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INVESTIGATION OF THE WITTIG REACTION WITH ELECTROGENERATED BASES: INFLUENCE OF EXPERIMENTAL CONDITIONS ON THE YIELD AND STEREOCHEMISTRY

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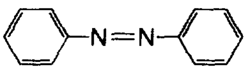
Abstract

The influence of experimental parameters on the yields and stereochemistry of the Wittig reaction was studied using the synthesis of stilbene initiated by different electrogenerated bases as a model reaction. Electrolyses were carried out in batch cells under different conditions, including constant potential or constant current with different electrode materials and using solvents of different polarity. It is shown that proper selection of experimental conditions in Wittig reactions allows a choice of stereoselectivity in the reactions and the optimization of yields.

Keywords: Electrogenerated bases, Wittig reactions, Electrosynthesis

The Wittig reaction [1,2] is a powerful method for the regio- and stereocontrolled construction of carbon-carbon double bonds.

Different techniques have been employed to deprotonate the phosphonium salt and generate the ylide [1,2]. We report herein experiments using cathodically generated anion-radicals and dianions as electrogenerated bases (EGBs). The term probase (PB) is used to describe the organic precursor which on reduction is converted into the intermediate EGB. Three different probases, azobenzene **1**, dicyano(fluoren-9-ylidene)methane **2** and fuchsone **3**, were used in this work. Both the reduction mechanism and the species acting as base are different.



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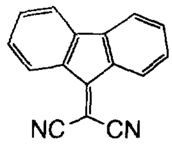

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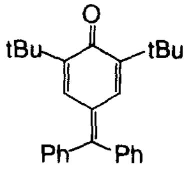

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The advantages of the use of EGBs stem from the possibility of *in situ* generation with adequate control of base strength and base concentration. The PBs used in this work are all readily available, have low reduction potentials and have an easy work-up [3,4]. Another factor which determines basicity is the reaction medium; hence, the effect of solvent was also examined and the EGBs were effectively produced in dimethylsulfoxide, N,N-dimethylformamide, tetrahydrofuran or toluene.

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An important development in the use of EGBs is a recent study [5] on the kinetics of proton transfer from phosphonium ions to EGBs. This quantitative approach can lead to the optimization of reaction conditions that avoid the use of bases stronger than it is strictly necessary with supression of secondary reactions.

In order to carry out a systematic study of the influence of experimental parameters on the yield and stereochemistry of stilbene (PhCH=CHPh) electrosynthesis by the Wittig reaction, preparative electrolyses of solutions containing the probase, the phosphonium bromide ($Ph_3P^+CH_2Ph,Br^-$) and benzaldehyde (PhCHO) were performed in batch cells. The electrolyses were carried out at different experimental conditions such as, constant current, constant potential, different electrode materials, several probases and solvents of different polarity. It should be noted that previous studies employing EGBs for the electrosynthesis of stilbene were restricted to the use of mercury electrodes. Considering the recognized constraints associated with the manipulation of mercury, an attempt was made in the present study to employ other electrode materials which proved to be equally successful.

The study was initiated by carrying out electrolyses in a batch divided cell [6] and comparing the yields and stereochemistry obtained under conditions of constant current with those obtained at constant potential. Both in *N,N*-dimethylformamide and dimethylsulfoxide the yields were high (above 78%), although the yield obtained at constant current in dimethylsulfoxide was slightly higher. The *Z:E* ratio was approximately the same in all cases (2.0) but the use of an undivided cell led to a smaller value (1.4 in *N,N*-dimethylformamide).

The influence of the probase nature [3] on the electrosynthesis of stilbene was also investigated and the results obtained are presented in Table 1. It is apparent that both the yield and the proportion of isomers formed are affected by the base used to deprotonate the phosphonium salt and the ratio probase/$Ph_3P^+CH_2Ph$, Br^- slightly affects the *Z:E* ratio.

Table 1 - Results of constant potential electrolyses carried out to prepare stilbene, using different probases, $Ph_3P^+CH_2Ph$, Br^- (1×10^{-2} mol dm^{-3}) and benzaldehyde (1×10^{-2} mol dm^{-3}). The electrolyses were performed in a divided cell [6] at a vitreous carbon cathode, in *N,N*-dimethylformamide.

