Tetrahedron Letters 55 (2014) 2711–2714

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Highly selective N-allylation of anilines under microwave irradiation

Meiyu Liu, Xie Wang, Xiaoliang Sun, Wei He *

Department of Chemistry, School of Pharmacy, Fourth Military Medical University, Xi'an 710032, PR China

ARTICLE INFO

Article history:
Received 19 December 2013
Revised 28 February 2014
Accepted 9 March 2014
Available online 14 March 2014

Keywords:
Aniline
Allyl bromine
Microwave irradiation
Allylation
Selectivity

ABSTRACT

An easy and rapid procedure for the preparation of a variety of mono- and bis-allylated anilines via the reaction of allyl bromide with a wide range of anilines under microwave irradiation is described. This approach allows use of mild conditions and short reaction times to give high selectivities and excellent yields.

N-allylation of aniline is a well-established process for the construction of C—N bonds. Bis-allylation of aniline is often used to protect the amino group, and subsequent deprotection can be easily achieved.[1] In addition, many mono- and bis-allyl substituted anilines are frameworks for many natural products and biologically active agents. For example, the *N*-substituted 1-benzazepine derivative OPC-31260 (procyanidin) has a favorable curative effect on cardiopathy.[2] Many synthetic approaches using direct allylation are hindered by over-allylation of the aniline, which leads to low yields and poor selectivity.[3,4] Therefore, the development of new methods to prepare *N*-allylanilines with high selectivity has been of great interest over past decades.

Traditionally, bases such as Na_2CO_3, K_2CO_3, NaH, and BuLi have been employed in the allylation of anilines, but this often leads to long reaction times or low yields of desired products.[5] Recently, Basu and co-workers reported a new method of N-alkylation of amines on recyclable silica with alkyl halides to give mono- or bis-alkylated amines selectively in the absence of base.[6] Metal catalyzed allylation of aniline using allyl alcohol as the allylating agent has been established as a versatile method for the formation of C—N bonds. Palladium catalysts have been successfully used to afford bis-allylanilines and mono-allylanilines, respectively,[7] while Pt-catalyzed reactions of allyl alcohol with primary amines have been employed for the selective formation of secondary amines.[8] While these methods have obvious advantages, the metal catalysts are costly, and may lead to possible environmental problems. Therefore, a selective, efficient, widely applicable, and low cost method of N-allylation is still highly desired.

It is well known that polar compounds absorb microwave radiation selectively.[9] Varma and Ju have reported the selective formation of tertiary amines via N-alkylation in aqueous alkaline medium under microwave irradiation.[10] Based on the polar nature of allyl bromide and aniline and its derivatives, we anticipated that the nucleophilic substitution reaction would be accelerated by microwave energy. Our studies have confirmed that allylation of anilines can indeed be achieved efficiently in a very short period of time under microwave irradiation conditions, and herein, we report our results on the direct synthesis of secondary and tertiary amines under these conditions. We also show that the selectivity of the reaction is dependent on the reaction conditions.

Initially, 2-iodoaniline and allyl bromide were selected as model substrates to screen for optimal reaction conditions under controlled microwave heating. The major products of these reactions were secondary and tertiary amines, with no quaternary ammonium salts being detected. The different reaction conditions investigated are outlined in Table 1. The investigation was initiated in polar solvents under 850 W power microwave irradiation using K_2CO_3 as the base. Different solvents have different boiling points. To prevent liquid flooding under microwave irradiation, the reaction temperature was chosen at different temperatures. When the reaction was carried out in water, the mono-substituted product was obtained selectively in moderate yield, even though a two-fold excess of allyl bromide was used (Table 1, entry 1). DMSO and MeCN also tended to give the mono-substituted product (Table 1, entries 2 and 3). However, in DMF, the bis-substituted product was obtained in 47% isolated yield, with a 3:1 ratio of bis- to

* Corresponding author. Tel.: +86 2984774470.
E-mail address: heweichem@126.com (W. He).

