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Synthetic Study on the Unique Dimeric Arylpiperazine: Access to the Minor Contaminant of Aripiprazole

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Abstract—The dimeric derivative of Aripiprazole was synthesized via the two notable synthetic technologies as a key step: (1) efficient aldehyde bis-arylation by $Bi(OTf)_3$ and (2) facile Wynberg amination at room temperature. The synthesis has established the structural identity with the minor contaminant sometimes present in Aripiprazole.

Arylpiperazine skeleton has been widely recognized as an important and essential pharmacophore in contemporary medicinal chemistry, especially in close relation to some serotonin receptor ligand or other CNS modulators. Thus, many structural variants of arylpiperazines have been prepared in order to attain specific biological profile. Trends of such medicinal research mostly focused on the specified ring-substituted derivatives of arylpiperazines.

Very few examples of dimeric or polymeric arylpiperazines have so far emerged as a promising candidate for drug substance. As part of our process research on antipsychotic agent Aripiprazole (**1**),[1] a trace amount of dimeric derivative was detected in a raw bulk material, causing problem in further characterization and purification.

For the precise characterization, a careful inspection by NMR (^1H and ^{13}C) indicated the bis-arylpiperazine structure (**2**), in which two moles of Aripiprazole was connected by 1,1-diarylethane bridge as shown in Figure 1. To identify the proposed structure (**2**) and further to detect the origin of this contaminant, we started the chemical synthesis of **2**. We report herein the whole story regarding the synthesis of **2** along with some speculations regarding the most probable origin of **2**.

Our synthesis is based on the two new technologies developed for the improvement of the classical aldehyde bis-arylation reaction, as well as uncommon piperazine introduction reaction by the lithium amide species. These tactics are briefly summarized in Figure 1.

Thus, aldehyde bis-arylation was first examined with the substrates (**A** and **B**). After that, arylpiperazine introduction was investigated thoroughly with the substrates which bears 1,1-diarylethane skeleton (**C**) as detailed in Scheme 1.

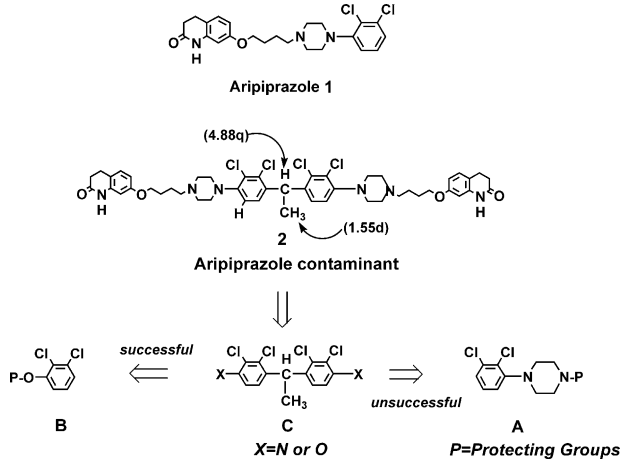

Figure 1. Dimeric arylpiperazines.

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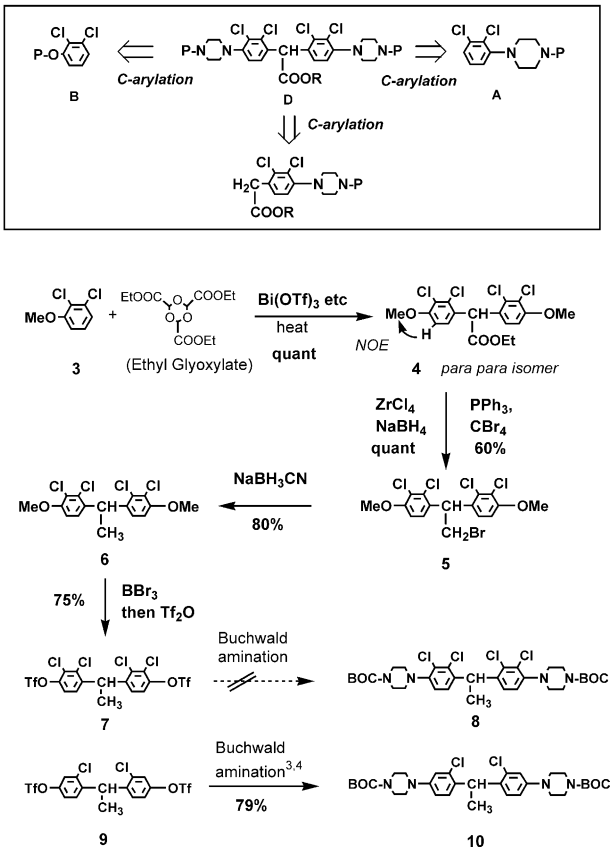


