HETEROCYCLES, Vol. 65, No. 9, 2005, pp. 2071 - 2081
Received, 23rd May, 2005, Accepted, 25th July, 2005, Published online, 2nd August, 2005

NUCLEOPHILIC SUBSTITUTION REACTION OF AMINES WITH 3-BROMO-4-NITROPYRIDINE (AND 2-NITROPYRIDINE): A NEW NITRO-GROUP MIGRATION

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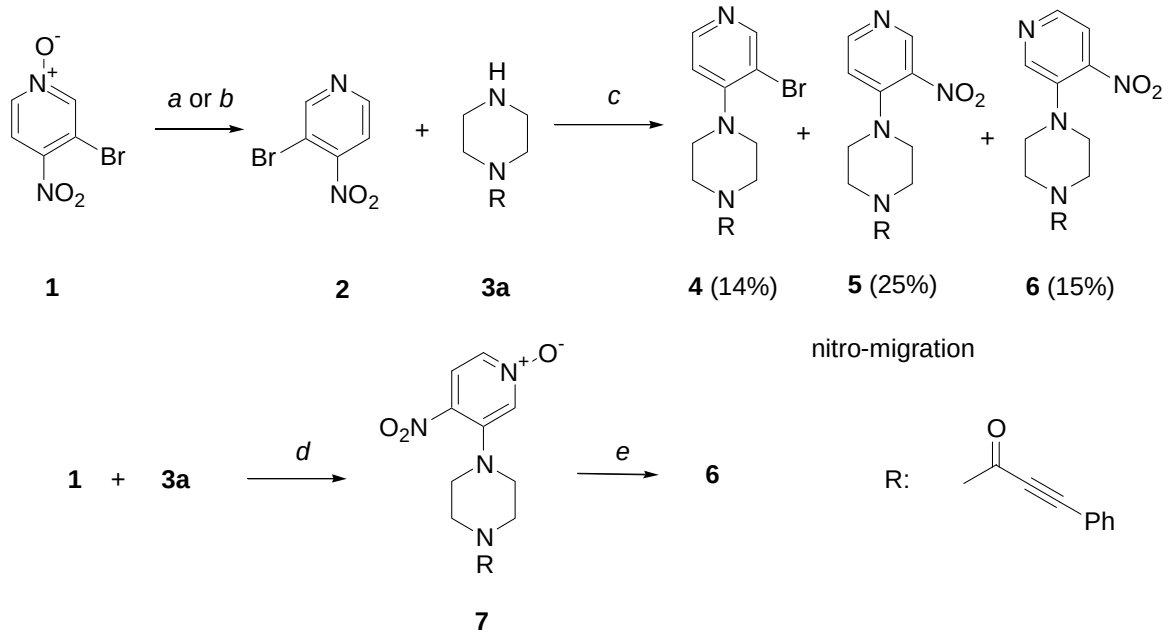
Abstract – On the reaction 3-bromo-4-nitropyridine with amine, three in stead of two expected products are separated. 2D NMR spectral data indicate the major product was an unexpected nitro-group migration product. To explore the rearrangement mechanism, a systematic study with various solvents and bases was undertaken. Results obtained indicate that nitro-group migration occurs in polar aprotic solvents; while expected nucleophilic substitution took place under all tested conditions.

INTRODUCTION

While undertaking the systematic synthesis of amino-substituted nitropyridines, we separated an unexpected product, in which the nitro-group migrated from the 4-position to the 3-position. Further investigations revealed that the 2-nitropyridine could also undergo a migration on the pyridine ring. Although reactions involving halo-substituted nitropyridines with amines have been described in detail, and used in the synthesis of biologically active compounds,[1-3] nitro-group migration had yet to be reported for this system, as far as we know. A similar nitro-migration has been described in the reaction of amine with 4-bromo-5-nitroimidazole[4] and 3-bromo-2-nitrobenzothiophene,[5] but the reaction proceeds in different mechanism. In the reaction of nitroimidazole, the migration occurred through the *N*-dealkylation, followed by *N*-realkylation on the other nitrogen. For the reaction of nitrobenzothiophene, the migration proceeds through a three-member-ring intermediate. The nitro-group migrations have also been reported on some other aromatic rings under specific conditions: for example, the aromatic nitration,[6] the

acid-catalyzed nitroamine rearrangement,[7,8] the MeI-catalyzed rearrangement of nitroimidazole,[9] the metabolite of nitroimidazole,[10] and the thermal rearrangement of *N*-nitropyrrazole.[11] In order to gain an understanding of the mechanism behind this rearrangement and improve the product selectivity, we conducted 17 controlled experiments to explore the effects of temperature, solvent and base on nitro group migration.

