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Synthesis of new chiral pyrylium salts and their phosphinine and pyridine derivatives

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In memory of Professor Masahisa Hasegawa who recently passed away

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ABSTRACT

Despite their versatility, chiral pyryliums are almost unknown in the literature. Reported here is the synthesis of several new chiral pyrylium salts and the corresponding pyridines and phosphinines. This work more than doubles the number of reported chiral pyryliums, and also represents the first racemizable/epimerizable pyryliums. The derived phosphinines and pyridines represent rare α-chiral ligands for transition metals.

Introduction

Pyrylium salts are versatile synthetic intermediates, easily transformed into various heterocycles, including pyridines, phosphinines, *N*-alkyl pyridiniums, and thiopyryliums.[1] Pyrylium salts are also interesting for their electronic properties, being strongly electron-accepting.[2]

Pyrylium salts can be synthesized by a variety of methods that allow various substitution patterns, though in practice aryl substituents are far more common than alkyl groups.[2] Polymerization is often a major problem in the formation of pyryliums, resulting in tar with little or no product formation in unfavorable cases. Surprisingly, chiral pyrylium salts are almost unknown in the literature. By our count, only three compounds have been reported to date (Fig. 1): the C_2-chiral pyrylium recently synthesized in our group (**1**),[3] a racemic atropisomer (**2**),[4] and a C_1-chiral camphor derivative (**3**).[5] We attribute this paucity of examples to difficulties in the synthesis of non-aryl-substituted pyryliums, having encountered many tar-forming reactions ourselves.

We have found that the reaction of acyl chlorides with dypnone, first developed by LeFevre[6] and modified by Katritkzky and coworkers,[7] is widely applicable to the preparation of simple chiral pyryliums (Scheme 1). Four chiral pyryliums (**4a**–**d**) and two non-chiral examples (**4e**,**f**) were made and characterized (Table 1). The yields were modest (23–70%), as is typical of many pyrylium syntheses. The pyrylium products were isolated by simple dilution with ether, taking advantage of their near-universal insolubility in that solvent.[1] The ^{13}C NMR spectrum exhibited the characteristic pyrylium peaks (165–185 ppm), further downfield than the typical aromatic region.

Pyryliums **4a** and **4b** were prepared from campholic and fenchoilic acids, respectively, and derived from (+)-camphor and (−)-fenchone, respectively, by the method of Whitesides.[8] Both (+)-camphor[9] and fenchone[10] are regarded as enantiomerically pure materials. Pyrylium **4c** was prepared from ibuprofen. Pyrylium **4d** was prepared from the commercially available 86:14 mixture of cis:trans 2-methylcyclohexanecarboxylic acid.[11] We found that the cis isomer had a larger coupling (7.1 Hz) for the methyl doublet than did the trans isomer (6.5 Hz), and this was consistent (6.3–6.5 Hz) in all of the derivatives **4d**, **6d**, and **7d**, allowing assignment of the stereochemistry. Also consistent was that the methyl doublet for the cis isomer was always downfield of that for the trans. Finally, the benzylic tertiary hydrogen in every case exhibited two large axial–axial couplings (11–15.6 Hz) consistent with the trans isomer. Pyrylium **4e** was a single diastereomer, even though it was made from 4-*tert*-buytlcyclohexane carboxylic acid which was a 95:5 mixture of trans:cis isomers.

It is evident from this work that pyryliums with α-chiral centers bearing a hydrogen are relatively easily racemized or epimerized. To our knowledge, no epimerizable pyryliums have been reported previously in the literature. The only indication of epimerizability has been from deuterium exchange experiments.[12,13] The diastereomer ratios (39:61 cis:trans) for pyrylium **4d** (determined by

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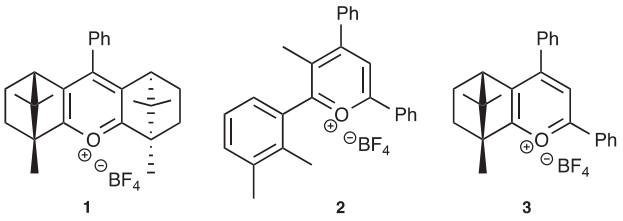
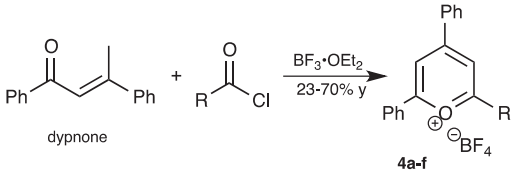
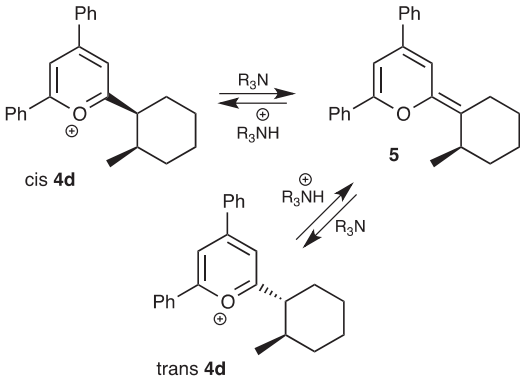


Figure 1. Existing chiral pyryliums.



Scheme 1. Preparation of pyryliums from dypnone.[7]

^{1}H NMR) deviate measurably from the cis:trans ratio (86:14) of the carboxylic acid starting material.[11] This could, of course, be attributed to several factors: equilibration during acid chloride formation, differential reactivity in pyrylium formation, or isolation efficiency, especially given the low yields. All of these are probably occurring to some extent. Indeed, when (*S*)-ibuprofen was used to prepare **4c**, racemic pyrylium was obtained. More significantly, however, we have observed that pyrylium **4d** is readily epimerized by catalytic amounts of *N*-methylmorpholine, yielding a 9:91 ratio of cis:trans isomers (Scheme 2). This clearly proceeds through the well-known[7] 'pseudobase' intermediates (**5**), which can be observed or even isolated when any of the pyryliums **4c**, **4d**, **4e**, or **4f** are treated with stoichiometric triethylamine. A detailed study of the epimerization of these and other pyryliums is in progress.

