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MICROWAVE-ASSISTED APPROACH TO NITROANILINE/AMINOPYRIDINE AND ITS INHIBITION ACTIVITY OF SEED GERMINATION

Zhi-you Huang,^{1*} Wen-sheng Li,² Bo He,³ Ning Zhang,¹ Zi-Ying Guo,¹
Xiao-Hong Li,¹ and Xian-Jun Yang¹

¹ College of Urban and Rural Construction, Shaoyang University, Shaoyang, 422000, P.R.China; ² Shaoyang City Sixteen middle School, Shaoyang, 422000, P.R.China; ³ Key Laboratory of Integrated Management of Crop Disease and Pests, Ministry of Education, Nanjing Agricultural University, Nanjing, 210095, P.R.China. Email Address: huangzhiyou@syxy247.wecom.work (Zhi-You Huang).

Abstract – An efficient approach to nitroaniline/aminopyridine was developed under microwave irradiation. The sulphamide and halogenated nitrobenzene/pyridine were used as starting materials. With low consumption, environment friendly, gram-scale synthesis, good substrate scope and excellent product yields, this methodology is superior to the existing approach. Additionally, these compounds **3a-3s** could inhibit soybean seed germination at the concentration of 50 μ M. Especially, the inhibition rate of compound **3m** was higher than 90%.

Nitroaniline/aminopyridine is popular in pesticide and pharmaceutical active molecules, such as fluridamine (fungicide),¹ bufluride (herbicide),² nitroaniline analogues (PMs, the molecule could enhance plant drought resistance) and the vinecola tablet (BCL2 inhibitor, treatment of lymphocytic leukemia) and CHIR98014 (GSK3 inhibitor, oral hypoglycemic drug).³⁻⁵ In addition, nitroaniline/aminopyridine is important intermediate and industrial chemical, which are widely used in the synthesis of (aza)benzimidazole derivatives,⁶ such as the flubenzimidazole (broad-spectrum anthelmintic agent),⁷ omeprazole (proton pump inhibitor),⁸ tetoprazole (higher activity than omeprazole),⁹ thimazole (dilation of blood vessels).¹⁰

Until now, the most common approaches to nitroaniline/aminopyridine are as follow: ① 7 equivalents of ammonia (**Scheme 1, 1a, 16h**),¹¹ or 20 equivalents of aqueous ammonia (**1b**, high temperature and pressure),¹² or 35-80 equivalents of aqueous ammonia were reacted with halogenated nitrobenzene (**1c**);¹³

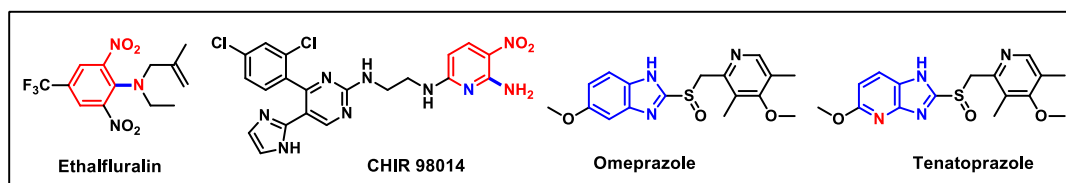
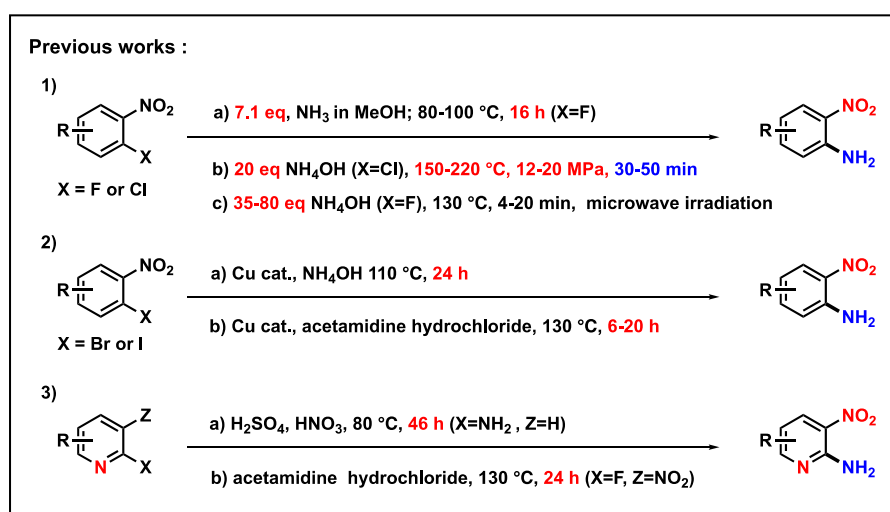


