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K_2CO_3/Ni(OAc)$_2$ 催化下的以苯甲酰胺和 *N*,*N*-二溴苯甲酰胺为氮溴源的胺溴化反应

陈 晟[1] 韩建林*,[1,2] 李桂根[2,3] 潘 毅*,[1,2]

([1]南京大学化学化工学院,配位化学国家重点实验室,南京 210093)

([2]南京大学化学与生物医学科学研究所,南京 210093)

([3]化学与生物化学系,德克萨斯理工大学,79409-1061,美国)

摘要:本文报道了一个高效的以苯甲酰胺和 *N*,*N*-二溴苯甲酰胺为氮溴源的胺溴化反应。这个反应有广泛的底物适应性、很好的产率及较高的非对映选择性。本文报道的胺溴化反应用金属无机盐和碱作为共同催化剂,与作者们以前报道的胺卤化反应不同。

关键词:胺溴化;苯甲酰胺;β-甲基-β-硝基苯乙烯

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K_2CO_3/Ni(OAc)$_2$ Catalyzed Aminobromination of β-Methyl-β-nitrostyrenes with Benzamide/*N*, *N*-Dibromobenzamide as Nitrogen/Bromine Source

CHEN Sheng[1] HAN Jian-Lin*,[1,2] LI Gui-Gen[2,3] PAN Yi*,[1,2]

([1]*School of Chemistry and Chemical Engineering, State Key Laboratory of Coordination, Nanjing University, Nanjing* 210093, *China*)

([2]*Institute for Chemistry & BioMedical Sciences, Nanjing University, Nanjing* 210093, *China*)

([3]*Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas* 79409-1061, *USA*)

Abstract: An efficient and facile aminobromination reaction of β-methyl-β-nitrostyrenes with $PhCONH_2$/$PhCONBr_2$ as nitrogen/bromine source has been developed, which could tolerate a wide scope of substrates with good chemical yield and diastereoselectivity. This aminobrominaiton system uses metal salt and base as the co-catalyst, which is different from our previous reported systems.

Key words: aminobromination; benzamide; β-methyl-β-nitrostyrenes; haloamines

0 Introduction

Aminohalogenation of functionalized olefins plays an important role among all the methodologies for the preparation of vicinal haloamines[1], because it can construct carbon-nitrogen and carbon-halogen bonds in tandem fashions at the same time[2-11]. The vicinal haloamines are also an important class of building blocks in organic and medicinal chemistry[12], as the halogen group can serve as a reactive functional group in substitution and coupling reactions, which have been demonstrated broad utility for the fine chemicals, synthetic intermediates and natural products[13-17]. In the past decade, great development has been made on

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*通讯联系人。E-mail:hanjl@nju.edu.cn,yipan@nju.edu.cn

aminohalogenation reaction due to the exploration of several functionalized alkenes, such as α,β-unsaturated carboxylic esters[18-19], α,β-unsaturated nitriles[20], α,β-unsaturated ketones [21-25] and so on [26-27]. Especially, β-nitrostyrenes were employed as a new class of substrates for aminohalogenation, which have many advantages, including facile reaction conditions, diversification of nitrogen source, opposite regiochemistry and dramatically shorter reaction time[28-39]. Also, the resulted vicinal nitro haloamine products can be easily converted into vicinal diamines[40-41].

Recently, several nitrogen sources, such as imide[31], amide[30] and carbamate[32-36] have been used for β-nitrostyrene, and dihalogenated nitro amino compounds were formed. Our previous reports have shown that the nitrogen/halogen sources have a great effect on the formation of the final products in these systems, especially when β-methyl-β-nitrostyrenes are used as alkenes substrates[39,42]. Furthermore, we can investigate the stereochemistry of aminohalogenation by using β-methyl-β-nitrostyrenes as substrates. So, it is essential to develope more efficient nitrogen source for aminohalogenation of β-methyl-β-nitrostyrenes.

Benzoyl is a useful group in synthetic and medicinal chemistry, especially with a halogen group on adjacent position, such as for the preparation of isoxazole, as well as for the synthesis of Pro-Drug[43-44]. So, using benzamide as nitrogen source for aminohalogenation of β-methyl-β-nitrostyrenes becomes very interesting and challenging. Herein, we report a new aminobromination reaction of β-methyl-β-nitrostyrenes with benzamide/*N*,*N*-dibromobenzamide as nitrogen/bromine source by using K_2CO_3/$Ni(OAc)_2$ as co-catalyst.

