

Intramolecular Acylation of Aryl- and Aroyl-Aliphatic Acids by the Action of Pyrophosphoryl Chloride and Phosphorus Oxychloride

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Abstract: Both pyrophosphoryl chloride and phosphorus oxychloride react with aryl aliphatic acids to form mixed anhydrides which undergo intramolecular acylation to afford cyclic ketones without the addition of a Friedel-Crafts catalyst. Aryl and aroyl-benzoic acids could be cyclized to the corresponding anthrones and anthraquinones respectively.

Keywords: Pyrophosphoryl chloride, Phosphorus oxychloride, Cyclodehydration, Cyclic ketones, Anthraquinones.

Introduction:

Intramolecular acylation of aryl aliphatic acids is an important route for the preparation of cyclic ketones. A very useful method for effecting such acylation is the Friedel-Crafts reaction that employs the acid chloride or anhydride in the presence of catalysts like aluminum chloride or stannic chloride. The acylation can also be achieved by treating the free acid with a variety of condensing agents. These include liquid hydrogen fluoride [1], concentrated sulfuric acid [2], phosphorus pentoxide [3], polyphosphoric acid [4] and fluorosulfonic acid [5]. Shah used a combination of phosphorus oxychloride and zinc chloride to synthesize 4-hydroxycoumarins from phenols and malonic acid [6]. In some cases, cyclic ketones could be obtained by heating the free acid chloride under reduced pressure [7].

The Friedel-Crafts type of reaction involving the action of aluminum chloride or stannic chloride on the acid chloride requires the conversion of the acid into the corresponding chloride by thionyl chloride or phosphorus pentachloride. Purification of the resulting acid chloride is wasteful and may lead to decomposition. Acylation by liquid hydrogen fluoride has some drawbacks. The reagent is very difficult to handle as it is highly corrosive to tissues and its vapors are very toxic. Cyclization by concentrated sulfuric acid is more prone to undesired side-reactions such as enolization and aromatic substitution.

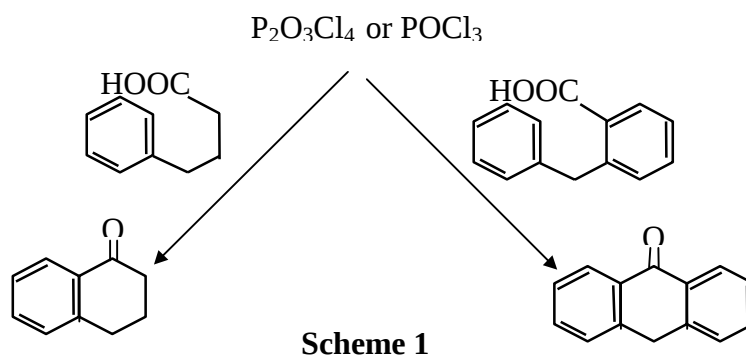
In view of these precedents, we sought to investigate the potential of pyrophosphoryl chloride and phosphorus oxychloride in effecting intramolecular acylation, thus hoping to overcome some of the shortcomings of other condensing reagents. Pyrophosphoryl chloride is a mobile liquid and it is reasonably easy to handle. It can be prepared by heating phosphorus pentoxide with phosphorus pentachloride according to the method developed by Crofts [8]. Both pyrophosphoryl chloride and phosphorus oxychloride are commercially available from a number of suppliers.

Both reagents had been used to prepare aryl- and alkylcarboxylic dichlorophosphoric anhydrides, which were fully characterized by Effenberger [9,10]. Their high reactivity was demonstrated by their ability to form esters of tertiary alcohols under mild conditions [10]. Furthermore, these anhydrides reacted with activated arenes without the addition of Friedel-Crafts catalyst to give good yields of aryl ketones [11]. In a related reaction, Heaney and Shuhaibar [12] used pyrophosphoryl chloride to effect Bischler-Napieralski reaction which is essentially a cyclodehydration process that affords heterocyclic compounds.