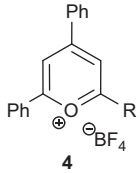
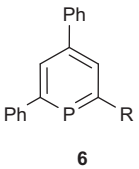
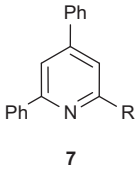
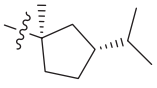
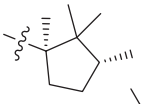
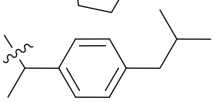
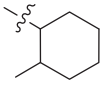
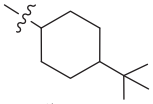
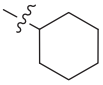


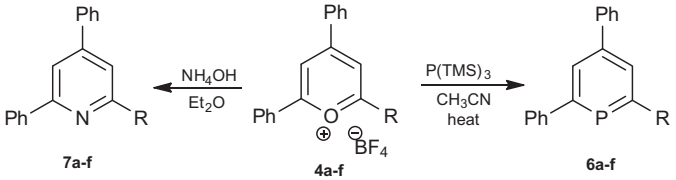
Scheme 2. Amine-catalyzed epimerization mechanism.

Pyrylium salts are partly of interest because of the potential to convert them into the corresponding phosphinines and pyridines, which are often good ligands for transition metals. Phosphinines have a combination of poor σ-donating ability with strong π-accepting capacity that makes them attractive ligands for the stabilization of highly electron-rich metal centers.[14] Interestingly, only a few examples of chiral phosphinines have been reported in the literature.[3,15,16] Incorporation of chirality directly (i.e., α to the pyrylium ring) in these otherwise planar systems has proven to be difficult. From our pyrylium salts (**6a–f**) we have synthesized new phosphinines with the chirality as close as possible to the phosphorus center.

The pyrylium salts were converted into the corresponding phosphinines by treatment with excess of tris-(trimethyl-

Table 1
Yields of pyryliums (**4**), phosphinines (**6**), and pyridines (**7**)

R =	 **4**	 **6**	 **7**
	4a (23%)	6a (46%)	7a (90%)
	4b (25%)	6b (57%)	7b (98%)
	4c (23%)	6c (31%)	7c (79%)
	4d (25%; 39:61) cis:trans	6d (38%; 10:90) cis:trans	7d (77%; 22:78) cis:trans
	4e (70%, trans)	6e (70%, trans)	7e (85%, trans)
	4f (49%)	6f (49%)	7f (80%)



Scheme 3. Synthesis of substituted C_1 phosphinines and pyridines.

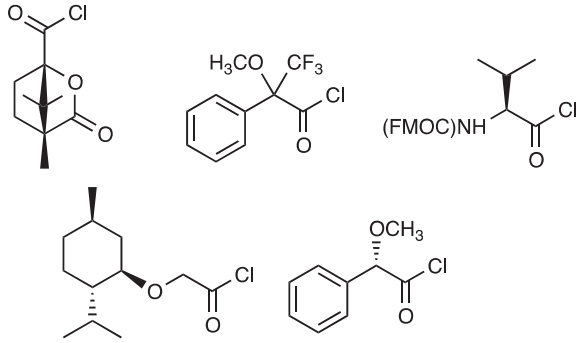


Figure 2. Acyl chlorides that do not yield the desired pyryliums.

silyl)phosphine ($P(TMS)_3$) in refluxing anhydrous acetonitrile for 24 h (Scheme 3).[17] After column chromatography the phosphinines were obtained as brown oils. The phosphinines showed the typical downfield resonance at δ 180 ppm in the ^{31}P NMR spectrum.

Chiral pyridine ligands have been known for some time but the development of their applications in asymmetric catalysis had been lacking until 1981, when the first report of chiral pyridine ligands and their application in asymmetric catalysis appeared.[18] Interestingly, no examples can be found in the literature that use the conversion of chiral pyrylium salts to the corresponding chiral pyridines.

The pyridine derivatives were obtained in high yields by stirring the pyrylium salts with ammonium hydroxide and diethyl ether for 30 min. In the case of the most hindered pyrylium salt (**4b**), the reaction required reflux with ammonium hydroxide for 6 h. After acid workup and without further purification the compounds were obtained as brown oils (Scheme 3).[19] The ^{13}C NMR spectrum displayed downfield aromatic peaks indicative of the trisubstituted pyridine (five peaks between 140 and 167 ppm).

In the course of our investigation, we found that certain acyl chlorides did not form the desired pyrylium salt, instead produce triphenyl pyrylium tetrafluoroborate. We believe that when the acyl chloride is not reactive enough for reaction, the dypnone undergoes a retroaldol to produce acetophenone. Excess acetophenone in the presence of boron trifluoride is known to yield triphenyl pyrilium salt. We notice that acyl chlorides that bear ether or ester functionalities (Fig. 2) inevitably fail to produce the desired pyrylium, perhaps because these functionalities are reacting with the excess boron trifluoride. The formation of triphenyl pyrylium salt from dypnone was also reported by Balaban.[20]

In summary, we have synthesized six new pyrylium salts, four of them chiral, and the corresponding phosphinine and pyridine derivatives. This provides the first racemizable/epimerizable chiral pyryliums, and kinetic studies of the equilibration of these are in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.006.

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