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Efficient microwave-assisted three-component one-pot preparation of 1-aryl-4-(2-acetoxyethyl)piperazines and 1-aryl-4-(2-acetoxyethyl)piperidines

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ABSTRACT

A highly efficient one-pot, three-component microwave-assisted procedure has been developed for the preparation of 1-(*para*-substituted-aryl)-4-(2-acetoxyethyl)piperazines and 1-(*para*-substituted-aryl)-4-(2-acetoxyethyl)piperidines. Microwave-accelerated heating of electron-deficient aryl halides and potassium acetate with either 1,4-diazabicyclo[2.2.2]octane (DABCO) or quinuclidine at 180 °C for 120 min provided the title products in good yields and with general substrate scope. Similarly, subjection of potassium pthalimide instead of potassium acetate to the same conditions provided good yields of 1-arylpiperazines and 1-arylpiperidines containing a 2-phthalimidoethyl substituent at the C-4 position.

1. Introduction

In medicinal chemistry, any given active pharmaceutical ingredient (API) is directed at hundreds of biological targets. In an era of rising competition and research costs, the desire for molecules that are both biologically active and therapeutically versatile is strong. Thus emerges the 'privileged structure' concept,[1] in which particular small molecules (MW <500 Da) can bind to multiple receptors, resulting in a great potential for diverse uses. Aryl piperazines and aryl piperidines are such structures, with applications across several therapeutic areas.[2–7] This basic structure can be used both as a substituent and as a series core in combinatorial libraries (Fig. 1).

In 1963, Ross and Finkelstein reported on the observation that a high-temperature reaction between 4-chloronitrobenzene (**1**) and 1,4-diazabicyclo[2.2.2]octane (DABCO, **2**) in benzyl alcohol did not lead to the expected *N*-aryl quaternary ammonium salt **3**, but instead exclusively produced the quaternary ammonium salt **4** (Scheme 1).[10] This product **4** was thought to arise from the addition of excess DABCO to the initial S_NAr salt product **3**, proceeding through a ring-opening *N*-dealkylative process. Over two decades later, Ibata et al.[11] reported that a similar aromatic nucleophilic substitution reaction of **1** with N-substituted pyrrolidines **5** under high pressure gave the ring-opening salt products **6** as well as N-dealkylation 4-pyrrolidinonitrobenzene products **7** in a ratio that depended on the steric bulk and electronics of the amine substituent R.

In this Letter we demonstrate the ability to create 1-(*para*-substituted-aryl)-4-(alkyl)piperazines in which the alkyl substituent is an acetate or a phthalimide group tethered by a two-methylene unit. The corresponding piperidine congeners are also prepared by this method. The procedure uses the microwave synthesizer to efficiently achieve the appropriate reaction conditions reported by thermal methods,[12] but under very short times.

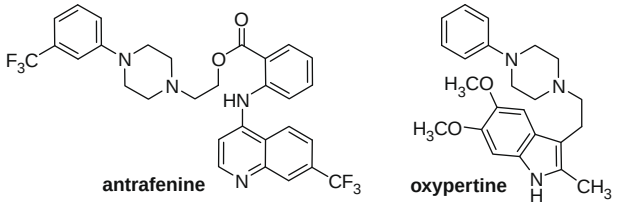

Figure 1. Two 4-arylpiperazine APIs: antrafenine, an analgesic,[8] and oxypertine, a neuroleptic.[9]

2. Preliminary reactions

Recently we reported a procedure in which the reaction between DABCO, activated hetaryl chlorides (e.g., **8**) and an excess of a third nucleophile can undergo a three-component, one-pot microwave-assisted reaction to generate 1-hetaryl-4-(alkyl)piperazines **10**, in which the alkyl group on nitrogen was a 2-substituted ethyl group (Scheme 2).[13] Although this two-step procedure was conducted without isolation of the intermediates, it is possible that any one of the three structures **9a–c** are viable adducts from the first step, and would be capable of reacting with a second nucleophile (or excess DABCO) to generate products **10**.