Scheme 1. C-Arylation tactics.

Aldehyde Bis-arylation

Direct reaction of phenylpiperazines (**A**) with acetaldehyde and its derivatives (i.e., **A** into **C**) simply led to the recovery of SM. This made us find a good reaction partners and catalysts for aldehyde bis-arylation. Among the reaction candidates shown in Scheme 1, we found that 2,3-dichloroanisole (**3**) was a good substrate (in reactivity and availability), which gave 2,2-diarylacetate (**4**) in nearly quantitatively, via the reaction with ethyl glyoxylate polymer by the aid of a catalytic metal triflate [$Sc(OTf)_3$, $Bi(OTf)_3$].[2] We did not detect any demethylation reaction, which was often occurred by the use of a classical Lewis acid catalyst such as $AlCl_3$.

Furthermore, the key *para para* dimeric structure was secured on the basis of cosy and noesy spectra as shown. Predominant formation of the one isomer (**4**) was crucial for further elaboration to **2**.

As other reaction candidates, amine derivatives such as 2,3-dichloroaniline and 2,3-dichlorophenylpiperazines (structure: **A**) were very sluggish in this glyoxylate bis-arylation reaction. Use of more selective catalysts including Clay and Zeorite were ineffective.

Conversion of **4** into the desired 1,1-diarylethane (**6**) was carried out in a straightforward way as shown in Scheme 1. (1) Reduction of **4** by $ZrCl_4/NaBH_4$ afforded the alcohol (nearly quantitative). (2) Bromination of the alcohol by Ph_3P/CBr_4 gave the bromide (**5**) (80% from alcohol). (3) Reduction of the bromide by $NaBH_3CN$ furnished the requisite 1,1-diarylethane (**6**) (80%). The overall yield from **4** to **6** was at first around 60% using crystallization in each step. Improvements of reagent combination of each step have been attained successfully, and the whole story of this progress has already been detailed in another article.[2b]

Piperazine Introduction

The most important task after aldehyde bis-arylation was an introduction of two piperazine units into **6**. There were two notable (complementary) pathways for the conversion of anisole derivative into arylpiperazines: Buchwald amination and Wynberg amination. We made intensive study along this line until our development of useful modifications as summarized below.

Buchwald amination

The direct catalytic amination of aromatic halides has become popular since 1995, when Buchwald and Hartwig independently reported clever reagent systems by the choice of bulky phosphine in combination with a strong base. There were many follow-up of this amination technology including some applications to arylpiperazine synthesis in medicinal chemistry research.

Like others, we reported some successful applications in the closely related substrates (**9**).[3] In order to apply this protocol to the present substrate, we examined the reaction of the triflate (**7**), which was stable and easily obtainable from **6** by the standard transformations (demethylation by BBr_3 in CH_2Cl_2 followed by the treatment of Tf_2O and pyridine).

In contrast to our expectations, however, the attempted Buchwald amination of **7** with *N*-Boc piperazine gave no desired arylpiperazines even under our optimized conditions (i.e., **9** into **10**).[3,4]

Instead, the reaction of **7** turned out to be very slow and we only isolated the phenol by-products (derived from hydrolysis of the triflate) along with a large amount of starting material (**7**).