In this paper, we will report the preliminary results of the nitro-group migration and their characterization by 1 and 2D NMR spectral studies. In order to confirm the substitution geometry identified by the NMR spectral data, an alternative route for the synthesis of **6** was devised. In addition, we report a convenient rhenium-catalyzed deoxygenation of nitropyridine *N*-oxide developed during the course of this study.

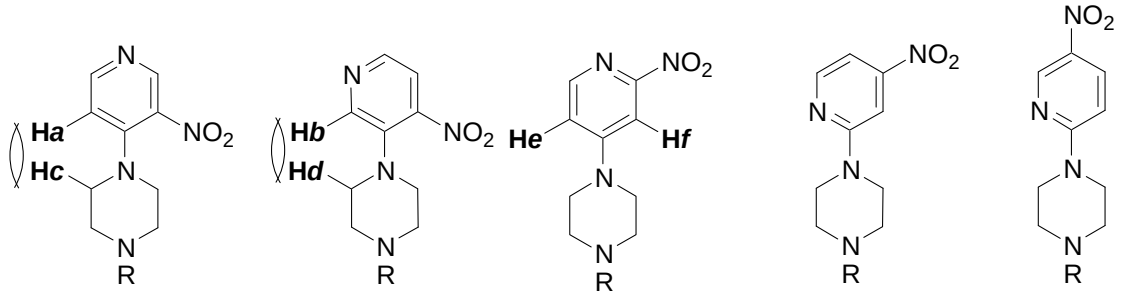


Scheme 1: Conditions: a, $PBr_3/CHCl_3$, rt, 4 h, 11%; b, $Re(O)(Ph_3P)_2Cl_3$, Ph_3P, CH_2Cl_2, rt, 1 h, then, 40 ℃, 2 h, 86%; c, DMSO/TEA, 90 ℃, 12 h; d, THF/TEA, 70 ℃, 16 h, 83%; e, $Re(O)(Ph_3P)_2Cl_3/Ph_3P$, CH_2Cl_2, 45 ℃, 2.5 h, 90%.

RESULTS AND DISCUSSION

Preparation of starting material: The starting material (**2**) has been synthesized from the deoxygenation of 3-bromo-4-nitropyridine *N*-oxide (**1**) (Scheme 1, condition *a*).[12] However, due to the reactivity of the nitro-group, the literature conditions either give poor yields or complicated mixtures of products[13] ($MeSO_2Cl$/TEA,[14] $ZrCl_4/NaBH_4$,[15] $LiCl/NaBH_4$,[16] HCO_2Na/*t*-BuCOCl.[17]). The recently reported transition-metal-catalyzed reactions provide an attractive way for the preparation of **2**.[18, 19] Unfortunately, the catalysts are not commercially available, and their preparation requires multiple steps to produce.[20, 21] We have found that the commercially available rhenium(V)-triphenylphosphine complex catalyzes the deoxygenation of **1** under mild conditions, affording **2** in 86% yield (Scheme 1, condition *b*).

The nitro-group migration of 4-nitropyridine: When a mixture of **2**, **3a**, TEA, and DMSO was heated to 90 °C for 12 h, and purified using flash chromatography, we obtained three products (**4**, **5** and **6**, Scheme 1). Compound (**4**) has a molecular weight (MW) consistent with nucleophilic substitution of the nitro-group. Compounds (**5**) and (**6**) gave identical MWs, based on MS spectral data, and $^{1}H/^{13}C$ NMR spectra consistent with the desired product (**6**); however, chemical shift and HPLC retention times were different. Following the logic that products (**5**) and (**6**) result from nucleophilic substitution of the bromo-group, five possible structures can be drawn (Figure 1), which match the observed ^{1}H NMR spectral patterns. Isomers (**9** and **10**) were excluded by comparison with the known compounds.[22] The remaining three isomers (**5**, **6** and **8**) were differentiated by 2D ^{1}H -NOESY cross-peak patterns,[23] following complete ^{1}H NMR spectral assignments using 2D ^{1}H-COSY,[24, 25] –HMQC[26] and –HMBC[27] spectra: One isomer's doublet peak (H_a, 6.90 ppm d, J = 5.9 Hz) has NOE with the H_c (3.30 – 3.34 ppm); the other isomer's singlet peak (H_b, 8.63 ppm, s) has NOE with H_d (3.20 – 3.26 ppm).