http://dx.doi.org/10.1016/j.tetlet.2014.03.044
0040-4039/

Table 1
The reaction of 2-iodoaniline with allyl bromide promoted with different bases at various temperatures and solvents[a]

Entry	Aniline/allyl Bromide	Solvent	Base	Temp (°C)	PTC	Mono product[d] (%)	Bis product[d] (%)
1	1:2	H_2O	K_2CO_3	80	—	50	Trace
2	1:2	DMSO	K_2CO_3	170	—	39	Trace
3	1:2	MeCN	K_2CO_3	60	—	38	Trace
4	1:2	DMF	K_2CO_3	130	—	15	47
5	1:2	Toluene	K_2CO_3	90	—	NR	NR[e]
6	1:2	*p*-Xylene	K_2CO_3	120	—	NR	NR
7	1:2	H_2O	KOH	80	—	81	Trace
8	1:2	H_2O	KOH	80	CTAB	92	Trace
9	1:4	H_2O	KOH	80	CTAB	94	Trace
10	1:4	DMF	K_2CO_3	130	—	18	59
11	1:4	DMF	KOH	130	—	64	Trace
12	1:4	DMF	Cs_2CO_3	130	—	21	60
13	1:4	DMF	Na_2CO_3	130	—	16	67
14	1:4	DMF	DABCO	130	—	21	Trace
15	1:4	DMF	DBU	130	—	18	Trace
16	1:4	DMF	DMAP	130	—	22	Trace
17	1:4	DMF	Na_2CO_3	130	CTAB	10	83
18[b]	1:4	DMF	Na_2CO_3	130	CTAB	10	85
19[b,c]	1:4	DMF	Na_2CO_3	130	CTAB	5	90

[a] All of the reactions were carried out under 850 W MW power for 10 min; 2 equiv of base were used.
[b] Reaction time was 20 min.
[c] Allyl bromide was added in two parts.
[d] Product isolated by chromatography.
[e] NR: No reaction was observed.

mono-substituted products (Table 1, entry 4). Less polar aromatic solvents were almost completely ineffective in giving mono- or bis-substituted products (Table 1, entries 5 and 6).

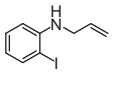
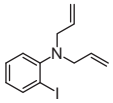
Use of the stronger base KOH rather than K_2CO_3 in H_2O solvent gave a significantly improved yield of the mono-allylaniline while retaining the selectivity (Table 1, entry 7). The poor solubility of the substrate in H_2O encouraged us to explore a phase transfer catalyst (PTC) to further improve the yields. Addition of hexadecyl trimethyl ammonium bromide (CTAB)[11] resulted in an excellent yield of the mono-allylaniline with complete selectivity. (Table 1, entry 8). Therefore, the optimal reaction conditions for the production of the mono-allylaniline was set up as follows: 850 W power MW irradiation at 80 °C in water, a 1:2 ratio of aniline and allyl bromide, 2 equiv of KOH and 10 mol % CTAB. This is designated as condition A.[12]

Attention then turned to optimizing conditions for the production of bis-allylanilines. We initially tried condition A with a large excess of allyl bromide (a 1:4 ratio of aniline to allyl bromide) but this still gave exclusive formation of the mono-allylaniline (Table 1, entry 9 vs entry 8). Given that we had found that use of DMF as solvent and K_2CO_3 as base gave predominant formation of the bis-allylaniline, we further investigated this system. A 1:4 mixture of aniline and allyl bromide afforded the bis- and mono-allylated anilines in a 3:1 ratio, but with only a slight improvement in yield and selectivity (Table 1, entry 10 vs entry 4). Surprisingly, the mono-allylaniline was obtained exclusively in good yield when potassium hydroxide, rather than K_2CO_3, was used as the base in DMF (Table 1, entry 11), while both Cs_2CO_3 and Na_2CO_3 gave similar results to K_2CO_3 (Table 1, entries 12 and 13). The organic bases DABCO, DBU, and DMAP all gave low yields of mono-substituted product with trace amounts of the bis-substituted product (Table 1, entries 14–16). We ultimately found that use of Na_2CO_3 as a base in the presence of CTAB led to a yield of bis-allylaniline of 83% (Table 1, entry 17). While longer reaction times did not give any further improvement (Table 1, entry 18), addition of 4 equiv of allyl bromide in two parts gave further improved selectivity (Table 1, entry 19). Thus, the optimal reaction conditions for the production of bis-allylaniline was set up as: 850 W power MW irradiation at 130 °C in DMF, a 1:4 ratio of aniline to allyl bromide, 2 equiv of Na_2CO_3 and 10 mol % CTAB. This is designated as condition B.[13]