This unsuccessful outcome of Buchwald catalytic amination prompted us to investigate the feasibility of Wynberg amination, which required very harsh conditions employing anisole and lithium amide under long h of reflux.[5]

Modified Wynberg amination

Wynberg has reported a protocol for amination, which enabled direct aromatic substitution reaction of anisole by the lithium amide in 1993. There were however very few application of this technology, partly because of the harsh reaction conditions and long reaction time with refluxing. In the original reported procedures, reactions usually required long h of reflux (>10 h) after tedious formation of lithium amide.[5]

To circumvent these inherent problems of the original protocol, and to find a clue for congested arylpiperazine synthesis, we conducted some model experiments with careful modification in solvent system and in the way of addition of alkyllitium reagents. Very simple modifications did work very well as summarized below.

In our model study, we found that the reaction of 2,3-dichloroanisole (**3**) and *N*-methylpiperazine (**11**) was feasible at room temperature during the slow addition of a solution of *n*-BuLi (3 M) to a stirred mixture of **3** and **11** in DME (not THF). This operation did simplify the time-consuming protocol originally reported by Wynberg.[5] Reactions with other polar solvents (DMF, DMA, NMP, DMSO) were unsuccessful which accompanied substantial formation of unwanted side products derived from the reaction of solvent itself. As originally reported by Wynberg, ethereal solvents (DME, THF) were essential for this transformation under Ar atmosphere. The yields were usually higher in DME (75–80%) than in THF (50–55%).

In the real substrate (**6**), our modified protocol worked quite well, affording the desired bis-arylpiperazine (**12**) by the slow addition (exothermic) of excess *n*-BuLi (2.5 to 3.5 equiv to **6**) to the stirred solution of **6** and **11** (3.5 to 4 equiv to **6**) in DME. After stirring for ca. 2 h at rt, NMR analysis of the crude extracts indicated ca. 85% yield of the desired bis-arylpiperazine (**9**).

As indicated in Table 1 in Scheme 2, key to the reproducible result was a slight excess piperazine and *n*-BuLi and the rate of addition of BuLi so as to keep the mixture below 55 °C under Ar.

We also attempted this reaction with different piperazines and bases. As a more convenient base, we attempted to use LiOR or other alkoxides (MOR), but almost no reactions were observed in DME at ambient temperature. Only a trace of product was formed after heating. Attempted reactions with other piperazine derivatives such as *N*-benzylpiperazine and *N*-Boc piperazine were sluggish and found to be impractical for our synthesis. As far as we surveyed with various anisole derivatives, reaction of *N*-methylpiperazine in DME as solvent gave the best result as shown above.

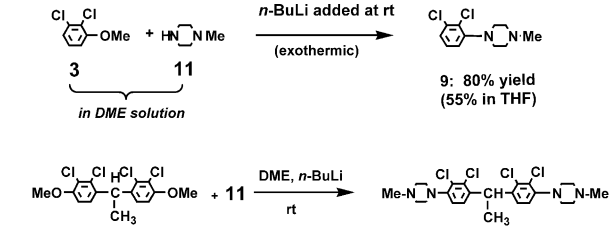


Table 1

run	6	11	BuLi	stirring	12
1	32 mM	3.5 eq	3.5 eq	rt, 2 hr	19.0 g (solid)
2	32 mM	4.5 eq	2.5 eq	rt, 3 hr	22.5 g (solid)

Scheme 2.

Transformation to 2

To obtain our target molecule (**2**), de-methylation of **12** was investigated next. Two protocols were available for this purpose: 1-chloroethyl chloroformate (ACE-Cl) and trichroloethyl chloroformate (TROC-Cl). Successful one-pot de-methylation was possible by the choice of ACE-Cl in EDC followed by refluxing in MeOH as summarized in Scheme 3. Simple evaporation of all volatile materials under reduced pressure afforded the hydrochloride (**13**) as a brown caramel, which was purified by precipitation in EtOH to afford the solid hydrochloride (**13**) with good purity. Partial deprotection product (mono *N*-Me derivative of **12**) or other side products were removed in the filtrate. The solid material (**13**) was then subjected to the next *N*-alkylation in a usual manner as shown in Scheme 3.