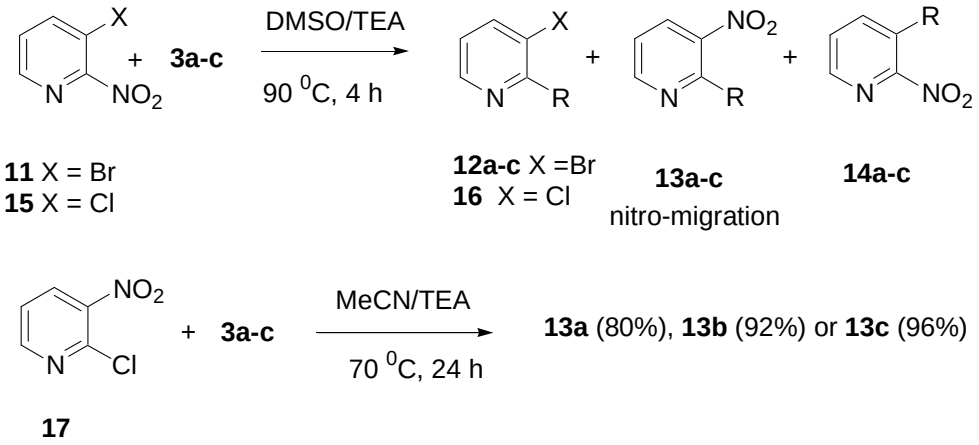
5 **6** **8** **9** known **10** known

Figure 1: The above five structures would yield ^{1}H NMR aromatic resonances consistent with the observed ^{1}H NMR spectrum, one singlet and two doublet. Connections between bold protons on structures (5) and (6) represent cross peaks observed in 2D NOESY spectra.

In order to confirm the structures of **5** and **6**, we decided to make the isomer (**6**) through a different route. It has been reported that the reaction of **1** with a nucleophile affords the bromo-substituted product in good yield,[28, 29] so we planned and carried out the reactions (Scheme 1, *d* and *e*). The reaction of **3a** with **1** exclusively gives the bromo-substituted product (**7**) in 83% yield; and the rhenium-catalyzed deoxygenation of **7** affords **6** in 90% yield. LCMS, TLC, ^{1}H NMR, and ^{13}C NMR spectral data confirm this product is identical to isomer (**6**).

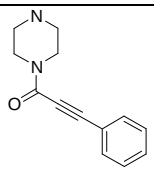
The nitro-migration of 2-nitropyridine *vs* 3-nitropyridine. Under the same conditions as the reaction of **2** with **3a**, the reactions of **11** with amines (**3a-c**) also yielded nitro-migration products (**13a-c**), in addition to the expected nucleophilic substitution products (Scheme 2). We characterized the structures (**13a-c**) of the nitro-group migration products by synthesizing **13a-c** *via* a different route (Scheme 2).[30, 31] As shown in Scheme 2, the isolated yields of the nitro-migration product vary between amines: the reaction of benzylamine (**3c**) gives **13c** (30%) as the major product; while, the reaction of piperidine (**3b**) affords

13b (14%) as a minor product. We also compared the reaction of 3-chloro-2-nitropyridine (**15**) and 2-chloro-3-nitropyridine (**17**) with **3b** (Table 1, Reactions 4 and 5). The reaction of **15** with **3b** yields the nitro-migration product (**13b**) in addition to the nitro- and chloro-substituted products (**16** and **14b**). On the other hand, there is no nitro-migration in the reaction of **17** with **3b** under the same conditions (DMSO/TEA) or the literature conditions (Scheme 2, TEA/MeCN);[33] in these cases only the halo-substituted product (**13b**) is observed.



Scheme 2: The comparision of 2-nitropyridine vs 3-nitropyridine (for detail, see Table 1)

Table 1: The reaction results of 2-nitropyridine and 3-nitropyridine

Reaction	Starting material		R	Product, yield (%)[a]		
1	*11*	*3a*		**12a** (20)	**13a** (23)	**14a** (15)
2	*11*	*3b*		**12b** (19)	**13b** (14)	**14b** (17)
3	*11*	*3c*	$C_6H_5CH_2NH$	**12c** (18)	**13c** (30)	**14c** (5)
4	*15*	*3b*		**16** (58)[b]	**13b** (18)[b]	**14b** (24)[b]
5	*17*	*3b*			**13b** (100)[b]	

[a] Isolated yield; [b] ^{1}H NMR spectral yield.