To compare the effect of microwave irradiation with conventional heating, reactions were carried out under the optimal conditions, but using heating in an oil bath for 12 h. Using condition A, the reaction of 2-iodoaniline with allyl bromide gave an increased yield of bis-allylated product (14%), and a decreased yield of mono-allylated product (77%) (Table 2, entry 2 vs entry 1). Similarly, the reaction using condition B afforded lower selectivity and the yield of bis-allylated product was decreased dramatically (Table 2, entries 3 and 4). Obviously, the microwave-assisted syntheses give significantly reduced reaction times, higher selectivities, and higher yields than those using conventional heating.

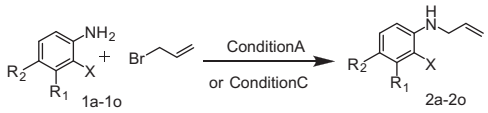
Such remarkable selectivity under simple reaction conditions prompted us to investigate the reactivity and selectivity of a series of anilines. Firstly, mono-allylated products were successfully prepared from different anilines under MW irradiation. As shown in Table 3, the electronic effect of substituents on the aromatic ring had a significant influence on the yields of the mono-*N*-allylated anilines. All of the 2-halogenated anilines afforded the desired mono-*N*-allylated anilines in high yields under condition A (Table 3, entries 1–3). 4-chloro-2-iodoaniline also gave the mono-allylated product in excellent yield with excellent selectivity (Table 3, entry 4). However, when another stronger electron-withdrawing group, which do not possess resonance donating effect like chlorine atom,

Table 2
N-allylation of 2-iodoaniline by allyl bromide using conventional heating[a]

Reaction condition	Products and yields[b]	
		
MW, 80 °C, 10 min (Condition A)	92%	Trace
H_2O, KOH (2 equiv) CTAB (10% mmol) Heated at 80 °C, 12 h	77%	14%
MW, 130 °C, 20 min (Condition B)	Trace	90%
DMF, Na_2CO_3 (2 equiv) CTAB (10% mmol) Heated at 130 °C, 12 h	67%	18%

[a] All the reactions were carried out at 0.5 mmol of aniline scale.
[b] Yield of the isolated product after chromatography.

Table 3
Synthesis of various substituted mono-allylations of anilines[a]



Entry	Condition	X	R_1	R_2	Product	Conver.	Yield[b] (%)
1	A	I	H	H	**2a**	95	92
2	A	Cl	H	H	**2b**	93	90
3	A	Br	H	H	**2c**	95	90
4	A	I	H	Cl	**2d**	92	89
5	A	I	H	CF_3	**2e**	74	70
6	A	I	H	CN	**2f**	67	63
7	A	Br	H	CN	**2g**	70	67
8	A	CF_3	H	H	**2h**	79	76
9[c]	A	OCH_3	H	H	**2i**	95	75,
10[d]	A	I	H	CH_3	**2j**	97	90
11	C	OCH_3	H	H	**2i**	92	89
12	C	H	H	OCH_3	**2k**	90	88
13	C	H	H	CH_3	**2l**	87	85
14	C	H	H	$CH(CH_3)_2$	**2m**	90	88
15	C	H	I	CH_3	**2n**	94	92
16	C	H	H	H	**2o**	95	93

