Pergamon

Tetrahedron Letters 43 (2002) 3359–3363

TETRAHEDRON LETTERS

Mono *N*-arylation of piperazine(III): metal-catalyzed *N*-arylation and its application to the novel preparations of the antifungal posaconazole and its advanced intermediate

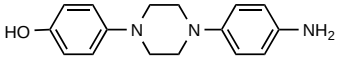
Michael Hepperle, Jeffrey Eckert, Dinesh Gala,* Lan Shen, C. Anderson Evans and Andrew Goodman

Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA

Received 25 January 2002; revised 7 March 2002; accepted 12 March 2002

Abstract—A novel application of Pd^0-catalyzed arylation to mono *N*-arylated piperazines, its mechanism, and its application towards the novel syntheses of the key differentially *N*,*N*′-diarylated piperazine antifungal intermediate *N*-(4-hydroxyphenyl)-*N*′-(4-aminophenyl)piperazine **5** as well as posaconazole **1** are described.

Mono and diarylated piperazines are key moieties of a variety of biologically active compounds such as Neuropeptide Y antagonists, G-Protein-coupled receptor ligands, cholesterol ester transfer protein inhibitors, 5-HT_{1D} receptor agonists GPIIb/IIIa antagonist, serotonin-3 antagonists, and orally active broad-spectrum triazole antifungals (**1**–**4**), the compounds of interest for the current manuscript.[1–7] These triazole antifungals such as Sch 51048, Sch 56592, itraconazole, and hydroxyitraconazole[3] utilize an unsymmetrically *N*,*N*′-diarylated piperazine moiety **5**.



5: Common antifungal intermediate

Typical synthetic routes[1–6] to these differentially *N*,*N*′-diaryl substituted piperazines encompass the reaction of anilines to the mono *N*-aryl piperazines (via carcinogenic intermediates under high pressure and/or temperature and specialized catalyst conditions) which are then reacted with appropriate arylhalides. Alternately these differentially substituted piperazines are made by reacting electron withdrawing groups containing arylhalides either with a large excess of piperazine under harsh reaction conditions or with mono-*N* protected piperazine, usually as a carbamate, to avoid a mixture of mono-, di-, and unsubstituted piperazines which require chromatographic purifications.[7,8] Our interest has been in seeking a mild, selective method for mono-*N*-arylation of piperazine which could be utilized for preparation of **5**.

In previous publications[1,2] we described a direct sequential *N*-arylation of piperazine nitrogens for the preparation of the common antifungal intermediate **5**. There it was shown that the reaction of equimolar amounts of electron deficient arylhalides with piperazine, without the use of catalyst, led to the mono *N*-arylated piperazines which were then converted to the differentially *N*,*N*′-diaryl substituted piperazines. Electron rich aromatic halides do not react with piperazine under these conditions. Thus, towards the synthesis of antifungal intermediate **5** we reported that the reaction of piperazine **7** with *p*-chloro or bromonitrobenzene **6** led to the mono arylated piperazine **8** (Scheme 1), which reacted with boronic acid derivative **10** to generate **11**.

Interestingly, under standard Pd^0 coupling conditions[9,10] **8** reacted very slowly with *p*-bromoanisole **9** as after 3 days it led to 58% isolated yield of **11**. Compound **11** produced via either of the above reactions were indistinguishable from the one obtained via alternate synthesis and could be converted to the desired compound **5** as shown in Scheme 1. For a large scale preparation of **5**, the use of **9** is more desirable compared to the use of **10**.[11] The slow arylation of piperazine **9** with **8** was intriguing. Very little information is available in the literature pertaining to Pd^0-catalyzed *N*-arylation of piperazine.[12] In view of novel and useful results obtained in our laboratory on piperazine

* Corresponding author.