In order to understand what factors contribute to nitro-group migration in this system, we performed 17 controlled experiments to examine the effects of: (i) starting material ratios, (ii) temperature, and (iii) solvents and bases, on product selectivity. ^{1}H NMR spectra of starting material (**11**), and the three products (**12b**, **13b**, and **14b**) can be clearly identified in the aromatic region (Figure 2). The 17 controlled reaction mixtures are analyzed by ^{1}HNMR spectroscopy and are summarized in Table 2. The nucleophilic

substitution products (**12b** and **14b**) are formed under all of the tested conditions, while the nitro-migration only occurs in polar aprotic solvent. The best condition for nitro-migration product (**13b**, 31%) is the reaction of **15** in *N*-methyl-2-pyrrolidinone (NMP). In non-polar solvents or protic

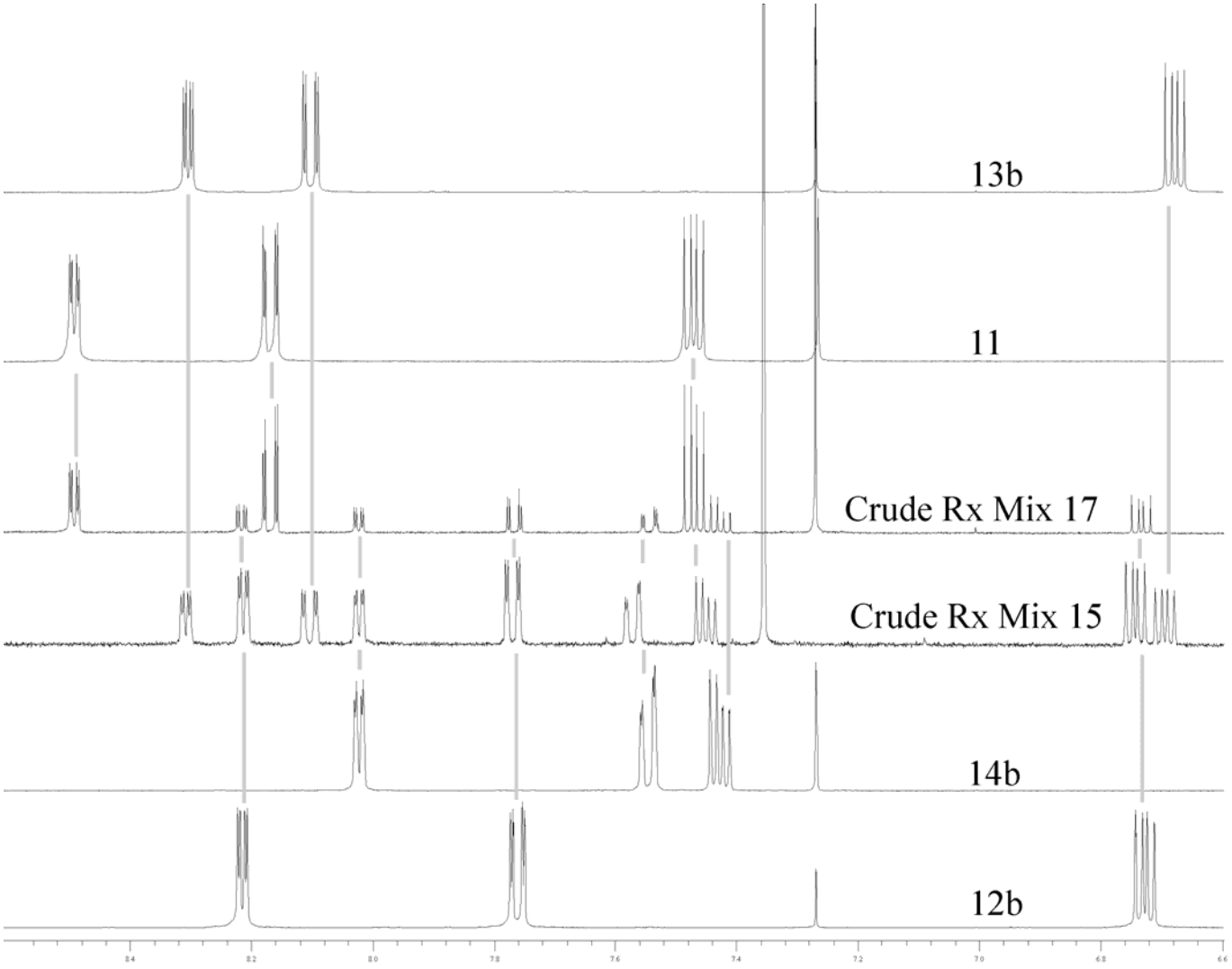


Figure 2: Part of the aromatic region of the ^{1}H NMR ($CDCl_3$) spectra for two crude reaction mixtures (15 and 17), starting material (11), and three purificed products (12b, 13b and 14b). Gray vertical lines associate proton resonances for know purified products with those in the crude reaction mixures. As depicted, the unique chemical shifts and coupling patterens for the known purified compounds afforded complete analysis of the crude reation mixtures.

