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# A QUANTITATIVE TITRIMETRIC METHOD AND FTIR MONITORING OF SOLID PHASE PALLADIUM-CATALYSED REACTIONS

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***RINGKASAN:*** *Suatu kaedah pentitratan mengkuantitikan kepegunan iodoanilin dan bromoanilin ke atas PS-TsCl (polystyrene sulfonyl chloride) dan kaedah kualitatif mengikut spectra FTIR reaktan, hasil pertengahan dan hasil akhir telah dibentangkan di sini. Pentitratan pelepasan ion klorida pada langkah pertama fasa pegun sintesis kombinatorial telah dilaksanakan mengguna kaedah Mohr. Pengiraan kuantitatif dilakukan mengikut larutan piawai NaCl. Keputusan menunjukkan bahawa kepegunan dan hasil tindak balas dengan bromoanilin adalah jauh lebih baik daripada iodoanilin dan kedua-dua tindak balas fasa pegun telah dioptimumkan pada jam ke 14. Ujian sensitiviti menunjukkan bahawa ion klorida boleh dikesan serendah 30 mg PS-TsCl. Kaedah kuantitatif yang ringkas dan cepat ini bukan sahaja bertindak sebagai kaedah pengesanan tetapi juga membolehkan perbandingkan kereaktifan pelbagai jenis anilin, melaksanakan kajian pengoptimuman dan mengkuantitikan hasil tindak balas. Spektroskopi FTIR telah digunakan untuk mengikuti tindak balas dari tahap kepegunan PS-TsCl sehingga pemutusannya dari hasil akhir apabila kumpulan R ditukar.*

**ABSTRACT:** A titration procedure quantifying the immobilisation of iodoaniline and bromoaniline onto PS-TsCl (polystyrene sulfonyl chloride) and a qualitative procedure following the FTIR spectra of the reactants, intermediate products and the final product is presented here. The titration of chloride ions released in the first step of the solid phase combinatorial synthesis was carried out using the Mohr method. Quantitative measurements were made using standard NaCl solution. Results show that the immobilisation and reaction yield with bromoaniline was far better than iodoaniline and that both solid phase reactions were optimised by the 14th hour. Sensitivity tests show that chloride ions can be detected with as low as 30 mg PS-TsCl. This simple and fast quantitative method not only serves as a detection method but allows us to compare the reactivities of various types of anilines, perform optimisation studies and quantify the reaction yields. FTIR spectroscopy was also used to follow the reaction from the immobilisation stage of the PS-TsCl until its cleavage from the final product, while varying the R groups.

**KEYWORDS:** solid phase, quantitative monitoring, palladium-catalysed, titrimetric

## INTRODUCTION

A critical step in the development of methods for solid-phase synthesis in combinatorial chemistry is the assessment of the extent of completion of the reactions carried out on the resin matrix. A great deal of effort has been dedicated over the years to find quick and reliable methods for monitoring solid-phase reactions (Scicinski *et al.*, 2002). The objective is to develop a method which equals simplicity and availability to that of TLC in solution phase synthesis. As alternatives to the cleavage of intermediates from the support and their characterisation in solution, various methods have been developed for analyses of support-bound intermediates. Several spectroscopic techniques have been successfully adapted to the analysis of synthetic intermediates directly on the resin. Among these, the most powerful and versatile techniques are NMR (Yan, 1998) using "magic angle spinning" pulse sequences, IR (Yan,1998) and MS (Riedl *et al.*,1998; Badyal *et al.*, 2001). A more direct and time-consuming alternative is cleavage of an aliquot of the resin-bound product and analysis by conventional analytical methods in solution.

The need for a simple procedure for monitoring is especially important in the case of repetitive solid-phase synthesis amenable to automation in the preparation of oligomeric compounds. Practical alternatives to TLC are the colour tests such as Ellman test for thiols (Egner and Bradley, 1997), the Kaiser test for primary amines (Ellman,1959; Jan *et al.*, 2003), the chloranil test for secondary versus tertiary amines (Kaiser *et al.*,1970; Vojkovsky,1995) and other tests for amines (Manabe and Ito, 2002; Vazquez and Albericio, 2001; Zhang *et al.*, 2000). Although very effective, these methods are exclusively for thiols and amines.

In solid-phase combinatorial synthesis, FTIR has been used for both quantitative and qualitative analyses (Bing *et al.*, 2001) for monitoring the reaction to its completion. IR spectroscopy is a fast and simple method for qualitative detection of certain functional groups on insoluble supports. However, it is not a very sensitive analytical tool and therefore not well suited for the detection of small amounts of material. However, if intermediates have intense and well resolved IR absorptions, the progress of their chemical transformations can be followed by IR spectroscopy.

Although there is a number of simple bead staining tests, akin to TLC, which provide qualitative analysis of solid-phase reactions, relatively few of these have been adapted to provide simple low cost methods for the quantifications of on-bead substrates. There is a need in solid phase combinatorial chemistry for the identification of organic functional groups for monitoring of the completeness of reactions. To the best of our knowledge, there is no qualitative or quantitative test available for monitoring solid phase palladium-catalysed reactions.

