.08 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz) 171.62, 148.60, 137.01, 131.64, 130.81, 124.30, 116.05, 61.53, 32.04, 18.93, 18.49; MS *m/z* (rel intensity) 283 (17, M^+), 240 (15) 238 (100); Anal. calcd for $C_{11}H_{13}N_3O_6$: C, 46.65; H, 4.63; N, 14.84. Found: C, 46.17; H, 4.87; N, 14.71.

***N*(2,4-Dinitrophenyl)-(*s*)-leucine.** Solid; mp 90–91°C; $[\alpha]_D^{25}=-45.3$ (c=1.0, acetone); IR (KBr) 3347 (NH), 3080 (OH), 1719 (C═O), 1518, 1337 cm^{-1}; ^1H NMR (400 MHz, acetone) 9.01 (d, J=2.8 Hz, 1H), 8.34 (dd, J=9.6, 2.8 Hz, 1H), 7.24 (d, J=9.6 Hz, 1H), 4.67 (m, 1H); 2.05 (m, 1H), 1.97 (m, 1H), 1.88 (m, 1H), 1.04 (d, J=6.4 Hz, 3H), 0.96 (d, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, acetone) 172.74, 148.39, 137.39, 131.1, 130.92, 124.33, 124.31, 115.99, 55.38, 41.70, 25.97, 23.14, 22.72; MS *m/z* (rel intensity) 27 (21, M^+), 252 (100); Anal. calcd for $C_{12}H_{15}N_3O_6$: C, 48.4; H, 5.09; N, 14.14. Found: C, 48.14; H, 4.42; N, 14.66.

***N*(2,4-Dinitrophenyl)-(*R*)-phenylglycine.** Solid; mp 203–204°C; $[\alpha]_D^{25}=+183.3$ (c=1.0, acetone); IR (KBr) 3329 (NH), 3095 (OH), 1726 (C═O), 1523, 1337 cm^{-1}; ^1H NMR (400 MHz) 8.74 (s, 1H), 7.95 (d, J=8.8 Hz, 1H), 7.51–7.15 (m, 5H), 6.66 (d, J=8.8 Hz, 1H); 5.30 (s, 1H); ^{13}C NMR (100 MHz) 172.74, 148.39, 137.39, 131.1, 130.92, 124.33, 124.31, 115.99, 55.38, 41.70, 25.97, 23.14, 22.72; MS *m/z* (rel intensity) 317 (2, M^+), 77 (100); Anal. calcd for $C_{14}H_{11}N_3O_6$: C, 53.00; H, 3.49; N, 13.25. Found: C, 53.52; H, 3.26; N, 13.83.

***N*(2,4-Dinitrophenyl)-(*s*)-phenylalnine.** Solid; mp185–186°C; $[\alpha]_D^{25}=-103.0$ (c=1.0, acetone); IR (KBr) 3324 (NH), 3109 (OH), 1748 (C═O), 1521, 1370 cm^{-1}; ^1H NMR (400 MHz, acetone) 8.98 (d, J=3.2 Hz, 1H), 8.27 (dd, J=9.6, 3.2 Hz, 1H),7.28–7.27 (m, 5H), 7.23 (d, J=9.6 Hz, 1H) 5.05 (t, J=5.8 Hz, 1H); 3.46 (dd, J=14.0, 5.6 Hz, 1H), 3.36 (dd, J=14.0, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, acetone) 171.22, 147.61, 136.78, 136.3 131.20, 130.38 2c), 129.02, 127.66, 123.95, 115.82, 57.04, 38.00; MS *m/z* (rel intensity) 331 (3, M^+), 240 (100); Anal. calcd for $C_{15}H_{13}N_3O_6$: C, 54.38; H, 3.6; N, 12.68. Found: C, 54.42; H, 3.40; N, 12.706.

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References

1. Zoltewicz, T. *Curr. Chem.* **1975**, *59*, 33–64.
2. Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273–412.
3. (a) Strauss, C. R. *Aust. J. Chem.* **1999**, *52*, 83–96. (b) Strauss, C. R.; Trainor, R. W. *Aust. J. Chem.* **1995**, *48*, 1665–1692. (c) Sridor, V. *Curr. Sci.* **1998**, *74*, 446–450. (d) Mingos, D. M. P. *Res. Chem. Intermed.* **1994**, *20*, 85–91. (e) Majetich, G.; Hick, R. *Radiat. Phys. Chem.* **1995**, *45*, 567–579. (f) Caddick, S. *Tetrahedron* **1995**, *51*, 10403–10432. (g) Morcuende, A.; Ors, M.; Valverde, S.; Herradon, B. *J. Org. Chem.* **1996**, *61*, 5264–5270. (h) 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*, 169–182. (i) Loupy, A.; Petit, A.; Hamelin, J.; Texier-boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213–1234. (j) Gelopujic, M.; Guibejampel, E.; Loupy, A.; Galema, S. A.; Mathe, D. *J. Chem. Soc. Perkin Trans. 1* **1996**, 2777–2780. (k) Giguere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945–4948. (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) Diazortiz, A.; Prieto, P.; Loupy, A.; Abenhaim, D. *Tetrahedron Lett.* **1996**, *37*, 1695–1698.
4. Cohen, J. C.; Norcup, J.; Ruzicka, J. H. A. *J. Chromatogr.* **1969**, *44*, 251.
5. Berlan, J. *Radiat. Phys. Chem.* **1995**, *45*, 581–589.
6. (a) Buck, P. *Angew. Chem., Int. Engl.* **1969**, *8*, 120–131. (b) Bunnett, J. F. *J. Chem. Ed.* **1974**, *51*, 312–315. (c) Bunnett, J. F.; Bernasconi, C. F. *J. Org. Chem.* **1970**, *35*, 70. (d) Kirby, A. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1965**, *87*, 3217. (e) Bunnett, J. F.; Garbisch, E. W.; Pruitt, K. M. *J. Am. Chem. Soc.* **1957**, *79*, 385. (f) Reinheimer, J. D.; Taylor, R. C.; Rohrbaugh, P. E. *J. Am. Chem. Soc.* **1961**, *83*, 835. (g) Parker, R. E.; Read, T. O. *J. Chem. Soc.* **1962**, *9*, 3149.