Figure 1. The nitroaniline/aminopyridine and arylimidazole derivatives

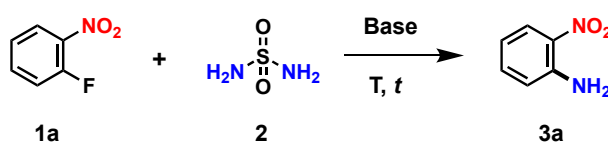
② Copper salt and 3 equivalents of aqueous ammonia (**2a**)¹⁴ or 1.2 equivalents of acetamide hydrochloride were used (**2b**);¹⁵ ③ Nitration of pyridine in the presence of mixed acid (**3a**) or the reaction of acetamide hydrochloride, NaOH and 2-fluoro-3-nitropyridine were carried at 130 °C for 24 h (**3b**).^{16,17} It is obvious that these methodologies (**1a-1c, 2a**) cost much amination agent. Especially, in the method **1c**, the greatly excessive aqueous ammonia could be decomposed to irritant NH₃ which was detrimental to skin, respiratory tract and brain nerve. What's worse, nitration of mixed acid could produce a large amount of waste acid (**3a**). Additionally, these methodologies (**1a, 2a, 2b, 3a, 3b**) took a long time. Thus, it is extremely urgent to develop a method with low consumption, environment friendly, good substrate scope and simple operation. In our previous works, the microwave radiation was used to synthesize the abscisic acid analogues with high efficiency and yield.^{3,18,19} Herein, we report a low-consumed and environment friendly microwave-assisted approach to nitroaniline/aminopyridine with excellent yields and broad substrate scope. Significantly, the inhibition rate of compound **3m** on soybean seed germination was higher than 90%.



Scheme 1. Selected methods to synthesize nitroaniline/aminopyridine

Although the conversion of halogenated nitrobenzene to nitroaniline/aminopyridine is known, it is still great challenge to find the optimum conditions to perform microwave-assisted approach which the sulphamide was used. For our initial researches, the reaction of 1-fluoro-2-nitrobenzene (**1a**) and sulphamide (**2**) in the presence of K_2CO_3 under microwave irradiation was chosen as a benchmark reaction (**Table 1**). To our surprise, 35% of **3a** was obtained with a temperature of 100 °C in 10 minutes (**Table 1, entry 1**). While, the starting material **1a** was remained. Therefore, in order to improve the yield, the reaction temperature was enhanced. Thus, the yield of **3a** was increased with an increase of temperature (**Entries 1-5**). Also, the ratio of **2** to **1a** is 1.3:1, which gave the better result (**Entries 4, 6-9**).