## MATERIALS AND METHODS

### Solid phase palladium-catalysed reaction and work-up prior to chloride analysis

To a solution of 2-iodoaniline (0.3 mmol, 65 mg) and pyridine (0.04 ml) in dichloromethane (2 ml) was added PS-TsCl resin (0.1 mmol, 60 mg) as described by Zhang *et al.* (2000). The suspension was stirred at 50°C and monitored for chloride ions using argentometric titrametric analysis or also known as the Mohr's method (Vojkovsky,1995). This was carried out at various times (0, 2, 6, 8, 14, 18 and 22 hours) after the work-up procedure, which involved filtering off the resin and washing with $CH_2Cl_2$ and water to a final volume of 100 ml. The above was repeated for sensitivity evaluation with 30 mg and 15 mg of PS-TsCl at similar molar ratios. The reactivity of 2-bromoaniline was also followed using the same molar ratios for 60, 30 and 15 mg PS-TsCl resin (0.3 mmol, 50 mg; 0.05 mmol, 25 mg and 0.02 mmol, 12 mg).

### Chloride Analysis and Calibration Curve

The filtrate from the above work-up was transferred into a conical flask followed by the addition of three drops of $K_2CrO_4$. 20 ml solutions were titrated against 0.01M $AgNO_3$ and the end point volumes were recorded for 3 replicates. Distilled water was taken as blank. The concentration of chloride ions were determined using the calibration curve, which was prepared using various concentrations of NaCl and following the same argentometric titrimetric analysis described above. Yields were calculated by taking the PS-TsCl loading capacity as 1.75 mmol/g where 60 mg of the resin will contain 0.11 mmol of $Cl^-$ ions.

### FTIR Analysis

Infrared spectra of PS-TsCl, 2-iodoaniline, PS-TsCl-bound precursor, were recorded as KBr pellets and compared.

## RESULTS AND DISCUSSION

1 mol of PS-TsCl(1) generates 1 mol of chloride ions and 1 mol of the PS-TsCl-bound precursor(3). Therefore, by following the chloride ions released in Figure 1 the first intermediate product(3) is quantifiable. For this, the release of chloride ions were quantified using the calibration curve in Figure 2.

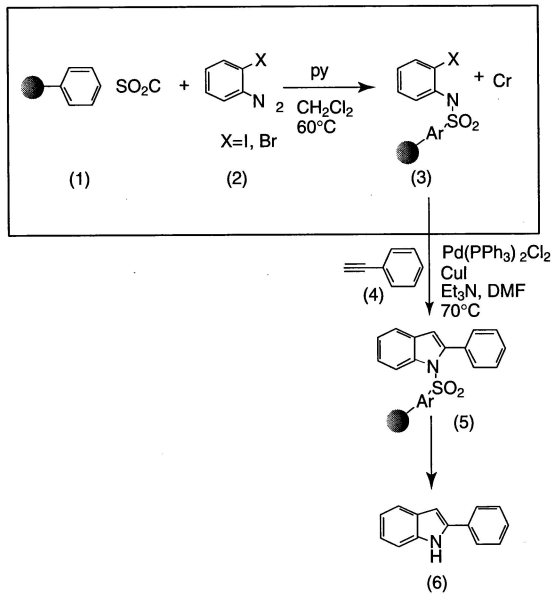


***Figure 1.*** *Solid phase palladium catalysed synthesis of indoles by Zhang et al. (2000)*

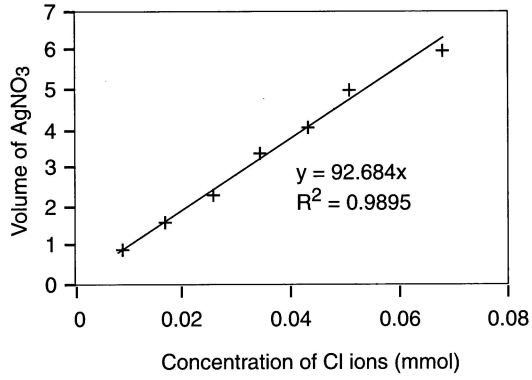


***Figure 2.*** *Calibration curve of concentration of chloride ions against volume of $AgNO_3$ (Mohr's method). The end point has been corrected by using blank titration*

The titration of chloride ions with silver nitrate forms a white precipitate and when using chromate ions as the end point indicator, a red precipitate occurs when it reacts with silver ion. To determine the sensitivity of the argentometric titration in the solid phase palladium-catalysed reaction reducing amounts of the PS-TsCl were used in the solid phase reaction. Figures 3 and 4 show the solid phase reactions for 22 hours and the chloride ions released were monitored after the addition of 2-iodoaniline and 2-bromoaniline, respectively. Three different amounts of PS-TsCl were used (60, 30 and 15 mg) to establish the sensitivity of this method.