solvents, the nitro-migration is completely inhibited (Reaction 10, 11 and 16), the yield of **13b** is 0%. In a strong polar aprotic solvent (DMF, DMSO, or DMP), the yield of **13b** varies from 22% to 31%. In addition to solvent, base also plays a pivotal role in nitro-migration. The use of excess TEA (1.0 eq., 2.0 eq. *vs* 4.0 eq.) increases the yield of **13b** from 17% to 22%. When increasing amounts of amine **3b** (1.0 eq., 2.0 eq. *vs* 3.0 eq.), in the presence of a base, the yield of nitro-migration product (**13b**) drops from 22% to 3% (Reactions 3, 4 and 5). In the absence of a base (Reaction 6, 2.0 eq. of amine **3b**), the yield of **13b** decreases to 2%. These various reaction conditions clearly indicate that excess amine inhibits

nitro-migration. Increasing the reaction temperature (50 °C, 70 °C *vs* 90 °C) provides higher yields of **13b** from 14% to 22% (Reactions 3, 7 and 8); however, the reaction mixture becomes too complicated to interpret above 100 °C.

Table 2: The effects of solvent, temperature, and base[a]

Reaction	3b/11[b]	Solvent	Base (eq) [b]	Temp (°C) Time(h)	11 (%)[c]	12b, 13b, 14b (%)[d]
1	1	DMSO	TEA (1)	90, 5	74	43, 17, 43
2	1	DMSO	TEA (2)	90, 5	80	43, 17, 43
3	1	DMSO	TEA (4)	90, 5	90	43, 22, 35
4	2	DMSO	TEA (4)	90, 5	95	50, 10, 40
5	3	DMSO	TEA (4)	90, 5	100	54, 3, 43
6	2	DMSO	—[e]	90, 5	100	48, 2, 48
7	1	DMSO	TEA (4)	50, 15	80	48, 14, 38
8	1	DMSO	TEA (4)	70, 15	90	45, 18, 37
9	1	DMF	TEA (4)	90, 5	97	45, 18, 37
10	1	*i*-PrOH	TEA (4)	90, 5	69	62, 0, 38
11	1		TEA (4)	90, 5	62	66, 0, 34
12	1	MeCN	TEA (4)	90, 5	90	50, 5, 25
13	1	DMSO	DIPEA (4)	90, 5	80	42, 25, 33
14	1	DMSO	K_2CO_3 (4)	90, 5	100	42, 16, 42
15	1		K_2CO_3 (4)	80, 12	100	38, 31, 31
16	2	Toluene	K_2CO_3 (4)	80, 12	100	77, 0, 23
17	2	$ClCH_2CH_2Cl$	K_2CO_3 (4)	80, 12	41	43, 0, 57

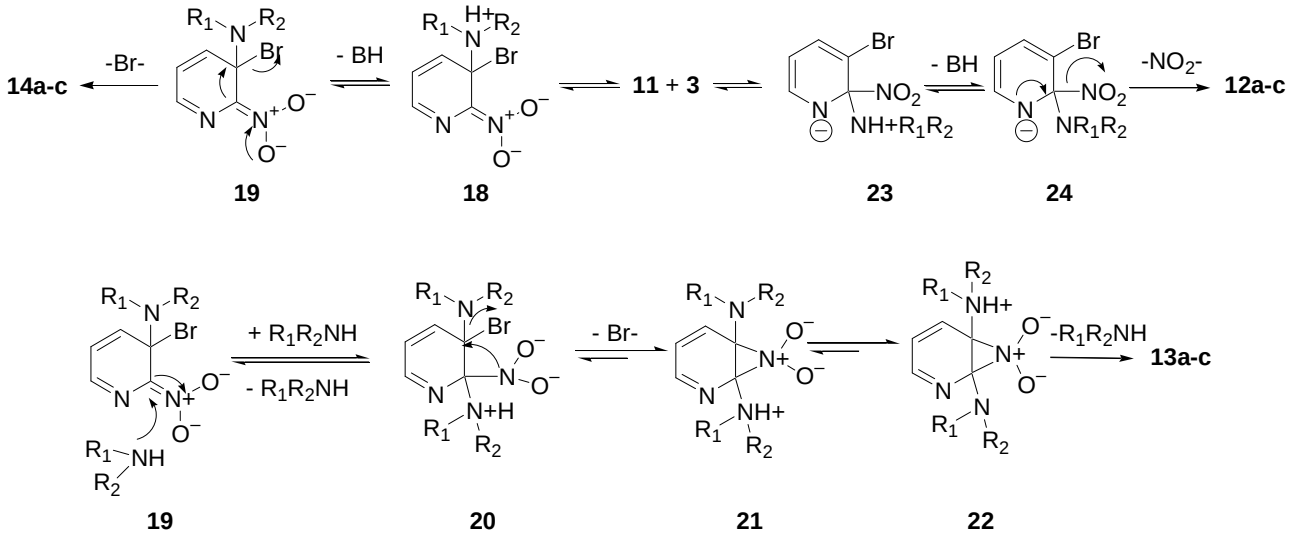
a, All reactions were performed on the same scale: 0.1 mmol of **11**, and 0.5 mL of solvent; *b,* the mole ratio to **11**; *c*, conversion of **11**; *d*, ^{1}H NMR spectral yield; *e*, no base, two eq. of **3b.**