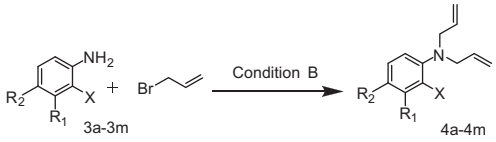
[a] All the reactions were carried out using 0.5 mmol of the aniline.
[b] Yield of the isolated product after chromatography.
[c] The bis-allylated product was isolated in 14% yield.
[d] The bis-allylated product was isolated in 3% yield.

was introduced to the 4-position of 2-halogenated anilines, the overall yield of mono-*N*-allylated products was decreased (Table 3, entries 5–7). Similarly, introduction of the strongly electron-withdrawing CF_3 group at the 2-position of the aniline decreased the yield of the mono-*N*-allylated product (Table 3, entry 8). These results indicated that the electronic property of substrate is very important for conversion of the reaction. Allylation of 2-methoxyaniline, which has an electron-donating group at the 2-position, yielded the mono-allylated product in 75% isolated yield, but the conversion was 95%, and the bis-allylated product was also isolated in 14% yield (Table 3, entry 9). Similarly, the mono-allylated product was obtained with the yield of 90% for 2-iodo-4-methylaniline, while the bis-allylated product was also isolated in 3% yield (Table 3, entry 10). And these two product phenomena were also observed for compounds **2k**, **2l**, **2m**, **2n**, and **2o** under condition A, and the minor bis-allylated products were not isolated.

These results show that electron-poor anilines tend to undergo mono-substitution exclusively, while the electron-rich substrate is more active toward allylation, making it difficult to avoid some bis-substitution. Despite this, we found the following conditions optimal for the mono-N-allylation of electron-rich anilines: 600 W power MW irradiation at 70 °C in mixed acetonitrile/water (8/1) solvent and a 1:2 ratio of 2-iodoaniline to allyl bromide. This is designated as condition C (Table 3, entry 11).[13] For all the electron-rich anilines tested, good conversions and selectivities were achieved in the absence of both base and a PTC (Table 3, entries 12–15). Aniline itself also reacted smoothly under condition C, to give a 93% isolated yield of *N*-allylaniline (Table 3, entry 16).

Bis-allylation of various substituted anilines was achieved in the presence of Na_2CO_3 and CTAB (condition B), and the results are shown in Table 4. Both electron-poor and electron-rich anilines displayed high conversions and selectivities, with the yields of tertiary anilines being up to 97%. Regardless of the position of the halogen atoms in the anilines, or a strong electron-withdrawing group trifluoromethyl as a substituent group, the bis-allylation proceeded smoothly to give excellent results (Table 4, entries 1–7). Only **3h**, which contains two halogens at the *ortho*- and *para*-positions, showed lower conversion, but the selectivity for

Table 4
Synthesis of various substituted bis-allylations of anilines[a]



Entry	X	R_1	R_2	Product	Conversion	Yield[b] (%)
1	I	H	H	**4a**	95	90
2	Cl	H	H	**4b**	90	87
3	Br	H	H	**4c**	90	85
4	H	H	Br	**4d**	100	95
5	H	F	H	**4e**	100	97
6	H	H	CF_3	**4f**	100	96
7	H	I	CH_3	**4g**	100	95
8	I	H	Cl	**4h**	79	75
9	H	H	H	**4i**	100	96
10	OCH_3	H	H	**4j**	100	94
11	H	H	OCH_3	**4k**	100	95
12	H	H	CH_3	**4l**	100	94
13	H	H	$CH(CH_3)_2$	**4m**	100	96

[a] All the reactions were carried out with condition B.
[b] Yield of the isolated product after chromatography.

bis-allylation was still noteworthy (Table 4, entry 8). Aniline reacted to give *N*,*N*-diallylaniline in a yield of 96% under condition B (Table 4, entry 9), while electron-rich anilines were converted almost quantitatively into the target tertiary aniline products (Table 4, entries 10–13).