Probase	[Probase] / mol dm^{-3}	Yield / % [7]	*Z:E* [7]
azobenzene	5×10^{-3}	79 ± 1	2.0
dicyano(fluoren-9-ylidene)methane	1×10^{-2}	80 ± 3	1.6
dicyano(fluoren-9-ylidene)methane	2×10^{-2}	74 ± 3	1.3
fuchsone	1×10^{-2}	58 ± 2	1.7

It is well recognized in the literature related to electrosynthetic reactions that yields and products may be strongly affected by the electrode material [8], but in the present case the deprotonation reaction is taking place in bulk solution since the relatively stable radical-anion (or dianion) diffuses away from the cathode. Hence, differences in the yields and stereochemistry are not expected to occur. The results of preparative electrolyses at vitreous carbon, platinum gauze and mercury pool electrodes are presented in Table 2. The yield of the reaction is not affected by the electrode material as expected; however, the proportion of *E*-stilbene is higher at mercury pool cathodes. The difference observed is more likely to be explained in terms of the different current densities applied and not attributed to the electrode material. Despite the difficulty in measuring the area of the platinum gauze in a first approximation it can be taken as similar to that of the vitreous carbon disc. However, the mercury pool electrode displayed a larger area and hence the density currents were smaller in this case and that fact may explain the different *Z:E* ratio observed.

Table 2 - Results of constant potential electrolyses carried out to prepare stilbene, using azobenzene (5×10^{-3} mol dm^{-3}) as probase, $Ph_3P^+CH_2Ph$, Br^- (1×10^{-2} mol dm^{-3}) and benzaldehyde (1×10^{-2} mol dm^{-3}). The electrolyses were performed in a divided cell [6] at different cathodes, in *N,N*-dimethylformamide.

Cathode material	Yield / % [7]	*Z:E* [7]
Vitreous carbon	79 ± 1	2.0
Platinum gauze	80 ± 2	2.0
Mercury pool	80	1.4

The influence of the solvent in the Wittig reaction has been the subject of much apparently contradictory work [1, 2, 9-11]. Constant current electrolyses using azobenzene as probase were carried out in solvents or mixtures of solvents of different polarity. Electrolyses were performed at constant current to allow the use of lower dielectric constant solvents such as tetrahydrofuran or toluene. The results of these electrolyses are presented in Table 3.

Table 3 - Results of constant current ($j = 0.7$ mA cm^{-2}) electrolyses carried out to prepare stilbene, using azobenzene (5×10^{-3} mol dm^{-3}) as probase, $Ph_3P^+CH_2Ph$, Br^- (1×10^{-2} mol dm^{-3}) and benzaldehyde (1×10^{-2} mol dm^{-3}). The electrolyses were performed in a divided cell [6] at a platinum gauze cathode, in different solvents. ε = dielectric constant.

Solvent	ε	Yield / % [7]	*Z:E* [7]
Dimethylsulfoxide	46.6	96 ± 4	2.0
N,N-dimethylformamide	36.7	78 ± 2	2.0
Toluene / *N,N*-dimethylformamide (70/30)	12.7	77 ± 3	1.6
Toluene / *N,N*-dimethylformamide (80/20)	9.2	60 ± 1	1.2
Dichloromethane	9.1	72 ± 2	1.0
Toluene / *N,N*-dimethylformamide (85/15)	7.5	61 ± 6	0.9
Tetrahydrofuran	7.4	28 ± 5	0.8

The reaction is strongly dependent on the solvent used and there is a trend of decreasing stilbene yield as the polarity of the solvent diminishes. The solvent also has a marked influence on the reaction stereochemistry and it is clear that an increase in the proportion of *E*-stilbene occurs with a decrease in the dielectric constant of the solvent.

A metal ion can play opposing roles in the Wittig reaction: it can activate the carbonyl bond but on the other hand it is based-weakening by virtue of coordination. Most importantly, it can stabilize carbanion intermediates influencing the stereochemistry. These effects were addressed in previous studies [3, 12] involving the use of $LiClO_4$ and $Mg(ClO_4)_2$ as electrolytes in *N,N*-dimethylformamide. In those studies the presence of lithium was associated with preferential formation of the product of kinetic control (the *Z* alkene) but only traces of alkene were detected when using $Mg(ClO_4)_2$. In the present work electrolyses were carried out in an undivided cell using a magnesium sacrificial anode [13] and when tetrahydrofuran was used as solvent the expectation of increasing the kinetic product was confirmed and the *Z:E* ratio increased up to 2.6; however, with *N,N*-dimethylformamide and under the same experimental conditions that ratio decreased to 0.9, indicating a less-effective stabilization of carbonionic intermediates in this solvent.

The aforecited results are of interest in several aspects. First, they demonstrate that the scope of electrosynthesis can be extended to low polarity solvents. Secondly, they show that by proper selection of the experimental conditions (EGB, solvent, cell geometry, constant potential or constant current, electrode material) the yields may be improved and the stereoselectivity conveniently chosen. Thirdly, it is important to emphasize that by using EGBs, reproducible experimental conditions can be easily achieved since the EGB is produced *in situ* and in a controlled fashion.

Further studies are under development to scale up the reactions (up to now carried out on a mg sacale) to a larger scale employing flow cells.

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[6] The separator in the divided cell was a glass frit; the auxiliary electrode was a platinum grid and the reference electrode was the saturated calomel electrode. The supporting electrolyte used was Bu_4NBF_4 (0.1 mol dm^{-3}).

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