Based on the results of the thermal reaction depicted in Scheme 1, we sought to adapt our microwave-based protocol in order to

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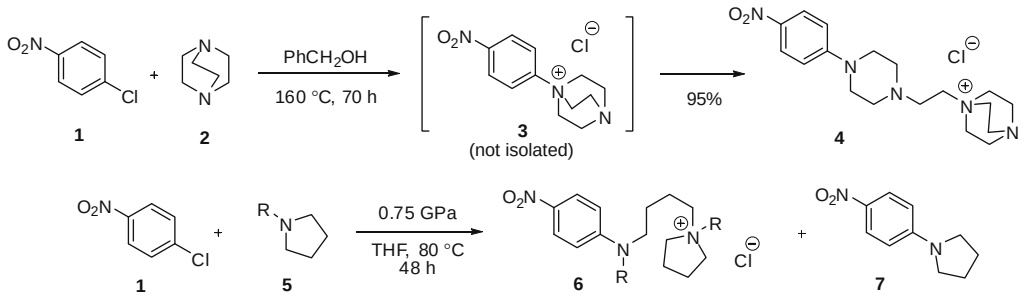
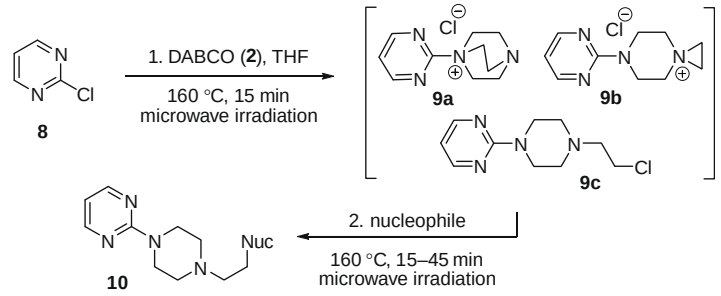
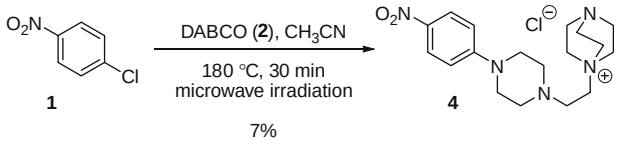


Scheme 1. First reported ring-opening reactions of quaternary salts generated thermally by S_NAr reactions with tertiary amine nucleophiles.



Scheme 2. Possible intermediates generated in the reaction of aryl halide **1** with DABCO (**4**).



Scheme 3. Formation of quaternary ammonium product **4**.

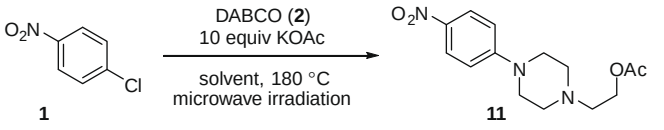
increase the utility of this transformation. In our initial studies, we heated a 1:1 mixture of DABCO and 4-chloronitrobenzene in acetonitrile at 180 °C in the microwave for 30 min. HPLC analysis of the resulting mixture showed 93% of the recovered starting material **1** with only a 7% yield of the desired quaternary ammonium product **4** (Scheme 3).

We decided to investigate these reactions using a three-component procedure, whereby interception of intermediates **9a** and/or **9b** with other nucleophiles would generate products akin to **10** in Scheme 2.

3. Results and discussion

We first decided to investigate the S_NAr/ring-opening reaction using DABCO and 4-chloronitrobenzene in various solvents with potassium acetate to serve as our secondary nucleophile (Table 1). Our procedure was anticipated to prepare 2-[4-(4-nitrophenyl)piperazin-1-yl]ethyl acetate (**11**), which to date has only been synthesized by a route using bromoethyl acetate.[14] Our hypothesis was that a suitable excess of potassium acetate would allow a high enough concentration to act as our second nucleophile onto the initial reaction intermediates (cf. Scheme 2). We soon discovered that the reaction worked moderately well in DMF, and progressed best when 3 M equiv of DABCO was used with 10 M equiv of potassium acetate (Table 1). In practice, however, we decided to limit the amount of DABCO to 2 equiv to better mimic the utility of the reagent in practical use.[15]

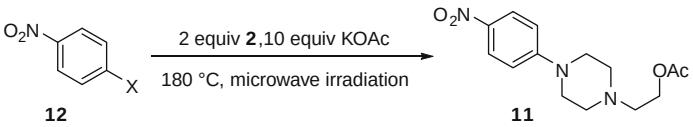
Table 1
Optimization of reagent equivalents and solvent



1 (equiv)	**2** (equiv)	Solvent	Time (min)	Yield (%)
1	1	DMF	40	43
1	2	DMF	40	56
1	2	DMF	60	57
1	2	CH_3CN	40	56
1	3	DMF	40	59
1	3	DMF	60	74

