

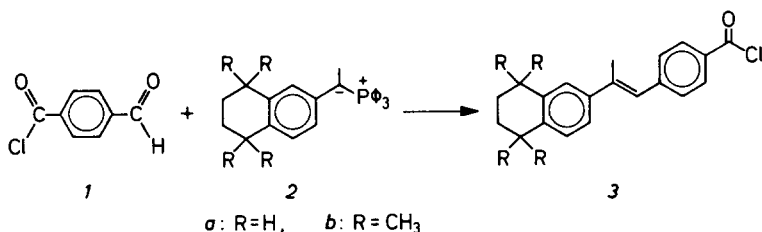
SELECTIVE REACTIONS OF  $\alpha$ -ARYL WITTIG REAGENTS WITH THE FORMYL  
 MOIETY OF 4-FORMYLBENZOYL CHLORIDE

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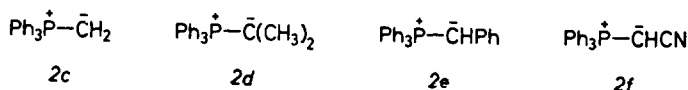
**Summary:** The benzylic Wittig reagents **2a**, **2b** and **2e** react with 4-formylbenzo-  
 zoyl chloride **1** to give 40-60% yields of products **3** derived from selective  
 attack at the formyl group of **1**; The same selectivity is not found for the  
 non-stabilized ylids **2c** and **2d** or the stabilized ylid **2f**.

In connection with the preparation of some potential drugs against ma-  
 lignant melanomas<sup>1</sup> we needed compounds of the type **3** as intermediates. After  
 several preparations by obvious routes, we decided to try the reaction between  
 the Wittig reagents **2a,b** and 4-formylbenzoyl chloride **1** in order to reduce  
 the number of reaction steps leading to derivatives of **3**. The reactions pro-  
 ceeded smoothly and allowed isolation of the benzoyl chlorides **3a,b** in ca.  
 40% yields. Only traces of the *Z*-isomers were detected.

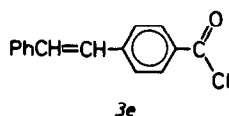


The Wittig reaction involving aldehydes is compatible with a wide range  
 of other functional groups in the molecule, including keto-, ester- and  
 amino groups.<sup>2</sup> The above results show that even the very reactive acid chlo-  
 ride group could be tolerated, which is surprising, since phosphorus ylids  
 are known to react readily with acid chlorides under normal Wittig reaction  
 conditions.<sup>3</sup>

We subsequently studied the reactions of **1** with some additional phos-  
 phorus ylids to see whether the selectivity between aldehyde and acid chlori-  
 de was general.<sup>4</sup> The ylids chosen were two non-stabilized, **2c** and **2d**, one  
 moderated, **2e**, and one stabilized ylid, **2f**. They were prepared from the cor-  
 responding phosphonium bromides and BuLi in ether and used, *in situ*, except  
**2f** which was premade.<sup>5</sup>

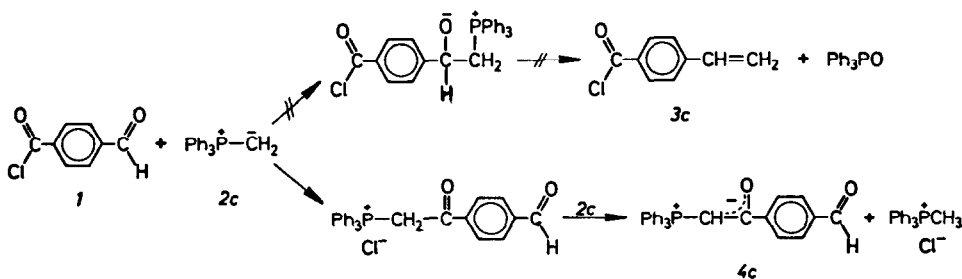


The reaction of **1** with **2e** gave a similar result to that of **1** with **2a** or **2b**. A 60% yield of **3e** (55% E, 45% Z) could be isolated when equimolar amount of the ylid were added to **1** at 0°C in ether. Reverse addition, *i.e.* **1** added



to the ylid, gave a mixture of products containing only small amounts of **3**. This shows that the ylid **2e**, like the other moderated ylids **2a** and **2b**, reacts preferentially with the aldehyde group of **1**, but that excess ylid should be avoided to suppress further reactions at the acid chloride group.

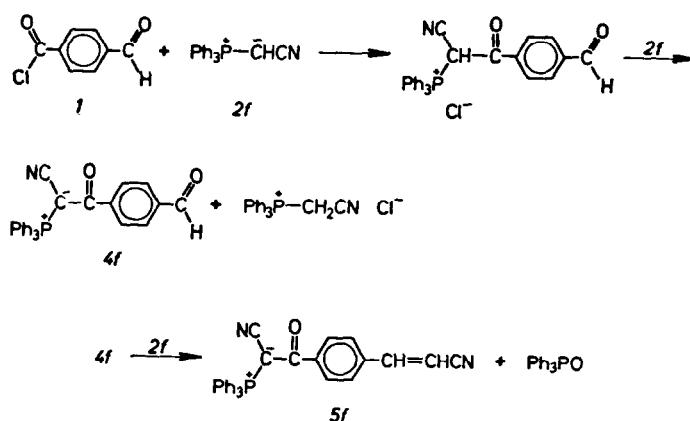
Under similar reaction conditions the non-stabilized ylids **2c** and **2d** did not give significant amounts of type **3** products. Very little material remained in solution, and the precipitate, according to  $^{31}\text{P}$  NMR, contained five-fifteen phosphorus products which proved very difficult to separate. The probable primary steps of the reaction of **1** with **2c** are outlined below. The "normal" product from attack at the acid chloride group, **4c**,<sup>3</sup> is easily acylated at the enolate oxygen by **1**,<sup>3,6</sup> and **2c** may further react with the