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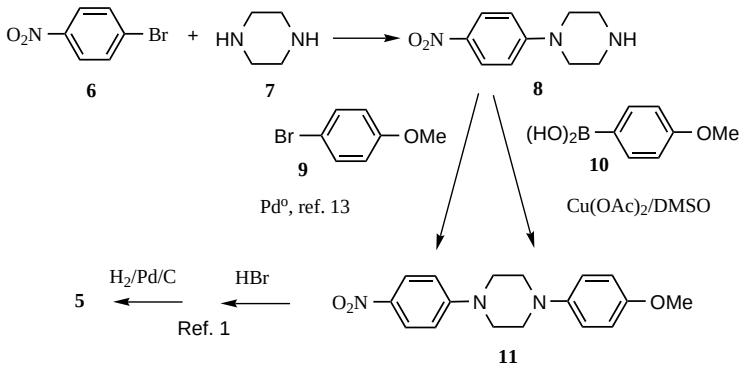
PII: S0040-4039(02)00556-7



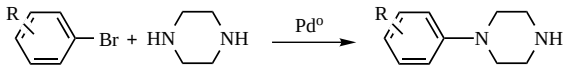
Scheme 1. Reactivity of *N*-*p*-nitrophenyl piperazine.

N-arylation with electron deficient aromatic halides,[1,2] we decided to investigate Pd^0-catalyzed piperazine *N*-arylation with non electron deficient aromatic halides in general. This work has led us to the discovery that almost equimolar amounts of non-electron deficient arylhalides and piperazine react in the presence of a Pd^0 catalyst to produce only mono *N*-arylated piperazines. This finding has been applied to the preparation of the common antifungal intermediate **5** as well as to posaconazole, **1**, and are described in this manuscript.

The results of piperazine mono *N*-arylation with Pd^0 catalysis (experimental conditions derived from Ref. 9 are described in Ref. 13) are shown in Table 1. In general the stronger the electron donating group on the arylhalide, the higher the piperazine *N*-arylation yield. A steric hindrance played a role (entries 4 and 5) in lowering yields. Most importantly for our work, compound **9** and **15** reacted with piperazine to produce intermediates that were suitable for the preparation of **5**.

Preliminary laboratory work undertaken to understand factors that govern Pd^0-catalyzed piperazine mono *N*-arylation is detailed below. The use of racemic Binap in place of chiral one during the formation of **18** did not alter the outcome of the reaction ruling out any facial selectivity imparted by the catalyst. Solubility of **9**, **11**–**15** and mono *N*-aryl piperazines **16**–**21** in toluene, the use of several lots of reagents, ligands, as well as catalyst eliminated the possibility that the selectivity was imparted by insolubility or specific set of reagents. Isolated **18** subjected to the reaction conditions with fresh reagents and the catalyst essentially resulted in a recovery of **18**. While this mechanism remained under investigation, we applied the above finding to the syntheses of **5** as detailed below.