1 Experimental

1.1 General methods

Solvents were dried and distilled prior to use. Flash chromatography was performed on silica gel 60 (GF-254) TCL plates (20 cm×20 cm). Melting points were uncorrected. IR spectra were collected with a Bruker Vector 22 instrument (KBr pellets). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) (TMS was used as internal standard) were recorded on a 300 MHz spectrometer. HR-MS of the new compounds were measured with a Mariner TOF-ESI mass spectrometer

1.2 General procedure for aminobromination

To a dry round-bottomed vial was added β-methyl-β-nitrostyrenes **1** (0.5 mmol), $PhCONH_2$ **2** (121 mg, 1 mmol), $PhCONBr_2$ **3** (278 mg, 1 mmol), K_2CO_3 (13.8 mg, 0.1 mmol, 20mol%) and $Ni(OAc)_2$ (1.8 mg, 1mol%). Then 5 mL acetone was added into the vial. The mixture was electromagnetically stirred at room temperature for 48 h. The resulting solution was quenched with saturated Na_2SO_3 (3.0 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 ×20 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was removed to give the crude product, which was purified by preparative TLC plate.

N-2-bromo-2-nitro-1-phenylpropyl)benzamide **4a**. White solid (157 mg, 82% yield). m.p. 91~92 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88~7.91 (m, 2H), 7.59~7.52 (m, 4H), 7.38~7.27 (m, 5H), 5.95 (d, *J*=9.6 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 134.1, 133.6, 132.2, 129.4, 129.1, 128.1, 124.5, 120.5, 96.0, 61.1, 29.7 HR-MS [M+Na$^+$]: Calcd. for $C_{16}H_{15}BrN_2O_3Na$: 385.015 8, Found: 385.015 0. IR (KBr): 3 277, 2 849, 1 703, 1 634, 1 600, 1 559, 1 530, 1 446, 1 228, 1 104 cm^{-1}.

N-(2-bromo-1-(2-chlorophenyl)-2-nitropropyl)benzamide **4b**. White solid (165 mg, 79% yield). m.p.: 136~138 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13~8.15 (m, 1H), 7.90~7.93 (m, 2H), 7.54~7.49 (m, 5H), 7.31~7.25 (m, 2H), 6.54 (d, *J*=8.4 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 134.9, 133.4, 132.7, 130.5, 129.0, 128.8, 128.0, 127.2, 124.4, 120.5, 94.2, 57.1, 28.1. HR-MS [M+Na$^+$]: Calcd. for $C_{16}H_{14}BrClN_2O_3Na$: 418.976 9, Found: 418.976 8. IR (KBr): 3 273, 2 924, 1 701, 1 638, 1 557, 1 530, 1 477, 1 229, 1 100 cm^{-1}.

N-(2-bromo-1-(3-methoxyphenyl)-2-nitropropyl)benzamide **4c**. White solid (145 mg, 70% yield). m.p.: 60~62 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88~7.90 (m, 3H), 7.51~7.58 (m, 4H), 8.88~8.92 (m, 3H), 5.91 (d, *J*=9.0 Hz, 1H), 3.80 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 159.8, 135.5, 133.6, 132.2,

130.2, 128.8, 127.8, 127.2, 120.4, 114.2, 95.8, 61.1, 55.3, 29.7. HR-MS [M+Na$^+$]: Calcd. for $C_{17}H_{17}BrN_2O_4Na$: 415.0261, Found: 415.0264. IR (KBr): 3 261, 2 924, 1 703, 1 645, 1 602, 1 558, 1 446, 1 386, 1 075 cm^{-1}.