Thus, the two segments (**13** and **14**) were refluxed in H_2O–IPA in the presence of K_2CO_3 for 6 h. After removing IPA, resulting mixture was diluted and extracted with CH_2Cl_2. Crude product was further purified by SiO_2 column chromatography (AcOEt–MeOH–Et_3N) to give nearly pure product **2** (40%) as a major product. The improved result was obtained by the addition of PTC catalyst (TBAI) or by performing this reaction in DMF–NaH composition (65–70%).[6] The product was crystallized from EtOH–AcOEt to furnish the solid material that was super-imposable with the authentic sample isolated from the raw Aripiprazole in ^1H NMR, and ^{13}C NMR, as shown below.

Dimerization of Aripiprazole

After having obtained the authentic samples of **2** as well as its precursor (**13**), we searched for their origin in Aripiprazole production. First of all, we attempted the direct reaction of Aripiprazole with acetaldehyde (or equivalents) to obtain **2** (or other dimeric products). Although we carried out many reaction conditions but none of the dimeric structure related **2** was obtained. Instead, we could isolate another type of dimer (**15**), under very harsh reaction conditions, whose structure was tentatively assigned as shown in the following Scheme 4.

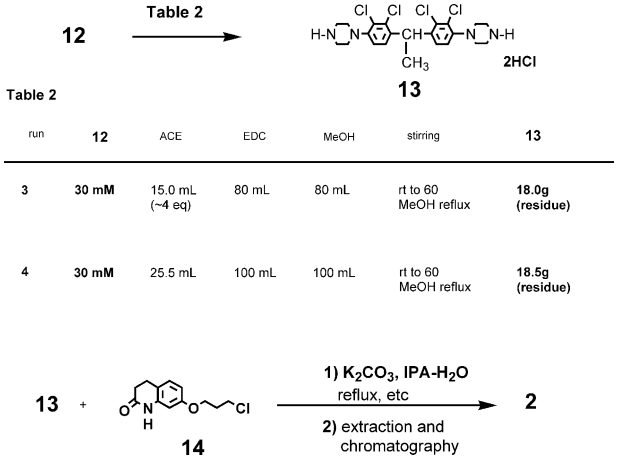
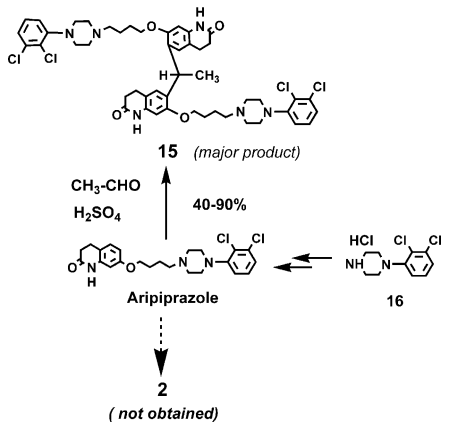


Table 2

run	12	ACE	EDC	MeOH	stirring	13
3	30 mM	15.0 mL (~4 eq)	80 mL	80 mL	rt to 60 MeOH reflux	18.0g (residue)
4	30 mM	25.5 mL	100 mL	100 mL	rt to 60 MeOH reflux	18.5g (residue)

Scheme 3.



Scheme 4.

In the meantime, we carried out careful inspection of the starting material supplied by the foreign bulk makers. This survey revealed the presence of **13** in the bulk material of arylpiperazine segment (**16**).[7] We thus tentatively speculate that the origin of the dimeric contaminant (**2**) must be the presence of **13** in the starting material (**16**). This means that pure Aripiprazole can be obtained from the pure starting material **16** definitely free from the contaminants formed during the preparation.[7]

In summary, we have succeeded in the synthesis of the dimeric derivative of Aripiprazole (**2**) by the newly devised synthetic technologies. The sequence shown here demonstrated the utility of Wynberg amination for the sterically demanding substrate such as **6**, instead of the catalytic amination developed recently. Some of the representative procedures are summarized below. Our synthesis also indicated the presence of the origin of the contaminant (**13**) in the bulk starting material (**16**).