Table 1. Pd^0-catalyzed piperazine mono *N*-arylation

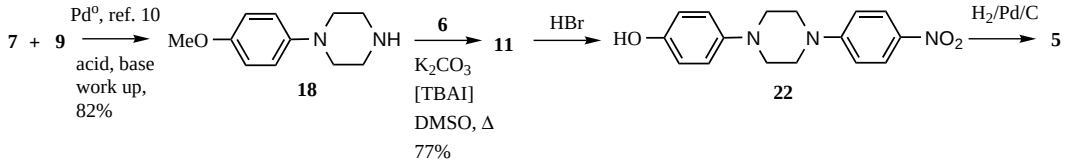


9, 11-15 **7** **16-21**

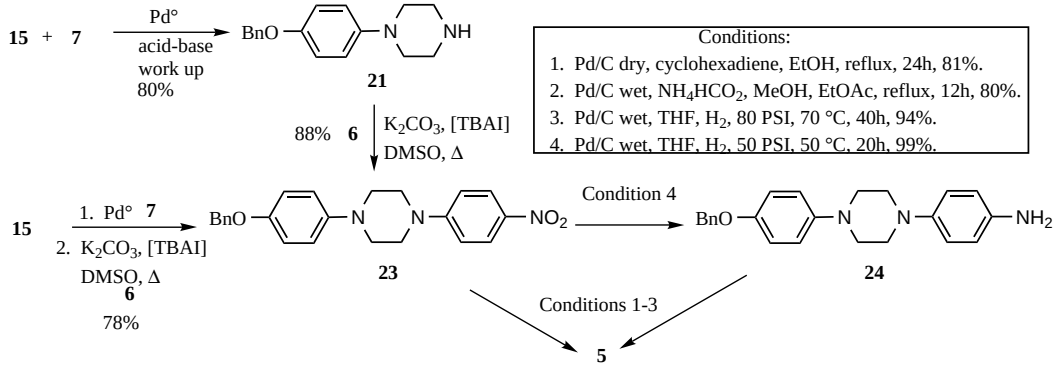
#	R	Product/% yield	Reaction time (h)
1	H (**11**)	**16**[4]/42	24
2	4-CH_3 (**12**)	**17**/69	48
3	4-OCH_3 (**9**)	**18**/82	24
4	2-CH_3 (**13**)	**19**/35	48
5	2-OCH_3 (**14**)	**20**/10	96
6	4-OCH_2Ph (**15**)	**21**/80	3[14]

As shown in Scheme 2, arylhalide **6** was reacted with **18** using conditions described previously for *N*-arylation of piperazine with electron deficient aryl halides[1] to obtain compound **11** indistinguishable from the one made via alternate routes shown in Scheme 1. Note that the one-pot, two-step conversion, i.e. Pd^0 coupling to crude **18** followed by its reaction with **6**, without acid base work up, can be carried out in one pot to obtain 75% isolated yield of **11**. The residual reagents and byproducts form Pd^0 coupling reaction did not interfere with the conversion of **18** to **11** and the removal of one acid–base work up minimized the loss of mass resulting in an improved yield. Compound **11** was then converted to the desired antifungal intermediate **5** via demethylation followed by hydrogenation. All yields reported in this manuscript are upoptimized. In this preparation of **5**, demethylation requires an excess of refluxing aqueous HBr for a prolonged period (24+ h) of time. The isolation of nitrophenol **22** from HBr requires a pH control, it is labor intensive, and moderate yielding (75–80%).

Changing the reaction order, i.e. hydrogenation prior to demethylation encountered difficulties as well. Although insolubility of **11** in many solvents slowed down the reduction, the main problems resided in the fact that the resultant aniline intermediate formed a HBr salt with aq. HBr. Thus, yet larger excess of HBr and much longer (2+ days) refluxing time was needed for the demethylation reaction. These difficulties were overcome by the use of benzyloxy group in place of methoxy group (Scheme 3). Benzyloxy derivative **23** is more soluble compared to **11**, and its deprotection does not require harsh HBr treatment. The reaction of piperazine with **15** in the presence of Pd^0 catalyst resulted in mono *N*-arylated piperazine **21**. The use of larger amount of the catalyst allowed for improved yield of **21** with short reaction time. Compound **21** readily reacted with the arylhalide **6** under the conditions described previously[1] to form **23**. Compound **23** was then con-



Scheme 2. Preparation of **5** via Pd^0-catalyzed mono-*N*-arylation of piperazine.



Scheme 3. A short, convenient synthesis of antifungal intermediate **5**.

verted to **5** via one of the several conditions depicted in the scheme. Further work towards streamlining the preparation of **5** showed that the isolation of **21** was unnecessary towards the preparation of **23** as **21**, prepared in situ, readily reacted with **6** to form **23**. Improved yield for one-pot preparation reflects the loss of **21** during the acid base workup. This two-pot synthesis (**15** to **23** to **5**) via the transfer hydrogenation (eliminating pressure reactor) is the most large scale amenable preparation of **5** reported to date. Note that the aniline **24** could be isolated, if needed, by using the milder hydrogenation conditions. Compound **24**, upon further hydrogenation as shown in conditions 1–3 could be converted to **5**.