In summary, we have reported an efficient and highly selective method for the allylation of anilines. Most reactions gave high yields and selectivities in a short period of time. A large range of secondary and tertiary aniline compounds with a series of different substituents were prepared under simple conditions using microwave irradiation. The expansion of this method toward the total synthesis of some bioactive molecules and the studies of some other allylation reactions under MW conditions are currently underway in our laboratory.

Acknowledgments

We gratefully acknowledge the funding support received for this project from the National Natural Science Foundation of China (21272272) and the Young Scholar Foundation of the Fourth Military Medical University.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.044.

References and notes

1. (a) Matthew, S. T.; Sames, D.; Halim, M. *J. Am. Chem. Soc.* **2007**, *129*, 7570; (b) Diana, K. Hunt; Roger, B. C.; He, M. S.; Achorn, C.; Chen, C.-L.; Deng, Y. H. *J. Med. Chem.* **2012**, *55*, 606; (c) He, W.; Yang, D.; Yip, K.-T.; Zhu, N.-Y. *Org. Lett.* **2009**, *11*, 5626; (d) Kushida, Y.; Nagano, T.; Hanaoka, K.; Komatsu, T.; Terai, T.; Ueno, T.; Yoshida, K.; Uchiyama, M. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3908.
2. (a) Ye, K.-Y.; You, S.-L.; Dai, L.-X. *Org. Biomol. Chem.* **2012**, *10*, 5932; (b) Narayana, V. V.; Ramachary, D. B. *Eur. J. Org. Chem.* **2011**, 3514; (c) Ghosh, D.; Chattopadhyay, S. K.; Thander, L.; Ghosh, S. K. *Synlett* **2008**, *19*, 3011; (d) Schultz, D. M.; Wolfe, J. P. *Org. lett.* **2010**, *12*, 1028; (e) Fang, X. Q.; Li, C. Z.; Liu, K. *J. Am. Chem. Soc.* **2010**, *132*, 2274; (f) London, C.; Hoyt, S. B.; Park, M. *Tetrahedron Lett.* **2009**, *50*, 1911.
3. (a) Correa, A.; Tellitu, I.; Dominguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 8316; (b) Moon, H.-S.; Jeong, J.-H.; Shen, L.-L.; Choi, Y.-S. WO 201196729, 2011; (c) Barrow, D. A.; Batoul, A-O.; Wirth, T. *Arkivoc* **2011**, *2011*, 26; (d) Krehl, S.; Bernd, S.; Eric, J. *Org. Biomol. Chem.* **2012**, *10*, 5119; (e) Vaillard, S. E.; Rossi, R. A.; Postigo, Al *J. Org. Chem.* **2002**, *67*, 8500.