N-(2-bromo-1-(4-fluorophenyl)-2-nitropropyl)benzamide **4d**. White solid (157 mg, 78% yield). m.p.: 136~137 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95~7.81 (m, 3H), 7.62~7.50 (m, 4H), 7.32 (m, 1H), 7.07~7.04 (m, 2H), 5.94 (d, *J*=9.6 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 164.8, 161.4, 133.4, 132.3, 130.5, 129.0, 127.8, 127.2, 120.5, 116.3 (d, *J*= 22.5 Hz), 115.9, 115.6, 96.1, 60.4, 29.6. HR-MS [M+Na$^+$]: Calcd. for $C_{16}H_{14}BrFN_2O_3Na$: 403.006 4, Found: 403.008 4. IR (KBr): 3 246, 2 959, 1 701, 1 664, 1 603, 1 556, 1 386, 1 340, 1 301, 1 076 cm^{-1}.

N-(2-bromo-1-(4-cyanophenyl)-2-nitropropyl)benzamide **4e**. White solid (132 mg, 64% yield). m.p.: 139~141 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80~7.89 (m, 3H), 7.63~7.70 (m, 3H), 7.53~7.49 (m, 4H), 5.99 (d, *J*=9.0 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 138.4, 133.4, 129.5, 129.1, 127.2, 120.5, 117.9, 113.5, 102.1, 95.7, 60.8, 29.7. HR-MS [M+Na$^+$]: Calcd. for $C_{17}H_{14}BrN_3O_3Na$: 410.011 1, Found: 410.010 5. IR (KBr): 3 098, 2 922, 2 231, 1 670, 1 636, 1 564, 1 522, 1 332, 1 276, 1 230, 1 143 cm^{-1}.

N-(2-bromo-1-(4-chlorophenyl)-2-nitropropyl)benzamide **4f**. White solid (155 mg, 74% yield). m.p.: 147~149 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89~7.87 (m, 3H), 7.60~7.52 (m, 4H), 7.34~7.28 (m, 3H), 5.92 (d, *J*=9.6 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 135.5, 133.3, 132.7, 129.9, 129.5, 127.9, 127.2, 120.4, 95.9, 60.5, 29.5. HR-MS [M+Na$^+$]: Calcd. for $C_{16}H_{14}BrClN_2O_3Na$: 418.976 9, Found: 418.973 3. IR (KBr): 3 246, 2 945, 1 700, 1 663, 1 558, 1 446, 1 385, 1 343, 1 077 cm^{-1}.

N-(2-bromo-2-nitro-1-*p*-tolylpropyl)benzamide **4g**. White solid (134 mg, 67% yield). m.p.: 125~128 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91~7.87 (m, 3H), 7.58~7.49 (m, 4H), 7.19~7.16 (m, 3H), 5.90 (d, *J*=9.6 Hz, 1H), 2.34 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 139.4, 133.8, 132.1, 131.1, 129.4, 127.9, 127.2, 120.4, 96.2, 57.8, 28.8, 21.2 ppm. HR-MS [M+Na$^+$]: Calcd. for $C_{17}H_{17}BrN_2O_3Na$: 399.031 5, Found: 399.0314. IR (KBr): 3 244, 2 943, 1 664, 1 558, 1 509, 1 482, 1 273, 1 077 cm^{-1}.

N-(2-bromo-1-(4-bromophenyl)-2-nitropropyl)benzamide **4h**. White solid (164 mg, 71% yield). m.p.: 150~152 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89~7.87 (m, 2H), 7.80~7.48 (m, 6H), 7.29~7.19 (m, 2H), 5.91 (d, *J*=9.0 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 133.4, 132.3, 128.9, 127.8, 127.2, 124.4, 123.7, 120.5, 95.8, 60.6, 29.5. HR-MS [M+Na$^+$]: Calcd. for $C_{16}H_{14}Br_2N_2O_3Na$: 462.926 3, Found: 462.928 6. IR (KBr): 2 945, 1 664, 1 600, 1 509, 1 482, 1 307, 1 076, 1 009 cm^{-1}.

N-(2-bromo-2-nitro-1-(4-nitrophenyl)propyl)benzamide **4i**. White solid (120 mg, 56% yield). m.p.: 123~124 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26~8.22 (m, 2H), 7.98~7.87 (m, 3H), 7.82~7.51 (m, 5H), 6.02 (d, *J*=9.0 Hz, 1H), 2.36 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 148.4, 141.2, 132.8, 129.8, 129.4, 127.8, 127.2, 123.8, 120.4, 95.7, 60.6, 29.8. HR-MS [M+Na$^+$]: Calcd. for $C_{16}H_{14}BrN_3O_5Na$: 430.000 9, Found: 430.000 6. IR (KBr): 3 172, 2 924, 1 660, 1 625, 1 578, 1 143, 1 026 cm^{-1}.

