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Synthesis of 3-Arylpiperidines by a Radical 1,4-Aryl Migration

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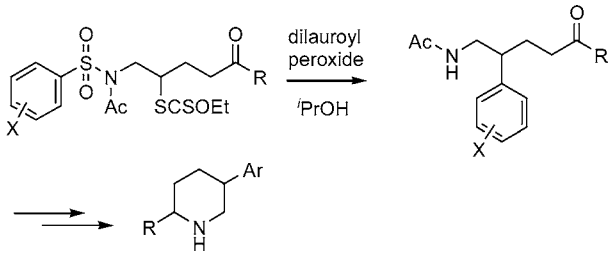
ABSTRACT



A route to 3-arylpiperidines, 3-arylpyridines, and 5-arylpiperidin-2-ones involving a radical 1,4-aryl migration has been explored. The sequence requires a xanthate addition to an *N*-allylarylsulfonamide, followed by acetylation and treatment with dilauroyl peroxide to give the 1,4-aryl transfer product, which upon acidic hydrolysis affords the desired piperidine derivative.

3-Arylpiperidines have been thoroughly investigated since the early 1980s in view of their interesting opioid[1] and dopaminergic activity.[2] One of the most interesting of these is preclamol (Figure 1), reported to be the first selective D_2-like dopamine autoreceptor agonist. Potent dopaminergic substances, such as preclamol and related compounds, have potential for the treatment of schizophrenia, Parkinson's disease, depression, and drug addiction. Moreover, in the past few years, the identification of 3-arylpiperidines as antagonists of the tachykinin system,[3] as inhibitors of the steroid 5α-reductase[4] or as ligands to the σ receptor,[5] makes them even more interesting targets.

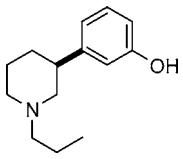


Figure 1. Preclamol, a dopamine autoreceptor agonist.

In contrast with their interesting pharmacological profile, few methods to construct 3-arylpiperidines have been reported to date.[6] The majority are based on a nickel cross-coupling between an arylmagnesium bromide and a bromopyridine,[7] a Heck[8] or a Suzuki[9] coupling. The resulting substituted pyridine is then reduced.

We now present a new synthesis of 2-substituted 5-arylpiperidines obtained via a key step involving a radical 1,4-aryl transfer. Our synthetic design, depicted in Scheme 1, relies on the rich chemistry of xanthates[10] and starts from *N*-allylsulfonamides **1a**−**g**.

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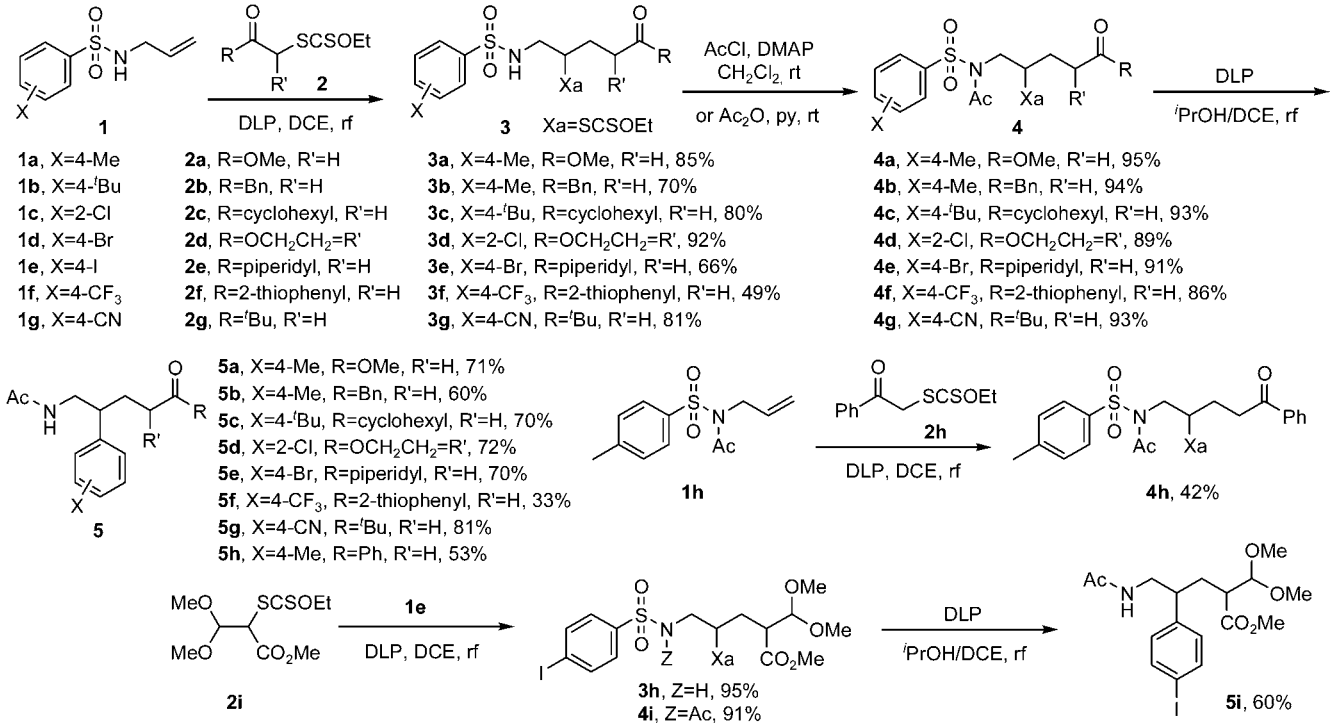
Scheme 1. Synthesis of β-Arylacetamides **5**