Next we investigated the application of the above methods to the preparation of the azole antifungal posaconazole **1**. The known[3–6] disconnections for the synthesis of the above azole antifungals are shown in Fig. 1. In the case of Sch 51048 and Sch 56592 the chiral tetrahydrofuran moiety was appended to the di-arylated piperazine containing the *N*,*N*′-substituted urea entity. This was then cyclized to the hydroxy protected triazolone, i.e. *O*-benzyl **1**.[4,6] For itraconazole, the original synthesis consisted of reacting the preformed triazolone containing piperazine to the dichlorophenyl dioxolane azole. This was then subjected to triazolone-*N*-alkylation to the desired product.[3] Sepracor has recently used Pd^0 catalysis to append the preformed haloaryl triazolone to the mono-*N*-substituted piperazine as shown in Fig. 1.[5] We recognized that the piperazine mono-*N*-arylation findings offered an alternate, novel convergent approach (Fig. 2) for the preparation of **1** similar to the one used above for the preparation of differentially-*N*,*N*′-diarylated piperazine **5**. Furthermore, this chemistry may be applicable to the preparation of a variety of bioactive classes of *N*,*N*′-substituted piperazines and to important piperazines for combinatorial library work.[1–7]

Initial work towards the preparation of antifungal **1** (Scheme 4) led to the following findings. The preparation of the arylhalide **27** from sulfonate **25** (available to us[6]) progressed well. Next, the Pd^0-catalyzed reaction between arylhalide **27** and **7** under above described conditions resulted in only the mono-*N*-aryl piperazine **28** albeit in small amount (~5% yield with 0.5 mol% catalyst). On the other the reaction of triazolone **29**[15] with **7** under previously described reaction conditions[1] led to degradation of **29** instead of the formation of **30**.

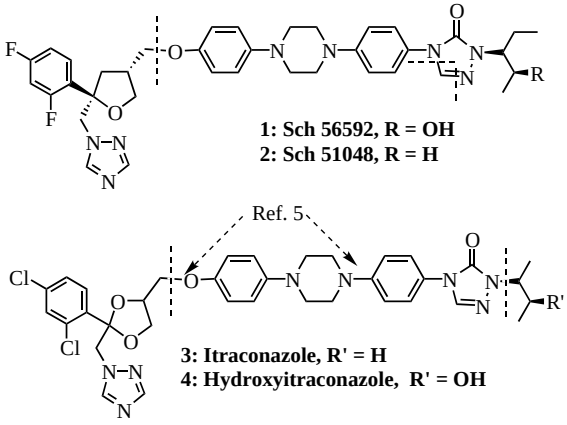


Figure 1. The antifungals and their synthetic disconnections.

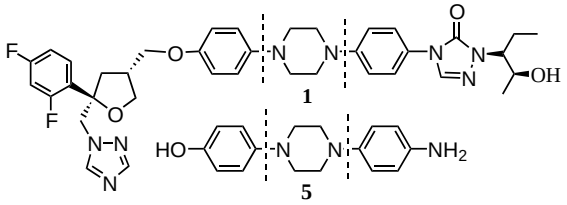
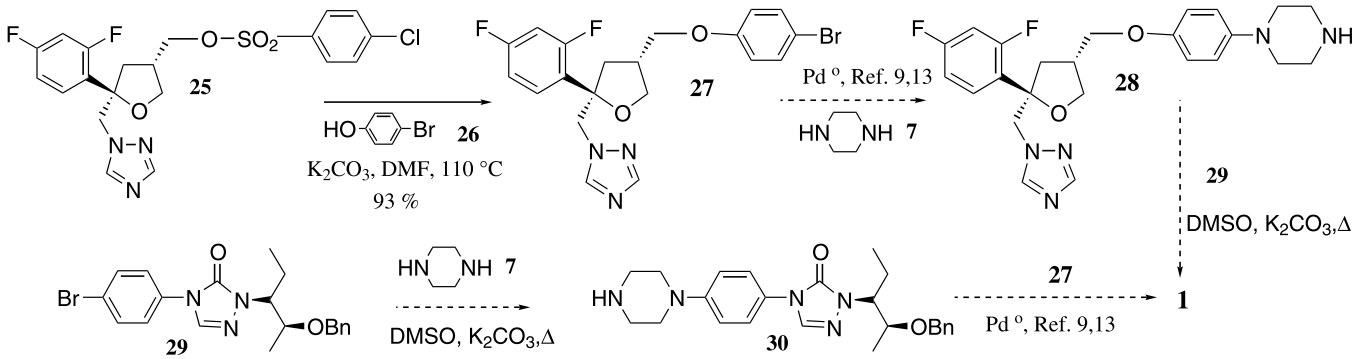


Figure 2. New disconnection for the synthesis of **1**, and **5**.