Selected Experimental Procedures

Modified Wynberg amination

To a stirred solution of **6** (31 mM)[2] and *N*-methylpiperazine (**11**, 4.5 equiv; distilled and flushed with Ar) in dry DME (Kanto, 100 mL) was added under cooling (25–30 °C), a solution of *n*-buthylithium in hexane (Kanto, ca. 2.5 M; 50 + 10 mL; ca. 2.5 equiv) via syringe (exothermic reaction; inner temp below 55 °C) under Ar. Resulting mixture was stirred without cooling for further 3 h, before it was quenched by the addition of H_2O (17 mL; added by drops). The resulting mixture was then diluted with AcOEt and stirred with Na_2SO_4. Filtration and evaporation of the organic layer afforded crude products, which was subjected to vacuum pumping to form a caramel or half-solid material (22.5 g). NMR analysis of this crude product was critical. Comparison with standard sample guaranteed that **12** was the sole product formed with trace of **11** after intensive vacuum pumping.

1-Chloroethyl chloroformate (TCI, 25.5 mL) was added at rt to a stirred solution of **12** obtained above (22.5 g; ca. 30 mM) in dry EDC (100 mL) under Ar. The resulting mixture was warmed at 50–60 °C for 5 h. TLC indicated the major formation of less polar spots (*N*-chloroethylformate derivatives). The mixture was further heated to reflux after addition of MeOH (100 mL) to form the hydrochloride (**13**). The dark mixture was stirred at ambient temperature to precipitate insoluble solid mass, which was subsequently removed by filtration. Evaporation of the filtrate afforded crude product as brown caramel (18.5 g), which was treated with hot EtOH to remove side products. Thus obtained solid material **13** (12.5 g) showed enough purity (85–95%) by HPLC analysis, which was directly subjected to the next *N*-alkylation to furnish **2**.

Selected data for **13**. ^{13}C NMR (DMSO-d_6) δ: 144.1, 134.5, 128.4; 122.9, 122.8, 115.4, 43.7, 38.9, 15.9. ^{1}H NMR (DMDO-d_6) δ: 9.50 (br, 4H), 7.20 (m, 4H), 4.78 (q like, 1H), 3.29, (m, 8H), 1.52 (d, 3H, $J = 7.2$ Hz).

Selected data for **2**. ^{13}C NMR ($CDCl_3$) δ: 172.1, 158.5, 149.1, 138.4, 138.1, 133.7, 18.5, 128.1, 125.9, 118.0, 115.5, 108.6, 102.1, 67.7, 58.1, 53.2, 51.2, 39.7, 31.0, 27.2, 24.4, 23.3, 20.0. ^{1}H NMR ($CDCl_3$) δ: 8.19 (br, 2H), 7.08 (d, $J = 7.1$ Hz, 2H), 6.98 (m, 4H), 6.56 (dd, $J = 7.1$, 2.4 Hz), 6.36 (d like, 2H), 4.89 (q like, 1H), 4.00 (t like, 4H), 3.09 (m, 8H), 2.93 (m, 5H), 2.66 (m, 12H), 2.52 (m, 4H), 1.86–1.70 (m, 12H), 1.55 (3H, d, $J = 7.0$ Hz).

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7. Careful inspection of the bulk material (**16**) revealed the presence of two minor contaminants. Beside **13**, we identified the new *sym*-triamine derivative ($ArNHCH_2CH_2NHCH_2CH_2NHAr$), which was fortunately eliminated during the transformation to Aripiprazole. Attempted *N*-alkylation of this triamine with excess **14** did not give any *N*-alkylated products under standard conditions. Details will be published elsewhere together with the contaminants of other arylpiperazines having different substituents.