When a solution of olefin **1** and xanthate **2** (1.5 equiv) in 1,2-dichloroethane (DCE) was heated to reflux in the presence of a small amount of lauroyl peroxide (DLP), adducts **3** were obtained in good yield. Because the subsequent radical transposition step proceeded in low yield with nonprotected sulfonamides **3** (vide infra), these adducts were protected as the corresponding acetamides with either acetyl chloride or acetic anhydride. Interestingly, when the acetyl group was first introduced on the allyl sulfonamides **1**, the radical addition proceeded in significantly lower yield. For example, addition of xanthate **2h** onto olefin **1h** afforded **4h** in only 42% yield. This was a consistent observation and appears to be due to the lowering of the HOMO of the olefin by the additional electron withdrawing effect of the acetyl group, and a consequent increase in the energy gap with the SOMO of the radical (note that all radicals derived from xanthates **2** are electrophilic in chararcter). Thus, the radical addition was carried out by using nonacetylated olefins, and protection of the nitrogen atom was performed later in the synthetic sequence. The addition products **4** were subjected to the action of the peroxide to trigger the intramolecular radical 1,4-aryl migration for the formation of the β-arylacetamides **5**, precursors of the desired 3-arylpiperidines.

The key aryl migration to give **5** proceeds by the mechanism depicted in Scheme 2. There are many examples of radical aryl migrations in the literature, the most extensively investigated being 1,2-aryl migrations (neophyl rearrangement),[11] but 1,4- and 1,5-aryl migrations[12] have also been the subject of several studies. Aryl migrations are not restricted to movement from a carbon centered to a carbon centered radical. The aryl transfer from an aryl sulfonamide to a carbon centered radical was first described by Speckamp in 1972.[13,14] With this process it is possible to transfer electron rich and poor arenes. Sulfonamides arising from cyclization

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(12) For a review on radical aryl migration reactions, see: (a) Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649. (b) Studer, A.; Bossart, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, p 62.

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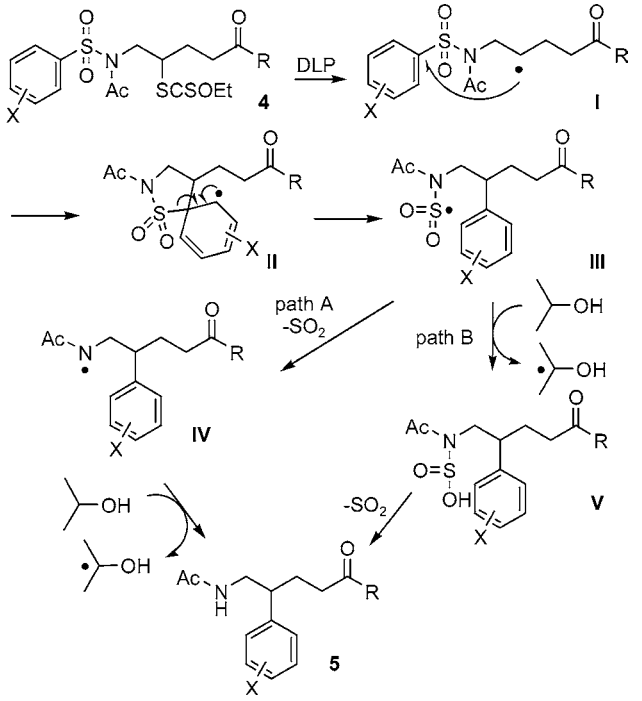
Scheme 2. Mechanism of 1,4-Aryl Transfer



to the aromatic ring and products of direct reduction have also been observed as side-products in these reactions.