Scheme 4. Synthesis of antifungal **1** via piperazine mono-*N*-arylations methods.

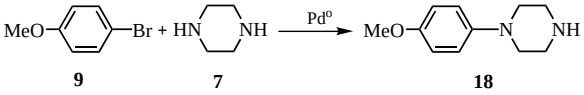
Thus, the outcomes of the initial efforts for both the Pd^0-catalyzed as the non-catalyzed piperazine mono *N*-arylation towards the preparation of **1** were discouraging.

In view of the above mono-*N*-arylation of piperazine with non-electron deficient aromatic halide, and in view of Pd^0-catalyzed amination of arylhalides in general,[12] the low yield for the reaction between **7** and **27** was intriguing. Good solubility of **7** and **27** in toluene, the use of several lots of reagents, ligands, as well as the catalyst eliminated the possibility that the low yield was imparted by specific set of reagents. Increasing the catalyst amount to 2 mol% led to ~20% solution yield of **9** suggesting a catalyst poisoning in this reaction.

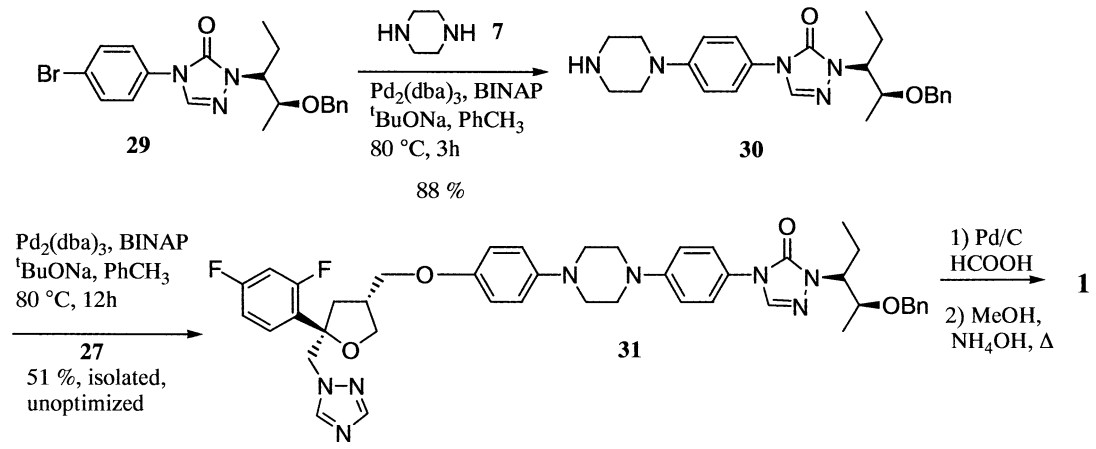
This prompted us to further investigate Pd^0-catalyzed arylation of piperazine. Due to simplicity of the substrates the reaction between **9** and **7** to form **18** (Scheme 5) was chosen as a model reaction to study the above mechanism with NMR. In one set of experiments the mixture of **18** and the catalyst (prepared as described previously)[9–13] was first subjected to the reaction conditions (80°C, toluene). The use of this pretreated catalyst for reaction between fresh **7** and **9** led to no additional product **18**. This suggested a catalyst deactivation during pretreatment with **18**. This deactivation can be either due to chelation of the catalyst with **18** or due to catalyst poisoning by non-specific binding. ^1H and ^{31}P NMR probing of this reaction showed that the formation of the catalyst progressed as reported previously.[16] When this catalyst was treated with **18** and warmed, ^{31}P NMR signals for the catalytic species significantly decreased and ^{31}P NMR signals for the BINAP increased correspondingly. The catalyst by itself did not generate BIINAP ^{31}P NMR signals upon heating. Thus, under the reaction conditions, mono *N*-arylpiperazine **18** appears to compete with BINAP for $Pd_2(dba)_3$ or displace BINAP from the catalytic spices interfering with the catalytic cycle.[9,16] This NMR study suggests that mono *N*-aryl piperazines displace BINAP from the catalytic species there by preventing its diarylation. Finally comparative rate/extent of catalyst deactivation by product compared to the rate of piperazine *N*-arylation govern the extent of mono *N*-arylation reaction. Although additional studies are needed to fully understand this mechanism, the above study generated sufficient information for us to complete the novel synthesis of **1**.