As for the reaction mechanism, we believe that **12a-c** and **14a-c** are formed through classic nucleophilic substitution (S_NAr)[32] as shown in Scheme 3. The intermediates proposed by Spinelli *et al.*[33,34] can explain the formation of **13a-c** and the solvent effects (Scheme 3). The key step for nitro-group migration is the addition of a second amine to **19,** forming intermediate **(20**). Intermediate (**19**) is a reactive dipolar molecule and will eliminate bromo to produce **14a-c**. However, the polar aprotic solvents (DMF, DMSO) have dual roles in accelerating the formation of **20**: Stabilizing intermediate (**19**), and increasing the nucleophilic reactivity of the amine.[35] Once intermediate (**20**) is formed, it undergoes a cyclization to form

21, relieving the two negative charges on the nitro-group. The aza induction makes intermediate (**22**) more stable than **21**, resulting in the elimination of amine (**22**) and yielding **13a-c**.

SUMMARY

In summary, we have reported a novel nitro-group migration on the pyridine ring. The nitro-migration only occurs with substrates of 2- or 4-nitropyridines (not 3-nitropyridine), and only occurs in polar aprotic solvents. We also reported a convenient deoxygenation condition for the nitropyridine *N*-oxide.



Scheme 3: The mechanism for 12, 13, and 14

EXPERIMENTAL

All commercially available solvents and reagents were used as received. NMR spectra were obtained at 400 MHz on a Brucker AVANCE400 spectrometer. Chemical shifts are reported in ppm downfield from TMS as an internal standard. Flash chromatography was done using EM science silical gel 60 (230-400 mesh). TLC was performed on Analtech silica gel GF pre-scored plates (250 μm). MS spectra and HPLC analysis was carried on Agilent 1100 Series LC/MSD equipment. Melting points were determined in open capillaries on Gallenkamp electrothermal apparatus.

3-Bromo-4-nitropyridine (**2**, condition *b*). A mixture of **1** (2.2 g, 10 mmol), trichlorooxobis(triphenylphosphine)rhenium(V) [$Re(O)(Ph_3P)_2Cl_3$, Aldrich, 50 mg, 0.08 mmol), and triphenyphosphine (2.7 g, 10.3 mmol) in dichloromethane (100 mL) was flushed with argon, and stirred at rt for 1 h, then, at 40 °C for 2 h. The reaction mixture was cooled to rt, and concentrated under vacuum. The residue was triturated with hexanes (300 mL), and the precipitated (triphenylphosphine oxide) was removed by filtration. The organic layer was concentrated, and purified by column (silica gel, EtOAc/hexanes 1/7) to give **2** as

yellow solid (1.8 g, 86%).