N-(2-bromo-1-(2, 3-dichlorophenyl)-2-nitropropyl) benzamide **4j**. White solid (170 mg, 75% yiled). m.p.: 154~156 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92~7.89 (m, 2H), 7.60~7.47 (m, 5H), 7.18~7.12 (m, 2H), 6.58 (d, *J*=8.4 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 135.2, 133.4, 131.4, 129.0, 128.9, 128.2, 127.5, 125.7, 124.5, 120.5, 93.8, 57.9, 29.2. HR-MS [M+Na$^+$]: Calcd. for $C_{16}H_{13}BrCl_2N_2O_3Na$: 452.937 9, Found: 452.939 4. IR (KBr): 3 261, 2 924, 1 700, 1 640, 1 559, 1 528, 1 181, 1 102 cm^{-1}.

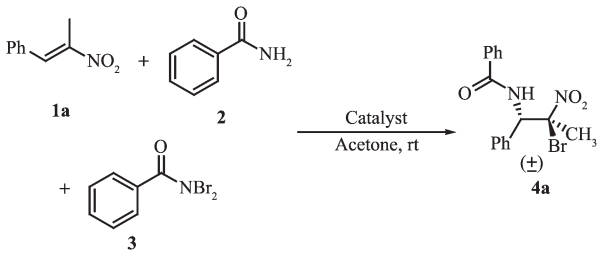
N-(2-bromo-1-(3-bromo-4-fluorophenyl)-2-nitropropyl)benzamide **4k**. White solid (149 mg, 62% yield). m.p.: 96~99 ℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90~7.87 (m, 3H), 7.60~7.52 (m, 5H), 7.28~7.09 (m, 1H), 5.88 (d, *J*=9.3 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 161.2, 157.8, 133.7, 133.5, 133.1, 132.7, 131.8, 129.5, 129.0, 127.3, 117.2 (d, *J*=22.5 Hz), 110.0, 95.6, 60.0, 30.4. HR-MS [M+Na$^+$]: Calcd. for $C_{16}H_{13}Br_2FN_2O_3Na$: 482.915 0, Found: 482.915 3. IR (KBr): 2 934, 1 665, 1 509, 1 481, 1 445, 1 248, 1 129, cm^{-1}.

2 Results and discussion

Initially, we chose NBS as model bromine source for the aminobromination of β-methyl-β-nitrostyrene and benzamide catalyzed by K_2CO_3 with CH_2Cl_2 as solvent. However, no desired product was obtained, even the reaction time was extended to 72 h. Then the combination of benzamide/*N*,*N*-dibromobenzamide was tried for this aminobromination (Table 1). No reaction was observed without any catalyst (entry 1). Then, a variety of inorganic bases, such as K_2CO_3, Na_2CO_3, KOH and K_3PO_4 were utilized as the catalyst for this reaction. However, no reaction was found for all these catalysts (entries 2~5). Metal catalyst also could not catalyze the reaction to form the desired bromoamine products (entries 6~8). After many trials, we found the reaction could give the desired product with 30% yield if the reaction is catalyzed by the combination of K_2CO_3/$MnSO_4$ (entry 9). To improve the yield, other metal salts with K_2CO_3 were examined (entries 10 and 11). Higher yield was obtained in the binary catalyst system consisted of K_2CO_3 and $Ni(OAc)_2$ (82%, entry 11). Three other bases were also investigated in the presence of $Ni(OAc)_2$, but no improvement was found (entries 12~14). Finally, the similar chemical yield was found when the loading amount of $Ni(OAc)_2$ was increased to 5mol% (entry 15). Organic base, like triethylamine was tried as catalyst with $Ni(OAc)_2$, however, no desired product was observed (entry 16).