Upon further investigation of the ability of 4-halonitrobenzenes **12** to facilitate the reaction, bromide proved to be the best leaving group, followed by chloro, then iodo and least of all fluoro, which gave very poor yields of the desired product **11** (Table 2). The

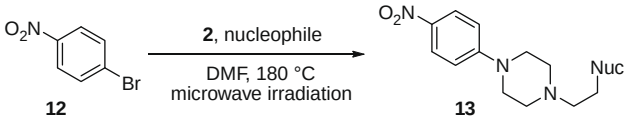
Table 2
Optimization of 4-halonitrobenzenes **12**



12 (equiv)	**2** (equiv)	X	Solvent	Time (min)	Yield (%)
1	2	Cl	DMF	60	57
1	2	Br	DMF	60	68
1	2	I	DMF	60	37
1	2	F	DMF	60	NP[a]
1	2	OAc	DMF	60	NP[a]

[a] No desired product isolated.

Table 3
Examination of other nucleophiles



12 13

1 (equiv)	**2** (equiv)	Nucleophile (Amt.)	Yield (%)
1	3	Potassium acetate (10 equiv)	69
1	2	Potassium phthalimide (5 equiv)	68
1	3	Potassium cyanide (10 equiv)	NP[a]
1	3	Potassium hydroxide (10 equiv)	NP[a]
1	2	Sodium methoxide (10 equiv)	NP[a]

[a] No desired product isolated.

acetate was unreactive, eliminating the possibility of acetate adding then being displaced.

Other alkali salts were examined for their ability to serve as secondary nucleophiles (Table 3). Of the other nucleophiles tested, potassium phthalimide was the only one which gave the desired product **13** (Nuc = phthalimide).

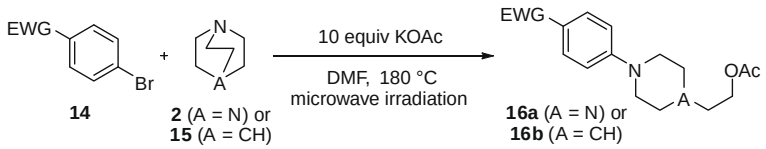
The evaluation of different electron-withdrawing groups on the *para*-position of the aryl bromide **14** was next explored to prepare a series of 1-(*para*-substituted-aryl)-4-(acetoxyethyl)piperazines **16a** (Table 4). This study provided an opportunity not only to observe the influence of different aryl substituents, but also to reveal that in addition to the use of DABCO (**2**, A = N), quinuclidine (**15**, A = CH) can be used in the transformation with aryl bromides to prepare 1-(*para*-substituted-aryl)-4-(acetoxyethyl)piperidines **16b**.

We were also interested to see the method applied to reactions with heterocyclic substrates, and were pleased to find that an activated bromopyridine **17** and two electron-deficient halothiophenes **19** and **21** provided desired products, albeit in moderate yields (Schemes 4 and 5). Combination of 5-bromopicolinonitrile (**17**) with 2 equiv of quinuclidine (**15**) resulted in the formation of the requisite 3-piperidino product **18** in good yield. Similarly, the reaction of 2-bromo-5-nitrothiophene (**19**) with 1 equiv of **15** generated piperidine **20** in 57% yield.

Combination of 2 equiv of DABCO with 3-chloro-2-cyanothiophene (**21**) under the optimized conditions did provide the 3-piperazinothiophene **22**, albeit in moderate yield after 3.5 h (Scheme 5). This product **22** with an electron-withdrawing functionality at the *ortho*-position relative to the piperazine is noteworthy, as our attempts to generate N-arylated piperazine products from the displacement of 2-halonitrobenzene and 3-halonitrobenzene were unsuccessful. We were, however, able to react DABCO with 4-bromo-3-chloronitrobenzene (**23**) and potassium acetate to provide the difunctional *N*-aryl adduct **24**, albeit in moderate yield.