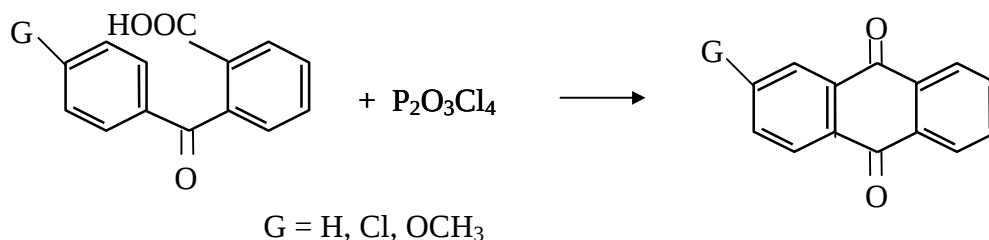
Results and Discussion:

Initial investigations indicated that pyrophosphoryl chloride effected the cyclization of o-benzylbenzoic acid to anthrone in excellent yield. Carboxylic acids with deactivating groups on the ring could be cyclized (with modest yields) by this method. The cyclization conditions and the reaction workup were simple.

Acylation of activated rings was achieved under mild conditions and generally gave excellent yields of the cyclized products. Thus, 2-benzylbenzoic and 4-phenylbutyric acid gave the corresponding ketones in excellent yields (Scheme 1, Table 1).

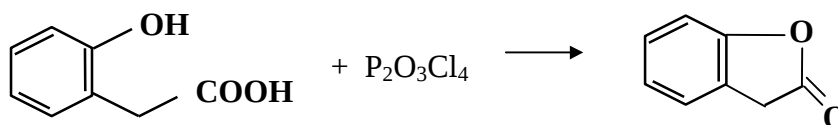


When 2-(4-substituted benzoyl) benzoic acids were used as substrates, the yield of the anthraquinone was very much dependent on the activation offered by the groups on the ring. While 2-(4-methoxybenzoyl)benzoic acid gave a good yield of the expected product, 2-benzoylbenzoic acid gave a moderate yield and 2-(4-chlorobenzoyl) benzoic acid gave a much lower yield. It appears that the presence of two deactivating groups on the ring ($-\text{Cl}$ and $-\text{C}=\text{O}$) caused a further reduction in yield (Table 1, Scheme 2) .



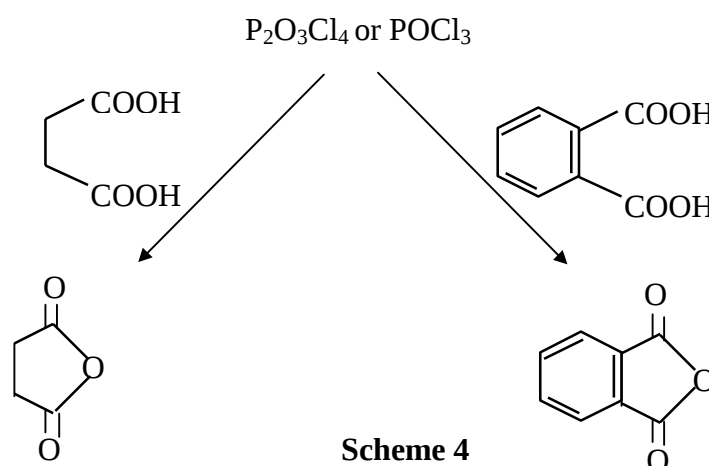
Scheme 2

While attempting to investigate the potential of pyrophosphoryl chloride to act on other substrates, we found that it converted 2-hydroxyphenylacetic acid into the lactone, 2-coumaronone, in nearly quantitative yield (Scheme 3).



Scheme 3

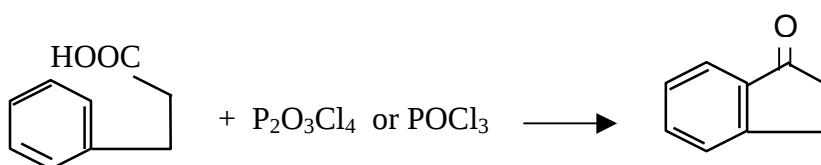
Our attempt to carry out double acylation of an ordinary ring gave an interesting result. Thus refluxing the reagent with phthalic acid in benzene afforded phthalic anhydride in a quantitative yield and no anthraquinone was obtained. Similarly, benzene could not be acylated by succinic acid. The refluxed mixture of pyrophosphoryl chloride, succinic acid and benzene gave succinic anhydride (Scheme 4).



Scheme 4

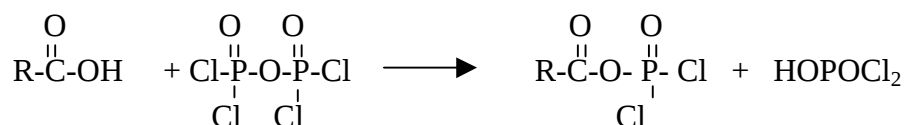
Our findings can be rationalized by considering the importance of intramolecular reactions. Whenever intramolecular dehydration is possible, it appears to be the preferred route. Thus, instead of reacting with the ring, a dicarboxylic acid favors dehydration to form the corresponding anhydride.