3-Phenyl-1-piperazin-1-ylpropynone (3a). To a solution of phenylpropynoic acid (10 g, 68 mmol), 1-hydroxybenzotriazole (HOBt, 1.0 g, 7 mmol), and piperazine-1-carboxylic acid *tert*-butyl ester (12 g, 63 mmol) in CH_2Cl_2 (200 mL) was added 1,3-diisopropylcarbodiimide (DIC, 11 mL, 70 mmol) over 15 min at 0 °C. After 30 min at 0 °C, the reaction was allowed to warm to rt in a period of 18 h. The reaction mixture was cooled with ice water, and the white solid was removed by filtration. The organic layer was washed with NaOH (2*N* aq solution, 80 mL), water (30 mL), and brine (30 mL). The solvent was removed under vacuum to afford Boc-protected **3a**. To a solution of BOC-protected **3a** in 30 mL of 1,4-dioxane was added 4 mL of HCl (4*N* solution in 1,4-dioxane, 16 mmol) at 0 °C. The reaction mixture was heated to 50 °C for 24 h. The solvent was removed under vacuum. The residue was washed with Et_2O (4x20 mL) to afford **3a** as HCl-salt (white solid, 1.3 g, 81%, mp 186 – 188 °C,). ^{1}H NMR (CD_3OD) δ 7.64 – 7.66 (m, 2H), 7.44 – 7.55 (m, 3H), 4.16 – 4.19 (m, 2H), 3.93 – 3.96 (m, 2H), 3.38 – 3.41 (m, 2H), 3.29 – 3.32 (m, 2H). Anal. Calcd for $C_{13}H_{15}N_2OCl$: C, 62.28; H, 6.03; N, 11.17. Found: C, 62.54; H, 5.74; N, 11.09.

General procedure for the preparation of 4, 5, 6, 12a, 13a, and 14a: A mixture of nitropyridine (**2** or **11**, 203 mg, 1.0 mmol), **3a** (214 mg, 1.0 mmol), TEA (0.4 mL, 2.8 mmol) and DMSO (2 mL) was heated to 90 °C for 12 h. The reaction mixture was cooled to rt, diluted with ethyl acetate (10 mL), and washed with water (2x5 mL). The organic layer was separated, concentrated under vacuum, and the residue was purified by column (silica gel, CH_2Cl_2/THF v/v, 20/3) to give the desired products.

1-[4-(3-Bromopyridin-4-yl)piperazin-1-yl]-3-phenylpropynone (4). Colorless oil, 14% yield. TLC (CH_2Cl_2/THF, 20/3, R_f 0.5). ^{1}H NMR ($CDCl_3$) δ 8.62 (s, 1H), 8.40 (d, J = 5.5, 1H), 7.55 – 7.58 (m, 2H), 7.36 – 7.46 (m, 3H), 6.83 (d, J = 5.5, 1H), 4.03 – 4.06 (m, 2H), 3.89 – 3.92 (m, 2H), 3.26 – 3.29 (m, 2H), 3.19 – 3.22 (m, 2H); MS (m/z): 370 (M + H). Anal. Calcd for $C_{18}H_{16}N_3OBr$: C, 58.39; H, 4.36; N, 11.35. Found: C, 57.99; H, 4.21; N, 11.02.

1-[4-(3-Nitropyridin-4-yl)piperazin-1-yl]-3-phenylpropynone (5). Yellow solid (mp 148 – 149 °C, 25%). TLC (CH_2Cl_2/THF, 20/3, R_f 0.3). ^{1}HNMR ($CDCl_3$) δ 8.94 (s, 1H), 8.48 (d, J = 5.8, 1H), 7.57 – 7.59 (m, 2H), 7.39 – 7.46 (m, 3H), 6.92 (d, J = 6.0, 1H), 4.05 – 4.08 (m, 2H), 3.90 – 3.93 (m, 2H), 3.32 – 3.35 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 153.7, 150.1, 148.7, 137.1, 132.8, 130.7, 129.0, 120.4, 113.3, 92.0, 80.9, 50.6, 49.3, 46.5, 41.2; MS (m/z): 336 (M + H), 359 (M + 23); Anal. Calcd for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.62; H, 4.52; N, 16.45.

1-[4-(4-Nitropyridin-3-yl)piperazin-1-yl]-3-phenylpropynone (6). Orange solid (mp 145 – 146 °C, 15%). TLC (CH_2Cl_2/THF, 20/3, R_f 0.6). ^{1}HNMR ($CDCl_3$) δ 8.62 (s, 1H), 8.47 (d, J = 5.3, 1H), 7.60 (d, J = 5.7, 1H), 7.55 – 7.58 (m, 2H), 7.36 – 7.46 (m, 3H), 4.01 – 4.04 (m, 2H), 3.87 – 3.90 (m, 2H), 3.23 – 3.26 (m, 2H), 3.19 – 3.22 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 153.6, 148.5, 145.8, 145.1, 139.4, 132.8, 130.7, 129.0, 120.6, 118.1, 91.8, 81.1, 52.4, 51.5, 47.4, 41.8; MS (m/z): 336 (M + H), 359 (M + 23); Anal. Calcd for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.8; H, 4.51; N, 16.21.