Table 1. The optimization microwave-assisted approach^a



Entry	$T / (^\circ\text{C})$	n (1a) : n (2)	t / (min)	Base	Solvent	Yield (3a) / % ^b
1	100	1 : 1	10	K_2CO_3 (3.0 eq)	DMF	35
2	110	1 : 1	10	K_2CO_3 (3.0 eq)	DMF	46
3	120	1 : 1	10	K_2CO_3 (3.0 eq)	DMF	64
4	130	1 : 1	10	K_2CO_3 (3.0 eq)	DMF	73
5	140	1 : 1	10	K_2CO_3 (3.0 eq)	DMF	73
6	130	1 : 1.1	10	K_2CO_3 (3.0 eq)	DMF	79
7	130	1 : 1.2	10	K_2CO_3 (3.0 eq)	DMF	85
8	130	1 : 1.3	10	K_2CO_3 (3.0 eq)	DMF	91
9	130	1 : 1.5	10	K_2CO_3 (3.0 eq)	DMF	91
10	130	1 : 1.3	15	K_2CO_3 (3.0 eq)	DMF	94
11	130	1 : 1.3	20	K_2CO_3 (3.0 eq)	DMF	94
12	130	1 : 1.3	15	K_3PO_4 (3.0 eq)	DMF	73
13	130	1 : 1.3	15	Na_2CO_3 (3.0 eq)	DMF	81
14	130	1 : 1.3	15	CS_2CO_3 (3.0 eq)	DMF	86
15	130	1 : 1.3	15	K_2CO_3 (2.8 eq)	DMF	94
16	130	1 : 1.3	15	K_2CO_3 (2.5 eq)	DMF	94
17	130	1 : 1.3	15	K_2CO_3 (2.0 eq)	DMF	84
18	130	1 : 1.3	15	K_2CO_3 (2.5 eq)	DMAc	89
19	130	1 : 1.3	15	K_2CO_3 (2.5 eq)	1,4-dioxane	82
20 ^c	130	1 : 1.3	120	K_2CO_3 (2.5 eq)	DMF	72
21 ^d	130	1 : 1.3	15	K_2CO_3 (2.5 eq)	DMF	0

^a Reaction conditions : **1a** 1.0 mmol, solvent 6.0 mL; ^b Isolated yield. ^c Conventional heating; ^dAmination agent was urea.

Then, prolonging the reaction time to 15 and 20 minutes could give the higher yield (**Entries 8, 10, 11**). Furthermore, the effect of bases was explored, and 2.5 equivalents of K_2CO_3 was identified as the best one (**Entries 10, 12-17**). Finally, the different solvents were screened, among these solvents, DMF was the most suitable (**Entries 16, 18, 19**). Compared with conventional heating method (**Entry 20**), microwave irradiation could significantly accelerate the reaction and notably improve the yield. Additionally, **3a** could not be obtained when the sulphamide was replaced with urea (**Entry 21**). As a result, the combination of 1.0 mmol **1a**, 1.3 mmol **2** and 2.5 mmol K_2CO_3 in DMF with a temperature of 130 °C in 15 minutes was fixed (**Entry 16**), as optimal conditions.

Once the optimized reaction conditions were identified, the limitations and scope of the microwave-assisted approach were examined. Various halogenated nitrobenzene/pyridine were explored, the results were shown in **Table 2**. The reaction between **1a-1m** ($X = F$) and **2** always went smoothly. Both electron-withdrawing and electron-donating groups, such as 4-trifluoromethyl (**3f**), 4-cyano (**3g**), 4-methoxycarbonyl (**3h**), 4-nitro (**3i**) and 4-methyl (**3b**), 4-halogen (**3c-3e**) afforded the desired products in excellent yields. In addition, 5- and 6-substituted nitroanilines also afforded **3j-3m**.