4. (a) Fryhle, C. B.; Solomons, T. W. G. *Organic Chemistry*; John Wiley & Sons Inc: New York, 2004. pp. 954; (b) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; John Wiley & Sons Inc: New York, 1992. pp. 411.
5. (a) Li, L.; Jones, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 10707; (b) Harring, L. S.; Molander, G. A. *J. Org. Chem.* **1990**, *55*, 6171; (c) Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797; (d) Carson, M. W.; Bailey, W. F. *J. Org. Chem.* **1998**, *63*, 9960; (e) Yoo, E. J.; Chang, S. *Org. Lett.* **2008**, *10*, 1163; (f) Sanchez, I.; Pujol, M. D. *Synthesis* **2006**, *11*, 1823; (g) Reada, M. L.; Gundersen, L.-L.; Krappb, A.; Miranda, P. O. *Tetrahedron* **2012**, *68*, 1869; (h) Rosa, O.; Miguel, Y.; Fernando, F. H. *Tetrahedron* **2003**, *59*, 8525.
6. Paul, S.; Basu, B.; Nanda, A. K. *Green Chem.* **2009**, *11*, 1115.
7. (a) Kimura, M.; Tamaru, Y.; Futamata, M.; Shibata, K. *Chem. Commun.* **2003**, 234; (b) Sawadjoon, S.; Samec, J. S. M. *Org. Biomol. Chem.* **2011**, *9*, 2548; (c) Chung, W.-H.; Yang, S.-C. *Indian J. Chem.* **1999**, *38B*, 897; (d) Okamoto, H.; Ozawa, F.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968; (e) Beck, H. P.; Weinrich, M. L. *Tetrahedron Lett.* **2009**, *50*, 6968; (f) Takagi, N.; Yokoyama, Y.; Hikawa, H., et al *Adv. Synth. Catal.* **2007**, *349*, 662.
8. Mashima, K.; Ohshima, T.; Utsunomiya, M.; Miyamoto, Y.; Ipposhi, J. *Org. Lett.* **2007**, *9*, 3371.
9. (a) Shore, G.; Organ, M. G. *Chem. Commun.* **2008**, 838; (b) De la Hoz, A.; Díaz-Ortiz, A.; Moreno, A. *Curr. Org. Chem.* **2004**, *8*, 903; (c) De la Hoz, A.; Díaz-Ortiz, A.; Moreno, A. *Adv. Org. Synth.* **2005**, *1*, 119; (d) Gabriel, S.; Gabriel, C.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213; (e) Moberg, C.; Larhed, M.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717; (f) Varma, R. S. *Pure Appl. Chem.* **2001**, *73*, 193; (g) Varma, R. S. *Green Chem.* **1999**, *1*, 43.
10. Ju, Y. H.; Varma, R. S. *Green Chem.* **2004**, *6*, 219.

11. Tetrabutyl ammonium bromide, polyethylene glycol 400, polyethylene glycol 2000, and 18-Crown-6 were also screened, and they provided lower conversion than CTAB.
12. *General procedure for the preparation of compound **2a–j**:* Aniline 1 (0.5 mmol), H_2O (5 mL), KOH (1 mmol, 2 equiv), and the CTAB (0.05 mmol, 10% mmol) were added to the reaction vessel stirring for 5 min. Allyl bromide (1 mmol, 2 equiv) was added, while maintaining the temperature at 80 °C for 10 min under microwave irradiation (850 W). After completion of the reaction, the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography (petroleum ether/ethyl acetate) to afford *N*-allylaniline **2a–j**. Compounds **2f** and **2g** are new compounds. For a detailed description of spectroscopic characterization of compounds see Supplementary data.
13. *General procedure for the preparation of compound **2i–o**:* Aniline 1 (0.5 mmol) was dissolved in mixed acetonitrile/water (8/1) solvent (5 mL). Allyl bromide (1 mmol, 2 equiv) was added, while maintaining the temperature at 70 °C for 10 min under microwave irradiation (600 W). After completion of the reaction, the acetonitrile was evaporated. The following procedures were similar with general procedure for the preparation of compound **2a–j**.
*General procedure for the preparation of compound **4a–4m**:* The aniline 3 (0.5 mmol) was dissolved in DMF (3 mL) in a reaction flask. Na_2CO_3 (2 equiv, 1 mmol) and CTAB (10% mmol) were subsequently added, and the solution was stirred for 5 min. After allyl bromide (4 equiv, 2 mmol) was added, the reaction mixture was exposed to MW irradiation at 130 °C for 10 min. Following, 2 equiv of allyl bromide were added to the reaction mixture solvent for another 10 min under MW irradiation (850 W). After the solution was cooled to ambient temperature, CH_2Cl_2 (20 ml) was added, the solution was washed with water (3 × 20 ml). The organic layer was separated, washed with brine (20 mL), dried over Na_2SO_4, and evaporated. The residue was purified by column chromatography (petroleum ether/ethyl acetate) to afford *N*,*N*-diallylaniline **4a–m**. Compound **4g** is a new compound. For a detailed description of spectroscopic characterization of compounds see Supplementary data.