Then, the reaction conditions were further optimized. As shown in Table 2, no desired products were observed when methanol or toluene was used as solvent (entries 5 and 6). The best solvent for the reaction was acetone, giving the corresponding product with the highest yield (82%, entry 1). The reaction with CH_2Cl_2, $CHCl_3$, acetonitrile or THF as solvent almost could not proceed, and only trace amount of haloamine products were detected (entries

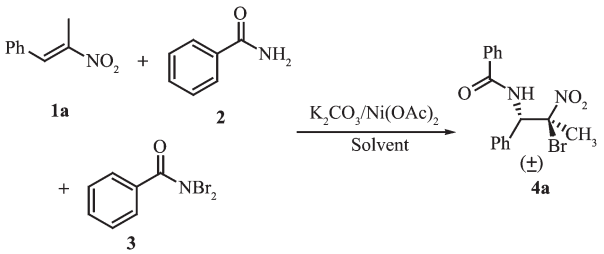
Table 1 Optimization of catalysts[a]



Entry	Catalyst / mol%	Time / h	Yield / %[b]
1	No	72	NR
2	K_2CO_3 (20)	72	NR
3	Na_2CO_3 (20)	72	NR
4	KOH (20)	72	NR
5	K_3PO_4 (20)	72	NR
6	$Ni(OAc)_2$ (20)	72	NR
7	$MnSO_4$ (10)	72	NR
8	CuCl (10)	72	NR
9	K_2CO_3 (20)/$MnSO_4$ (1)	48	30
10	K_2CO_3 (20)/CuCl (1)	48	22
11	K_2CO_3 (20)/$Ni(OAc)_2$ (1)	48	82
12	Na_2CO_3 (20)/$Ni(OAc)_2$ (1)	48	49
13	KOH (20)/$Ni(OAc)_2$ (1)	48	NR
14	K_3PO_4 (20)/$Ni(OAc)_2$ (1)	48	<10
15	K_2CO_3 (20)/$Ni(OAc)_2$ (5)	48	80
16	Et_3N (20)/$Ni(OAc)_2$ (1)	48	NR

[a] Reaction conditions: **1a** (0.5 mmol), **2** (1 mmol), **3** (1 mmol), in acetone (5 mL), at room temperature; [b] Isolated yield.

Table 2　Optimization of reaction conditions[a]



Entry	Solvent	Time / h	*T* / ℃	Yield / %[b]
1	Acetone	48	rt	82
2	CH_2Cl_2	48	rt	<10
3	$CHCl_3$	48	rt	<10
4	Acetonitrile	48	rt	<10
5	Toluene	48	rt	NR
6	MeOH	48	rt	NR
7	THF	48	rt	<10
8	Acetone	72	rt	83
9	Acetone	24	rt	55
10	Acetone	48	40	77
11	H_{20}	48	rt	NR

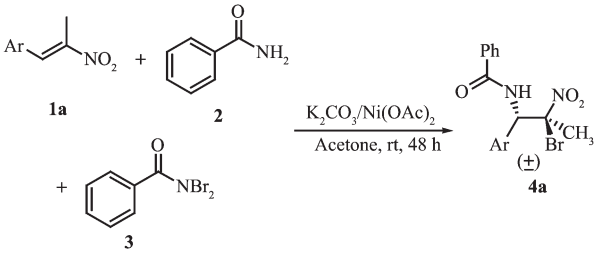
[a] Reaction conditions: **1a** (0.5 mmol), **2** (1 mmol), **3** (1 mmol), in solvent (5 mL) catalyzed by K_2CO_3 (20 mol%)/Ni(OAc)$_2$ (1mol%);
[b] Isolated yield.

2~4 and 7). Water was also tried as solvent for the reaction, but no reaction was observed. The reaction time also showed effects on the chemical yields. A dramatic lower chemical yield was obtained when the reaction was stopped at 24 h (55% yield, entry 9), although no better yield was obtained when the reaction time was extended to 72 h (entry 8). Increasing the temperature to 40 ℃ also gave no improvement on the yield (entry 10).