Table 2. Microwave-assisted reaction of **1** and **2**^a

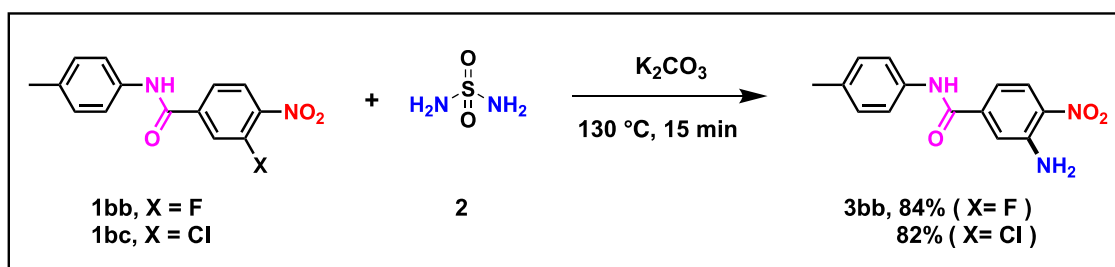
1a-1s ($X = F$) ^b	2					
1aa-1as ($X = Cl$) ^c	3a-3s ($Y = CH, N$)					
3a, 94% ^b , 91% ^c	3b, 91% ^b , 88% ^c	3c, 89% ^b , 86% ^c	3d, 91% ^b , 87% ^c	3e, 91% ^b , 87% ^c	3f, 91% ^b , 90% ^c	
3g, 91% ^b , 90% ^c	3h, 89% ^b , 88% ^c	3i, 90% ^b , 90% ^c	3j, 89% ^b , 84% ^c	3k, 90% ^b	3l, 91% ^b , 90% ^c	3m, 90% ^b , 89% ^c
3n, 93% ^b , 90% ^c	3o, 90% ^b , 88% ^c	3p, 93% ^b , 92% ^c	3q, 92% ^b , 89% ^c	3r, 91% ^b , 88% ^c	3s, 91% ^b , 87% ^c	

^a Reaction conditions : **1a-1s** 1.0 mmol, **2** 1.3 mmol, K_2CO_3 2.5 mmol, solvent 6.0 mL; Isolated yield;

^b $X = F$; ^c $X = Cl$.

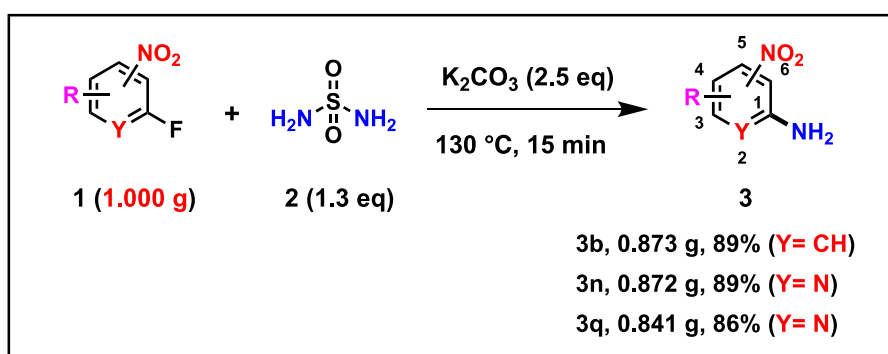
To increase the scope of microwave-assisted method, the reaction of fluoro-nitropyridine (**1n-1s**) and **2** was tested. The yields of **3n-3s** were higher than 90%. Furthermore, it was obvious that the reaction of chlorinated nitrobenzene/pyridine (X= Cl) and **2** could produce the target compounds in good to excellent yields (**Table 2**).

Notably, the reaction of **1bb**, **1bc** and **2** could give **3bb** in good yields (**Scheme 2**).



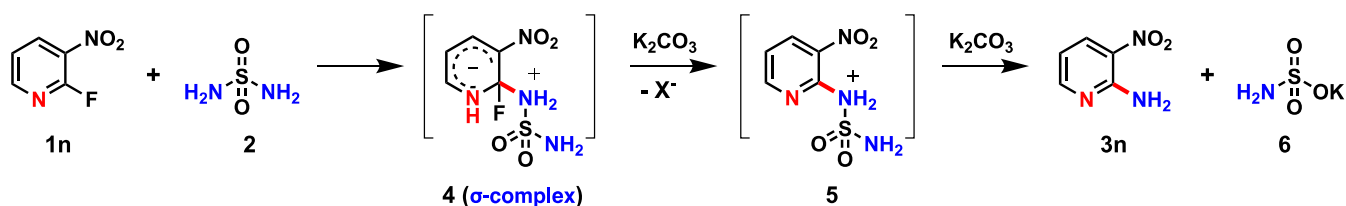
Scheme 2. Synthesis of **3bb**

To fully demonstrate the applicability of this methodology, a scale-up reaction for **1b**, **1n**, **1q** and **2** (sulphamide) were carried out. The yields were higher than 85% (**Scheme 3**).