Based on the above observations, the strategy for the synthesis of **1** was revised (Scheme 6). First triazolone **29** was reacted with **7** under Pd^0-catalyzed conditions to produce compound **30** in 88% isolated yield.[17] This may be due to the possibility that product **30** of this reaction forms faster than the catalyst deactivation. Coupling of **30**, with **27** to form **31** was then accomplished also via Pd^0 catalysis. This reaction was slower compared to the preparation of **30**.[18] Alternately, a one-pot coupling of piperazine with **29** followed by the reaction of **30** with **27** can be achieved in a reasonable time (1 day) with a fresh does of catalyst added to the reaction mixture after the formation of **30**. The product profile was less clean in the latter case. Compound **31** was debenzylated via the known transfer hydrogenation procedure[6] to obtain posaconazole **1**, identical to the one obtained via the previous route.[6]

In summary, a Pd^0-catalyzed method for the mono *N*-arylation of piperazine from commercially available inexpensive raw materials without the use of protecting groups, high pressure/temperature equipment, or chromatographic purification has been discovered. This method has been applied to a short, convenient preparation of the key differentially *N*,*N*′-diaryl substituted piperazine antifungal intermediate. After a limited mechanistic investigation, this mono-*N*-arylation finding has been used to develop a novel synthesis of the antifungal posaconazole. The Pd^0 catalysis method complements our recently published direct, mono *N*-arylation of piperazine with arylhalides containing electron withdrawing groups.



Scheme 5. Model reaction for mechanism study via NMR.



Scheme 6. Novel synthesis of **1** via Pd^0-catalyzed piperazine mono-*N*-arylation.

Acknowledgements

We thank Dr. George Wu for many discussions on the mechanism aspect of this project.

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11. Typically, the aromatic halides (Ar-X) are converted to Grignard reagents (Ar-Mg-X) which up on reaction with trimethylborate ($B(OMe)_3$) followed by hydrolysis lead to arylborates ($Ar\text{-}B(OH)_2$).
12. For reviews on Pd^0-catalyzed amination of aromatic halides, please see: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805; (b) Hartwig, J. F. *Synlett* **1997**, 329; (c) Frost, C. G.; Mendonça, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2615.
13. Typical experimental procedure (unless noted otherwise): To a solution of piperazine (5.5 mmol) in toluene was added $Pd_2(dba)_3$ (0.025 mmol) and (+), (−), or (±)-BINAP (0.075 mmol). Arylhalide (5 mmol) was added dropwise, followed by NaO^tBu (7.5 mmol) as a suspension in THF. The resulting mixture was heated to 80–90°C for prescribed amount of time. The reaction was cooled to ambient temperature and diluted with EtOAc and water. After separation of the layers, the organic phase was washed once with water. The combined aqueous layers were back extracted with EtOAc. The resulting combined organic layers were extracted with 1N HCl. The combined acidic layers were treated with NaOH to pH 12. The mixture was then extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the product. $CsCO_3$, NaHMDS, or KHMDS as bases offered no advantage over NaO^tBu.
14. Twice the amount of the catalyst/ligands added to shorten the reaction time.
15. A gift of this compound from Dr. Anantha Sudhakar is appreciated.
16. Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176.
17. Laboratory work had indicated that under the Pd^0 catalysis condition, electron withdrawing group containing **29** first monoarylates piperazine to form **30**. When **30** was allowed to react with fresh catalyst and more **29**, the bis arylation set in. The bis arylation was slow (required ~3 days for ~80% yield of the symmetrically *N*,*N*′-bis-substituted piperazine).
18. Presumably due to the steric bulk associated with the reacting species.