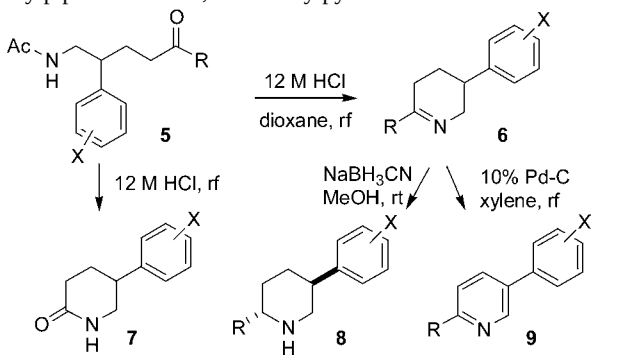
Hitherto, nearly all the examples of sulfur to carbon 1,4-aryl migrations use toxic tin hydrides. The present approach is not only tin-free, but also avoids high dilution and is experimentally very easy to perform. Lauroyl peroxide is simply added portion-wise to a refluxing solution of adduct **4** in a mixture of 2-propanol and 1,2-dichloroethane. 2-Propanol is a key element of the process. As outlined in Scheme 2, radical **I** must have enough lifetime to be able to undergo the desired aryl shift. Even though 2-propanol is capable of hydrogen atom transfer to a secondary radical such as **I**,[15] this process is relatively slow and does not compete efficiently with the *ipso* substitution leading to **III**. Extrusion of sulfur dioxide would then give a highly reactive electrophilic amidyl radical **IV**, which now is rapidly reduced by the 2-propanol. Hence the need to introduce an acetyl group in the first place. In its absence, the sequence would have furnished a much less reactive and more problematic aminyl radical. As for the ketyl radical derived from 2-propanol, it is simply oxidized into acetone by the peroxide, which must therefore be used in stoichiometric amounts. It is also possible that hydrogen abstraction from 2-propanol takes place at the level of radical **III**. Such amidosulfonyl radicals are electrophilic and loss of sulfur dioxide may be too slow to compete with the hydrogen abstraction.[16] This of course has no practical consequence on the outcome since ultimately amide **5** is formed through both pathways.

The aryl transfer products **5** were obtained in moderate to good yield (Scheme 1). In some examples we also recovered unreacted or deacetylated starting material, as well as what appeared to be the product of the reduction of radical **I**, which could account for the moderate yield in some runs. Previous trials showed 2-propanol to be the best hydrogen atom donating solvent, in comparison with toluene, cyclohexane, or isopropyl acetate. The use of carbamate instead of acetyl derivatives resulted in lower yields.

From the data in Scheme 1, it seems that the nature of the phenyl substituent X does not affect greatly the course of the reaction, as in both series of electron withdrawing and electron donating groups examples of good yields are found. As for the R substituent on the carbonyl group, it can be concluded that the best yields are found when there is an aliphatic ester or amide moiety (**4a**, R = OMe, 71%; **4d**, R,R′ = lactone, 70%; **4e**, R = piperidine, 70%). In the case of precursors **4f** and **4h**, the yield was lowered because of a competing cyclization of the intermediate radical (corresponding to **I** in Scheme 2) onto the thiophenyl and phenyl rings respectively to give the corresponding tetralone.[17] The best yield was obtained with sulfonamide **4g**, in which the aryl ring bears a cyano group and there is a bulky *tert*-butyl substituent on the carbonyl.

With compounds **5** in hand, we examined their conversion into piperidine derivatives. Acid hydrolysis of the acetamido group and subsequent cyclization afforded the desired substituted piperidines (Table 1). If the R substituent of the transfer product **5** is an alkyl or aryl group, the product obtained is an imine, which can be either reduced to the desired piperidine or oxidized to the corresponding pyridine. If the R radical is an alkoxy or an amine, the product is a piperidin-2-one.