In conclusion, we have demonstrated that it is possible to intercept the quaternary ammonium salt generated from 4-chloronitrobenzene and DABCO or quinuclidine with nucleophiles to provide 1-(*para*-substituted-aryl)-4-(alkyl)piperazines or 1-(*para*-substituted-aryl)-4-(alkyl)piperidines in which the alkyl substituent is an acetate or a phthalimide group tethered by a two-methylene

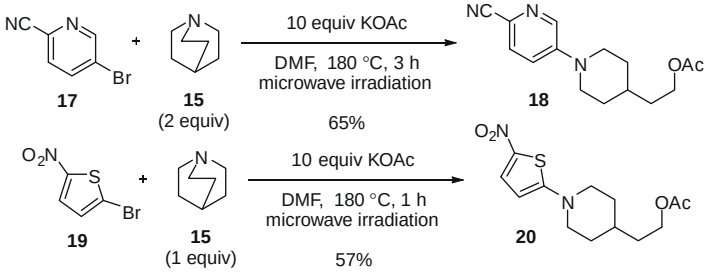
Table 4
Examination of aryl *para*-substitution



14 **2** (A = N) or **15** (A = CH) **16a** (A = N) or **16b** (A = CH)

EWG	Amine	Time (h)	Yield (%)
NO_2	**2** (A = N), 2 equiv	1	68
NO_2	**15** (A = CH), 2 equiv	1	62
$COCH_3$	**2** (A = N), 2 equiv	3	16
CN	**2** (A = N), 2 equiv	2	52
CN	**15** (A = CH), 2 equiv	4	60
COPh	**2** (A = N), 1 equiv	1	24
COPh	**15** (A = CH), 1 equiv	3	33
SO_2CH_3	**2** (A = N), 2 equiv	2	43
SO_2CH_3	**15** (A = CH), 2 equiv	2	51
CF_3	**2** (A = N), 2 equiv	1.5	9
CF_3	**15** (A = CH), 2 equiv	4	49
CO_2CH_3	**2** (A = N), 2 equiv	2	NP[a]
CO_2H	**2** (A = N), 2 equiv	2	NP[a]

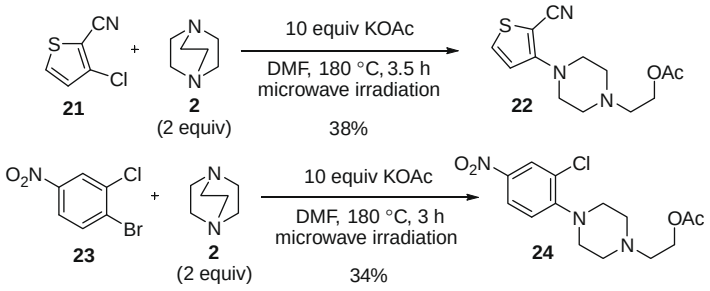
[a] No desired product isolated.



17 **15** (2 equiv) **18** 65%

19 **15** (1 equiv) **20** 57%

Scheme 4. Reaction of substituted heterocyclic halides with quinuclidine.



Scheme 5. *ortho*-Substituted aryl halide substrates.

unit. We have also shown that different electron-withdrawing groups can be used in place of the nitro moiety, and that heterocyclic aromatic compounds can react similarly to form *N*-pyridinyl- and *N*-thiophenyl-piperidine adducts as well as *N*-thiophenyl-piperazine derivatives. Thus, we have demonstrated the successful microwave-assisted method for the synthesis of cores useful for the generation of privileged structures.

Acknowledgment

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15. *Representative experimental procedure*: Preparation of 2-[4-(4-nitrophenyl)piperazin-1-yl]ethyl acetate (**11**). All reactions were run on a 100 mg scale of aryl halide. A 10 mL microwave reactor vial containing a magnetic stir bar was charged with a 4-chloronitrobenzene (**1**, 0.634 mmol), DABCO (**2**, 1.27 mmol), potassium acetate (6.34 mmol), and DMF (6 mL). The vial was sealed and irradiated in a SmithCreator™ microwave reactor to reach 180 °C over a 2-min ramp and held at 180 °C for up to 4 h. Reaction progress was monitored with a PESciex API 150ex mass spectrometer with a Shimadzu LC-10AD liquid chromatograph and LC SPD 10A UV–Vis detector. Upon completion of the reaction, the solids were removed by vacuum filtration through a Hirsch funnel, washing with dichloromethane (~20 mL). The solvents were removed and the amorphous residue was purified by chromatography on silica gel using a Teledyne-Isco CombiFlash unit. The corresponding fractions were collected, the solvents were removed, and the product was analyzed using a Bruker AV 300 MHz NMR spectrometer. Data for compound **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J = 9.3 Hz, 2H), 6.82 (d, J = 9.3 Hz, 2H), 4.23 (t, J = 5.2 Hz, 2H), 3.43 m, 4H), 2.70–2.64 (m, 6H), 2.08 (s, 3H); APCI MS m/z 294 $[M+H]^+$.