1-[4-(3-Bromopyridin-2-yl)piperazin-1-yl]-3-phenylpropynone (12a). White solid (mp 105 – 106 °C, 20%). TLC (EtOAc/hexanes, 7/3, R_f 0.72); ^{1}HNMR ($CDCl_3$) δ 8.25 (dd, J = 1.7, 4.8, 1H), 7.82 (dd, J = 1.5, 7.8, 1H), 7.55 – 7.58 (m, 2H), 7.36 – 7.45 (m, 3H), 6.84 (dd, J = 4.6, 7.7, 1H), 4.00 – 4.03 (m, 2H), 3.86 – 3.89 (m, 2H), 3.41 – 3.43 (m, 2H), 3.34 – 3.37 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 159.4, 153.7, 146.9, 142.8, 132.8, 130.5, 128.9, 120.8, 119.7, 113.5, 91.3, 80.5, 50.2, 49.7, 47.4, 41.9; MS (m/z): 371 (M + H); Anal. Calcd for $C_{18}H_{16}N_3OBr$: C, 58.39; H, 4.36; N, 11.35. Found: C, 58.47; H, 3.96; N, 10.97.

1-[4-(3-Nitropyridin-2-yl)piperazin-1-yl]-3-phenylpropynone (13a). Yellow solid (mp 156 – 158 °C, 23%). TLC (EtOAc/hexanes, 7/3, R_f 0.38); ^{1}H NMR ($CDCl_3$) δ 8.41 (dd, J = 1.7, 4.6, 1H), 8.22 (dd, J = 1.7, 7.9, 1H), 7.58 – 7.61 (m, 2H), 7.39 – 7.46 (m, 3H), 6.88 (dd, J = 4.7, 8.1, 1H), 4.01 – 4.04 (m, 2H), 3.86 – 3.88 (m, 2H), 3.53 – 3.58 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 153.7, 153.1, 152.4, 136.1, 133.9, 132.8, 130.7, 128.9, 120.6, 115.1, 91.6, 81.2, 48.9, 48.1, 46.9, 41.6; MS (m/z): 337 (M + H); Anal. Calcd for $C_{18}H_{16}N_4O_3$: C, 64.28; H, 4.79; N, 16.66. Found: C, 64.06; H, 4.75; N, 16.23.

1-[4-(2-Nitropyridin-3-yl)piperazin-1-yl]-3-phenylpropynone (14a). Yellow solid (mp 120 – 123 °C, 15%). TLC (EtOAc/hexanes, 7/3, R_f 0.12); ^{1}H NMR ($CDCl_3$) δ 8.21 (dd, J = 1.5, 4.4, 1H), 7.64 (dd, J = 1.5, 8.1, 1H), 7.55 – 7.58 (m, 2H), 7.53 (dd, J = 4.6, 8.1, 1H), 7.36 – 7.46 (m, 3H), 3.97 – 4.01 (m, 2H), 3.84 – 3.87 (m, 2H), 3.10 – 3.15 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 153.7, 153.6, 142.7, 140.3, 132.8, 132.0, 130.7, 129.0, 128.6, 120.5, 91.7, 81.1, 52.5, 51.3, 47.3, 41.8; MS (m/z): 337 (M + H); Anal. Calcd for C, 64.28; H, 4.79; N, 16.66; Found: C, 64.30; H, 4.72; N, 16.63.

Alternative route for the synthesis of 6: To a suspended solution of **1** (2.0 g, 9.1 mmol) and TEA (10 mL, 70 mmol) in 120 mL of THF was added amine (**3**) (2.0 g, 9.3 mmol). The reaction mixture was heated and stirred at 70 °C for 16 h under argon. After cooling to rt, the reaction mixture was diluted with dichloromethane (200 mL), then washed with water (20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4), concentrated under vacuum

and purified by column (silica gel, EtOAc) to give intermediate (**7**) as yellow solid (2.6 g, 83%). To a solution of **7** (500 mg, 1.4 mmol) in dichloromethane (20 mL) was added triphenylphosphine (450 mg, 1.7 mmol) under argon. The reaction mixture was flushed with argon, then, the catalyst $Rh(O)(Ph_3P)_2Cl_3$ (70 mg, 0.08 mmol) was added in one portion. After heating at 45 °C for 2.5 h under argon, the reaction mixture was cooled to rt, the solvent was removed under vacuum, and purified by column (silica gel, MeOH/CH_2Cl_2 2/100) to obtain **6** as yellow solid (0.45 g, yield, 95%).

ACKNOWLEDGEMENT

The authors would like to thank Dr. R. Richard Goehring and Dr. Parviz Gharagozloo for helpful discussion, and Mr. John Engel for reviewing the manuscript.

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