Table 1. Synthesis of 5-Arylpiperidines, 5-Arylpiperidin-2-ones, and 5-Arylpyridines



acetamide	X	R	heterocycle
5a	4-Me	OMe	**7** (88%)
5b	4-Me	Bn	**8a** (85%)
5c	4-^{t}Bu	cyclohexyl	**8b** (65%)
5f	4-CF_3	2-thiophenyl	**8c** (77%)
5h	4-Me	Ph	**8d** (89%)
5h	4-Me	Ph	**9** (83%)

877. (g) da Mata, M. L. E. N.; Motherwell, W. B.; Ujjainwalla, F. *Tetrahedron Lett.* **1997**, *38*, 137. (h) da Mata, M. L. E. N.; Motherwell, W. B.; Ujjainwalla, F. *Tetrahedron Lett.* **1997**, *38*, 141. (i) Bonfand, E.; Forslund, L.; Motherwell, W. B.; Vázquez, S. *Synlett* **2000**, 475.

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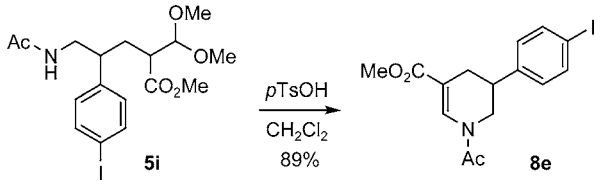
Hydrolysis was performed with concentrated HCl (Table 1), and the desired imines were used without purification as the hydrochlorides or the free imines. Reduction with sodium cyanoborohydride provided the desired 5-arylpiperidines in good yield and diastereoselectivity. In the case of acetamide-acetal **5i**, a cyclization induced by *p*-toluene sulfonic acid afforded piperidine **8e** in good yield (Scheme 3). This is an

Scheme 3. Synthesis of Nicotinic Acid Derivative **8e**

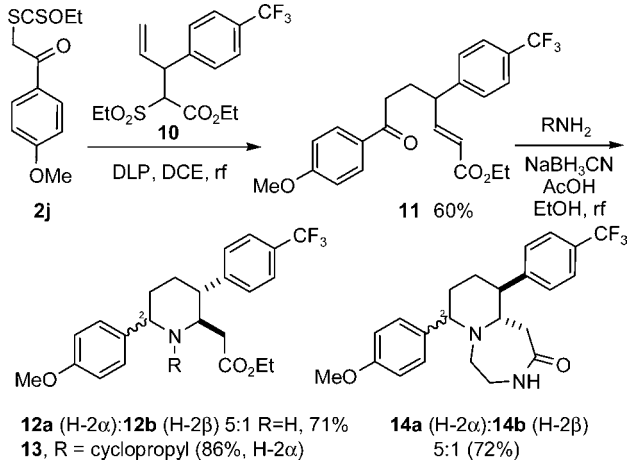


alternative route into nicotinic acid derivatives, and the unsaturation and iodine present in the molecule offer many possibilities for further functionalization.

The present approach to aryl substituted piperidines can be expanded by exploiting another sequence involving a 1,2-aryl migration we recently described.[18] As shown in Scheme 4, addition of xanthate **2j** to an olefin such as **10** results in the formation of derivative **11** in 60% yield through 1,2-shift of the trifluoromethylphenyl group and β-elimination of an ethyl sulfonyl radical.

Exposure of compound **11** to ammonia or a primary amine and sodium cyanoborohydride gave rise to the desired piperidine derivative. Thus, treatment of ester **11** with an excess of ammonium acetate and sodium cyanoborohydride in refluxing ethanol afforded the piperidine **12** in good yield and as a 5:1 mixture of diastereomers which could be separated by chromatography. When the reaction was performed with cyclopropylamine, however, the trisubstituted

Scheme 4. Synthesis of 2,5-Diarylpiperidines



12a (H-2α):**12b** (H-2β) 5:1 R=H, 71%
13, R = cyclopropyl (86%, H-2α)

14a (H-2α):**14b** (H-2β) 5:1 (72%)

piperidine **13** was obtained as a single diastereomer in excellent yield. With ethylenediamine, a second cyclization occurred and bicyclo derivative **14** was obtained as a mixture of two separable diastereomers in a 5:1 ratio (72%).

In summary, we have described a powerful, flexible, and convergent general strategy for constructing aryl substituted piperidines using readily available and cheap starting material. This approach, in combination with an earlier one involving addition of a xanthate to protected allylamine followed by ring-closure,[19] opens up a direct access to a vast number of more or less complex piperidine structures of interest to medicinal chemists. The sequence can be modified to provide the equally important substituted pyridines. It is also worth stressing the function group tolerance, in particular for aromatic iodides since these can act as springboards for numerous further transition metal based transformations.

Supporting Information Available: Detailed experimental procedures and spectra data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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