Then, several α, β-unsaturated nitro compounds were subjected to this reaction to examine the scope and limitation of the current aminobromination reaction (Table 3). As shown in Table 3, a wide scope of α, β-unsaturated nitro compounds worked well in the reaction, and proceeded completely within 48 h giving 56%~82% chemical yield. The electronegativity of the substituents on the aromatic rings showed almost no effects on the chemical yield. Both electron-rich (entries 3 and 7) and electron-deficient substrates (entries 2, 4~6 and 8~9) could participate well in the reaction, even for methoxy (entry 3) and fluoro (entry 4) groups. Notably, substrates with two substituent groups on aromatic ring were also well tolerated in this reaction (entries 10 and 11). These substrates showed moderate to good stereoselectivities, with ratios ranging from 3∶1 to 8∶1. Furthermore, only one regioisomer was observed for each of these cases.

According to the regio- and stereochemistry of the reaction and previous reports, a Michael addition pathway is proposed in Scheme 1 for this K_2CO_3/Ni(OAc)$_2$ catalyzed aminobromination reaction. In the initial step, *N*,*N*-dibromobenzamide reacts with benzamide forming the intermediate A, which undergoes deprotonation by K_3CO_3 and results in intermediate B. Here, the nucleophile B cannot add directly to nitrostyrene comparing to our previous reports[34-35]. This Michael addition needs the promotion of the catalyst Ni(OAc)$_2$, and gives the intermediate D. Then, the Br^+ ion migrates from N-Br of amide to the negative center to form intermediate E. The intermediate E obtains a proton from HCO_3^-, giving the final product **4a** and the catalyst CO_3^{2-}. In the proposed mechanism, one catalyst K_2CO_3 is used for deprotonation of nitrogen source, and the other catalyst Ni(OAc)$_2$

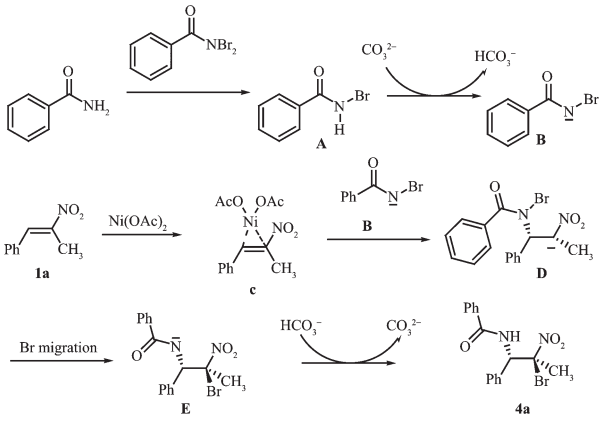
Table 3 Aminobromination of various β-methyl-β-nitrostyrenes derivatives[a]



Entry	Ar	Product	Yield / %[b]	Stereoselectivity (*anti*:*syn*)[c]
1	C_6H_5	**4a**	82	7:1
2	2-ClC_6H_4	**4b**	79	3:1
3	3-$MeOC_6H_4$	**4c**	70	7:1
4	4-FC_6H_4	**4d**	78	8:1
5	4-CNC_6H_4	**4e**	64	4:1
6	4-ClC_6H_4	**4f**	74	7:1
7	4-MeC_6H_4	**4g**	67	8:1
8	4-BrC_6H_4	**4h**	71	6:1
9	4-$NO_2C_6H_4$	**4i**	56	7:1
10	2,3-di-ClC_6H_3	**4j**	75	5:1
11	3-Br,4-FC_6H_3	**4k**	62	6:1

[a] Reaction conditions: **1** (0.5 mmol), **2** (1 mmol), **3** (1 mmol), in acetone (5 mL) catalyzed by K_2CO_3 (20mol%)/$Ni(OAc)_2$ (1mol%), at room temperature for 48 h; [b] Isolated yield; [c] Determined by ^1H NMR.

is used for the activation of nitrostyrene, which is different from the previous aminohalogenation reactions of nitrostyrenes[34-35].



Scheme 1 Michael addition pathway for the K_2CO_3/$Ni(OAc)_2$ catalyzed aminobromination reaction

3 Conclusions

In summary, we have developed a new aminobromination reaction of β-methyl-β-nitrostyrenes with benzamide/*N*,*N*-dibromobenzamide as nitrogen/bromine source, which needs K_2CO_3/$Ni(OAc)_2$ as the co-catalyst. This facile and efficient system tolerates a broad range of substrates, giving moderate to good yield and high regio- and stereoselectivity. Further study on aminobromination of this nitrogen source is focused on the asymmetric catalyst.

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