Scheme 3. Gram-scale synthesis

More importantly, the reaction mechanism to **3n** was shown in **Scheme 4**. The intermediate **5** was obtained through nucleophilic aromatic substitution ($\text{S}_{\text{N}}\text{Ar}$) reaction. Then, potassium sulfamate (**6**) was released in the presence of K_2CO_3 to obtain target compound **3n**.^{3, 20, 21}



Scheme 4. Proposed reaction mechanism

Finally, the effect of **3a-3s** on soybean seed germination was determined (**Table 3**). The inhibition activity of **3d**, **3g**, **3i**, **3m**, **3q-3s** were higher than 60%. Especially, the **3m** could significantly inhibited seed germination like to plant hormone abscisic acid (ABA).²²

Table 3. The inhibition activity of **3a-3s** on soybean seed germination (%)

Comp		50 μ M		Comp		50 μ M	
ound	Inhibition rate	Germination rate	ound	Inhibition rate	Germination rate	ound	Inhibition rate
3a	48.9 \pm 3.8	25.6 \pm 1.9	3l	44.4 \pm 3.8	27.8 \pm 1.9		
3b	57.8 \pm 3.8	21.1 \pm 1.9	3m	91.1\pm3.8	4.4 \pm 1.9		
3c	44.4 \pm 3.8	27.8 \pm 1.9	3n	57.8 \pm 3.8	21.1 \pm 1.9		
3d	62.2\pm3.8	18.9 \pm 1.9	3o	51.1 \pm 3.8	24.4 \pm 1.9		
3e	53.3 \pm 6.7	23.3 \pm 3.3	3p	53.3 \pm 0.0	23.3 \pm 0.0		
3f	51.1 \pm 3.8	24.4 \pm 1.9	3q	64.4\pm3.8	17.8 \pm 1.9		
3g	66.7\pm6.7	16.7 \pm 3.3	3r	66.7\pm6.7	16.7 \pm 3.3		
3h	53.3 \pm 6.7	23.3 \pm 3.3	3s	60.0\pm6.7	20.0 \pm 3.3		
3i	66.7\pm6.7	16.7 \pm 3.3	ABA	100.0 \pm 0.0	0.0 \pm 0.0		
3j	26.7 \pm 6.7	36.7 \pm 3.3	CK	50.0 \pm 3.3			
3k	40.0 \pm 0.0	30 \pm 0.0					

In summary, we have reported a microwave-assisted approach to nitroaniline/aminopyridine. With low consumption, environment friendly, gram-scale synthesis, good substrate scope and excellent product yields, this methodology is superior to the existing approach. Additionally, the target compounds **3a-3s** could inhibit soybean seed germination at the concentration of 50 μ M. Furthermore, the inhibition rate of **3d**, **3g**, **3i**, **3m**, **3q-3s** on soybean seed germination was more than 60%. Especially, the inhibition rate of compound **3m** was higher than 90%.