acid chloride group of **3c** and the aldehyde group of **4c**, to give several products. However, the absence of significant amounts of  $\text{Ph}_3\text{PO}$ , and the presence of substantial amounts of  $\text{Ph}_3\text{P}^+\text{CH}_3$ , indicate that the major pathway involves attack at the acid chloride group. An experiment with a "salt-free" solution

of **2c** in ether, prepared by the  $\text{NaNH}_2/\text{NH}_3$  method,<sup>7</sup> gave essentially the same result as the experiment above where  $\text{LiBr}$  was present. Therefore it is unlikely that lithium ions are responsible for the failure to obtain products **3** from non-stabilized ylids, *e.g.* by trapping the betaine intermediate en route to **3**.<sup>8</sup>

The stabilized ylid **2f** reacted slowly with **1** in boiling benzene to give a mixture of at least five phosphorus products. When performed with equimolar amounts, substantial parts of **1** remained unreacted, and only small  $^1\text{H}$  NMR signals from  $=\text{C}(\text{H})\text{CN}$  ( $\delta_{\text{H}}$  5.6-6.3 ppm) could be seen. With a one molar excess of **2f**, ca. 40% of **2f** was transformed to  $\text{Ph}_3\text{P}^+\text{CH}_2\text{CN Cl}^-$  ( $\delta_{\text{P}}$  21.5 ppm,  $\delta_{\text{H}}$  6.6 ppm (d,  $J$  15.4 Hz)), and accordingly<sup>3</sup> the other main product was **4f** ( $\delta_{\text{P}}$  22.0 ppm,  $\delta_{\text{H}}$  10.04 ppm (s, CHO),  $\nu_{\text{CN}}$  2170  $\text{cm}^{-1}$ ,  $\nu_{\text{CHO}}$  1700  $\text{cm}^{-1}$ ). This product, however, was contaminated with some **5f** ( $\delta_{\text{P}}$  22.1 and 22.2 ppm, E and Z,



$=\text{C}(\text{H})\text{CN}$  at  $\delta_{\text{H}}$  5.91 (d,  $J$  16.8 Hz) and 5.44 ppm (d,  $J$  12.1 Hz), respectively), which we were unable to remove by recrystallization or column chromatography. However, the result indicates that the stabilized ylid **2f** reacted preferentially with the acid chloride group of **1**.

We conclude that only moderated ylids, like **2a**, **2b** and **2e**, react preferentially with the aldehyde group of compounds, like **1**, which contain both aldehyde and acid chloride groups. Other ylids give product mixtures which are not synthetically useful.

## Experimental

**1 + 2e.** A solution of  $\text{BuLi}$  in hexane (ca. 1.6 M, 2 mmol) was added to a stirred suspension of benzyltriphenylphosphonium bromide (0.87 g, 2 mmol)

in dry ether (20 ml). After stirring at 25°C for 1 h the red suspension of the ylid was added, dropwise, to a stirred solution of 4-formylbenzoyl chloride (0.34 g, 2 mmol) in ether (20 ml) at 0°C, and the stirring continued for 1 h at 25°C. Filtration and concentration of the filtrate, *in vacuo*, gave the product (0.29 g, 60%) as a nearly colorless solid.  $^1\text{H}$  NMR showed it to be a nearly pure mixture of 55% E- and 45% Z-4-(2-phenylethenyl)benzoyl chloride (*3e*).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  6.64 (AB system, Z-CH=CH,  $J$  12.3 Hz), 7.12 (AB system, E-CH=CH,  $J$  16.5 Hz), 7.2-8.1 ppm (Ar, m). IR ( $\text{CCl}_4$ ): 1776  $\text{cm}^{-1}$  (COCl), 1601  $\text{cm}^{-1}$  (CH=CH). Recrystallization of a sample from dry hexane gave the Z-isomer, m.p. 124-126°C (lit.<sup>9</sup> 125-127°C).

1 + 2a gave similarly 3a (0.24 g, 38%) as a yellow oil. MS ( $m/z$ ): 310 ( $\text{M}^+$ , 59%), 275 ( $\text{M}^+ - \text{Cl}$ , 100%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  1.80 (m, 4H), 2.10 (d,  $J$  2 Hz, 3H), 2.75 (m, 4H), 6.80 (broad s, 1H), 7.0-8.3 ppm (m, 7H). No attempt was undertaken to obtain analytically pure material. However, 3a and 3b were used to prepare a series of their esters, which had the expected elemental analyses and spectroscopic signals.<sup>1</sup>

## References

1. F. Wätjen, O. Buchardt and E. Langvad, J. Med. Chem., 1982, 25, 956.
2. A. Maercker, in A. C. Cope (ed), Organic Reactions, John Wiley and Sons, Inc., N.Y. 1965, Vol. 14, p. 270.
3. H. J. Bestmann, Angew. Chem., 1965, 77, 651.
4. We have used 1 throughout since very few simple compounds containing both aldehyde and acid chloride groups are known.
5. G. P. Schiemenz and H. Engelhard, Chem. Ber., 1961, 94, 578.
6. P. A. Chopard, R. J. G. Searle and F. H. Devitt, J. Org. Chem., 1965, 30, 1015.
7. E. Vedejs, G. P. Meier and K. A. J. Snoble, J. Amer. Chem. Soc., 1981, 103, 2823.
8. M. Schlosser, H. Ba Tuong and C. Tarchini, Chimia, 1977, 31, 219.
9. G. Berti and F. Bottari, Gazz. Chim. Ital., 1959, 89, 2371.

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