It was surprising to find that β -phenylpropionic acid gave a poor yield of 1-indanone. The major product was an unidentified viscous liquid. Cyclization under milder conditions slightly improved the yield of 1-indanone (Scheme 5), but considerable amounts of the viscous liquid were obtained.



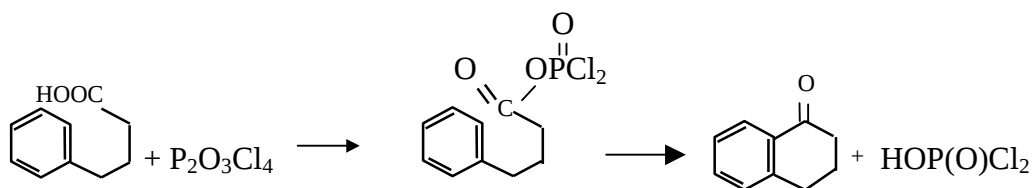
Scheme 5

The mode of action of pyrophosphoryl chloride on carboxylic acids had been investigated by Effenberger, König and Klenk. They proposed that pyrophosphoryl chloride reacts with carboxylic acids to produce mixed anhydrides (Scheme 6). The identity of these anhydrides was proved by NMR studies.



Scheme 6

Similarly, the reactions reported in this communication are expected to proceed via the mixed anhydride then cyclization follows by ejecting the good leaving group PO_2Cl_2^- (Scheme 7).



Scheme 7

Table 1: Yield of cyclized products obtained by cyclodehydration with POCl₃ and P₂O₃Cl₄

Cyclized Product	Dehydrating Agent: POCl ₃		Dehydrating Agent: P ₂ O ₃ Cl ₄	
	% Yield / Conditions		% Yield / Conditions	
Anthraquinone	53	reflux 3 hrs	65	Reflux in CH ₃ NO ₂ , 2.5 hrs
Anthrone	90	reflux 30 min	Quant *	Room temperature, 30 min.
2-Methoxyanthraquinone	43	reflux 1.5 hrs	75	Warm at 40°, 2 hrs
2-Chloroanthraquinone	20	reflux 3 hrs	20	Heat at 150°, 1 hr
1-Tetralone	70	room temp, 2 days	90	Room temperature, 30 min.
1-Indanone	18	reflux 5 min	20	Warm at 35°C, 30 min.,
2-Coumaranone	90	reflux 5 min.	Quant*	Warm at 35°C, 20 min.,

*Quant. = Quantitative

Conclusions

In conclusion, the use of pyrophosphoryl chloride and phosphorus oxychloride offers an attractive alternative for cyclodehydration. The procedure is simple and it obviates some difficulties encountered in other cyclodehydrating agents.

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Experimental

General

Mass spectra were measured on a Shimadzu GC-MS QB 500 spectrometer at 70 ev. IR spectra (nujol) were recorded on Perkin Elmer 843 spectrometer (ν in cm⁻¹). ¹H-NMR spectra were recorded on a Bruker AMX 300 spectrometer at 300 MHz, δ (ppm) are reported referenced to TMS used as an internal standard.

Synthetic procedures

In a typical experiment the carboxylic acid (0.01 mole) was mixed with a slight excess (0.015 mole) of pyrophosphoric chloride or a large excess of phosphorus oxychloride (0.05 mole). The mixture was warmed for a certain period of time, ranging from a few minutes for the active substrates to several hours for the less active ones (see Table 1). The reaction mixture was quenched with cold water and the ketone was extracted with ether or chloroform. The organic layer was washed with a

dilute solution of sodium bicarbonate and dried over MgSO_4 . Evaporation of the organic solvent afforded the cyclized product. The products were either recrystallized or purified by flash chromatography. Each product was identified by IR, NMR, melting point and mass spectra. The physical properties and the spectra were in agreement with those of authentic samples prepared according to literature procedures. An authentic sample of anthrone was prepared by the method outlined by Meyer [13]. The anthraquinones were prepared by cyclizing the parent carboxylic acid with polyphosphoric acid [14] or sulfuric acid [15]. 1-Indanone and α -tetralone were prepared according to the method of Thomson and coworkers [16]. An authentic sample of coumaranone was obtained by refluxing o-hydroxyphenyl acetic acid with p-toluenesulfonic acid according to the lactonization method of Johnson [17].