SUPPORTING INFORMATION

Supplementary (synthesis of the target molecule, ¹H and ¹³C NMR spectra, etc.) data associated with this article can be found, in the online version, at URL: <https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27667/104/8>

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REFERENCES

1. J. M. Arjona-Lopez, S. Tienda, I. Arjona-Girona, F. M. Cazorla, and C. Lopez-Herrera, *Biol. Control.*, 2019, **136**, 103996.
2. J. F. Serrano, E. Ruiz, P. Hellin, A. Lacasa, and P. Flores, *J. Agric. Food Chem.*, 2010, **58**, 2433.
3. Z. Y. Huang, M. Liu, Y. J. Mao, Y. D. Chen, Y. P. Wang, and C. Liu, *Tetrahedron Lett.*, 2019, **60**, 626.
4. D. A. DeGoey, H. J. Chen, P. B. Cox, and M. D. Wendt, *J. Med. Chem.*, 2018, **61**, 2636.
5. A. S. Wagman, R. S. Boyce, S. P. Brown, E. Fang, D. Goff, J. M. Jansen, V. P. Le, B. H. Levine, S. C. Ng, Z. J. Ni, J. M. Nuss, K. B. Pfister, S. Ramurthy, P. A. Renhowe, D. B. Ring, W. Shu, S. Subramanian, X. H. A. Zhou, C. M. Shafer, S. D. Harrison, K. W. Johnson, and D. E. Bussiere, *J. Med. Chem.*, 2017, **60**, 8482.
6. X. Liu, L. L. Su, Z. X. Zhou, L. P. Niu, L. G. Gao, H. H. Ju, F. X. Li, X. L. Li, and H. Chen, *Chin. J. Org. Chem.*, 2021, **41**, 2861.
7. Y. Y. Guo, X. J. Chen, S. W. Li, Z. H. Cai, and L. He, *Chin. J. Org. Chem.*, 2021, **41**, 3692.
8. L. M. Khachigian, *Cancer Lett.*, 2021, **522**, 57.
9. Q. Chi, Z. Q. Lv, and W. Song, *J. Trop. J. Pharm. Res.*, 2021, **20**, 2143.
10. T. K. Le, G. S. Cha, H. H. Jang, T. H. Nguyen, T. T. M. Doan, Y. J. Lee, K. D. Park, Y. Shin, D. H. Kim, and C. H. Yun, *Process Biochem.*, 2019, **87**, 95.
11. W. J. Coates, B. Connolly, D. Dhanak, S. T. Flynn, and A. Worby, *J. Med. Chem.*, 1993, **36**, 1387.
12. D. B. Yang and Z. M. Wang, CN 1693301A (Published Application Number), 2005 (in Chinese).
13. N. McConnell, B. Frett, and H. Li, *Green Chem. Lett. Rev.*, 2018, **11**, 286.
14. H. S. Jung, T. Yun, Y. Cho, and H. B. Jeon, *Tetrahedron*, 2016, **72**, 5988.
15. X. Huang, R. Xiao, C. R. You, T. Yan, and M. Z. Cai, *J. Chem. Res.*, 2017, **41**, 315.
16. S. X. Cai, J. C. Huang, S. A. Espitia, M. Tran, V. I. Ilyin, J. E. Hawkinson, R. M. Woodward, E. Weber, and J. F. W. Keana, *J. Med. Chem.*, 1997, **40**, 3679.
17. Y. B. Li, S. Huang, C. S. Liao, Y. Shao, and L. Chen, *Org. Biomol. Chem.*, 2018, **16**, 7564.
18. Z. Y. Huang, J. F. Yang, Q. Chen, R. J. Cao, W. Huang, G. F. Hao, and G. F. Yang, *RSC Adv.*, 2015, **5**, 75182.
19. Z. Y. Huang, J. F. Yang, K. Song, Q. Chen, S. L. Zhou, G. F. Hao, and G. F. Yang, *J. Org. Chem.*,

[2016, 81, 9647.](#)

20. R. G. David and J. G. Edward, *J. Chem. Soc., Chem. Commun.*, 1990, **12**, 881.
21. P. J. Ji, J. H. Atherton, and M. I. Page, [J. Org. Chem., 2011, 76, 3286.](#)
22. Z. Y. Huang, Z. Z. Li, B. He, W. S. Li, P. Yang, and L. J. Chen, *Chin. J. Org. Chem.*, 2022, (Doi: 10.6023/cjoc202201010).