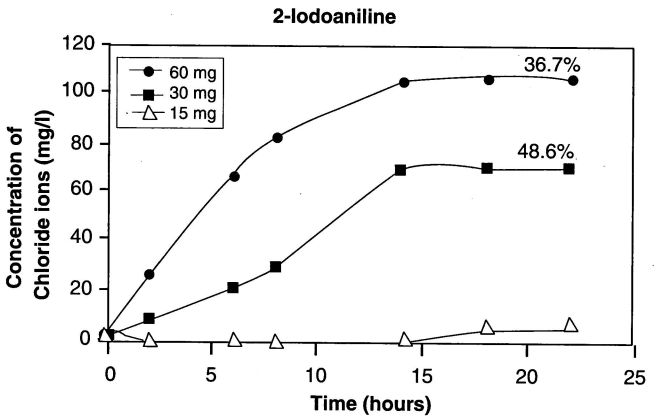


***Figure 3.*** *The release of chloride ions was followed titrimetrically at varying times and resin amounts when 2-iodoaniline was used. (Yields are shown as percentages)*

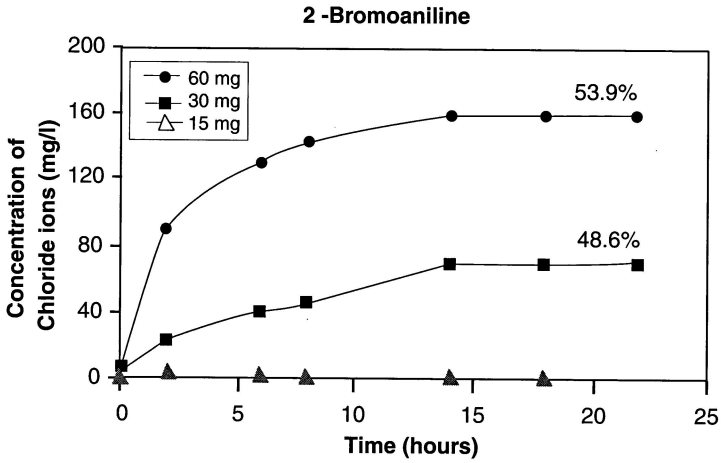


***Figure 4.*** *The release of chloride ions was followed titrimetrically at varying times and resin amounts when 2-bromoaniline was used. (Yields are shown as percentages)*

The figures show that the release of chloride ions corresponds with time and an optimum was reached by 14 hours for both 2-iodoaniline and 2-bromoaniline. With 2-bromoaniline the reaction was observed to be much faster in the first few hours as seen in Figure 3. In addition, the yields of the reaction with 2-bromoaniline (54.4 %, 60 mg) were far better than 2-iodoaniline (36.6 %, 60 mg). At the above reaction conditions, it was observed that this quantitative method was able to detect chloride ions even with as little as 30 mg of the resin PS-TsCl. However, this test was not sensitive for smaller amount of resin (15mg). This is probably due to the

sensitivity limitation of the Mohr's method which is only able to detect chloride ion ≥ 20mg/l (James,1999). There are however several factors that will need to be taken into account when using the Mohr's method for monitoring solid phase reactions. This method is sensitive to the presence of both chloride and bromide ions, must be performed in the pH range of 6.5 to 9.0 and for comparison purposes the titrations must be carried out at the same temperature. In addition to the titrimetric method, the IR spectra of PS-TsCl (1), 2-Iodoaniline (2) and PS-TsCl-bound precursor (3) were recorded for qualitative monitoring (Figure 5). The appearance of N-H stretch for secondary amine at 3436 $cm^{-1}$ in spectrum 3 indicated that the amine was coupled to the thioyl group on the resin.

We have demonstrated that the use of FTIR KBr pellet methodology could assist the monitoring of this solid phase reaction. The advantages of this analytical technique is that it is uninterrupted, non-destructive, accurate and allows the use of small amounts of sample.

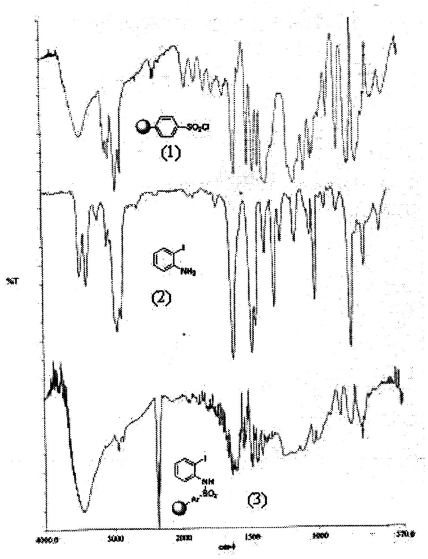


***Figure 5.*** *Reaction monitoring using FTIR (taken in KBr)*

## CONCLUSION

The titrimetric method described in this report is simple, rapid, relatively sensitive, and can be used to monitor and quantify solid phase reactions of this kind. In addition it can be used to optimise reactions, study substrate specificities and determine reaction yields. FTIR analysis offers a way of monitoring reactions on solid support without stopping them or cleaving product from the resin and often provides information that would be hard to obtain in any other way. Therefore, it is an effective analytical tool in the process of transferring solution-phase reactions to solid phase synthesis.

## ACKNOWLEDGMENTS

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