Spectral Data

Anthraquinone: mp 284° ; IR, cm^{-1} : 3320, 1700, 1624, 1574, 1450, 1375, 1205, 1165, 1100, 970, 912, 820, 720, 625; $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 7.83 (ddd, 8.1, 7.6, 1.2 Hz, 4H, aromatic), 8.34 (dd, 8.1, 1.2 Hz, 4H, aromatic); MS(%): 208 (M^+), 180, 152, 76.

Anthrone: mp 152° ; IR, cm^{-1} : 3068, 2870, 1660, 1590, 1480, 1466, 1451, 1402, 1387, 1325, 1180, 1160, 1105, 1080, 965, 925, 820, 720, 675; $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 4.38 (s, 2H, benzylic) 7.45 (~d, overlapping 4H), 7.58 (m-unresolved ddd, 2H, aromatic), 8.35 (dd, 8.0, 1.1 Hz, 2H); MS(%): 194 (M^+), 166, 165, 164, 139, 115, 83, 82, 63.

2-Methoxyanthraquinone: mp 196° ; IR, cm^{-1} : 3068, 2960, 1760, 1655, 1605, 1451, 1402, 1385, 1295, 1255, 1188, 1104, 1090, 1022, 925, 835, 755, 722, 698; $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 3.84 (s, 3H, $-\text{OCH}_3$) 7.38 (m, 2H), 7.65 (m, 1H), 7.86 (dd, 8.1, 1.5 Hz, 2H), 8.05 (m, 1H), 8.15 (d, 7.6 Hz, 1H); MS(%): 239, 238 (M^+), 224, 223, 196, 195, 194, 181, 167, 166, 152, 149, 139, 135, 105, 104, 103, 91, 76, 55.

2-Chloroanthraquinone: mp 209° ; IR, cm^{-1} : 3082, 2955, 1680, 1668, 1584, 1465, 1370, 1320, 1174, 1112, 1076, 972, 963, 912, 870, 817, 721, 655, 650; $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 7.48 (d, 8.0 Hz, 1H), 7.78 (m, 3H), 8.15 (dd, 7.4, 1.2 Hz, 1H) 8.21 (dd, 7.6, 1.5 Hz, 1H), 8.27 (d, 8.0 Hz, 1H); MS(%): 244 ($\text{M}+2^+$), 242 (M^+), 216, 214, 207, 188, 186, 179, 151, 150, 125, 107, 93, 75, 50.

1-Tetralone: bp $118\text{--}120^\circ/8\text{ mm.}$; IR, cm^{-1} : 3068, 2955, 2870, 1680, 1600, 1470, 1450, 1400, 1351, 1315, 1282, 1220, 1176, 1156, 1136, 1020, 900, 893, 794, 758, 730; $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 2.12 (m, 2H), 2.70 (m, 2H), 3.00 (m, 2H), 7.18 (d, 8.2 Hz, 1H), 7.29 (m, 1H), 7.43 (m, 1H), 8.05 (d, 7.7 Hz, 1H); MS(%): 146 (M^+), 131, 118, 115, 104, 91, 90, 89, 77, 63, 51.

1-Indanone: mp 40°C ; IR, cm^{-1} : 3072, 3050, 3030, 2925, 1710, 1600, 1775, 1440, 1402, 1320, 1277, 1244, 1203, 1176, 1150, 1088, 1034, 1015, 980, 880, 828, 770; $^1\text{H-NMR}$ (CDCl_3) δ (ppm): 2.70 (m,

2H), 3.15 (m, 2H), 7.38 (m, 1H), 7.47 (d, 7.5 Hz, 1H), 7.57(m, 1H), 7.74(d, 7.7 Hz, 1H); MS(%): 132 (M^+), 104, 103, 78, 77, 52, 50.

2-Coumaranone: mp 49°; IR, cm^{-1} : 1808, 1832, 1618, 1590, 1475, 1390, 1333, 1235, 1205, 1124, 1050, 952, 890, 826, 813, 750, 707, 670; $^1\text{H-NMR}(\text{CDCl}_3)$ δ (ppm): 3.73 (s,2H), 7.10 (d, 8.0 Hz, 1H), 7.14 (m,1H), 7.28 (d, 8.0 Hz, 1H), 7.30 (m, 1H); MS(%): Prominent Peaks: 134(M^+), 106, 78.

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