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Parallel fluorous biphasic synthesis of 3*H*-quinazolin-4-ones by an Aza-Wittig reaction employing perfluoroalkyl-tagged triphenylphosphine

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Abstract—A perfluoroalkyl-tagged triphenylphosphine was applied in a fluorous biphasic system for the efficient parallel synthesis of 3*H*-quinazolin-4-ones via an Aza-Wittig reaction. The products were isolated by solid-phase extraction on fluorous reversed-phase silica gel. A new solid-phase bound phosphine derivative was used for comparison and yielded similar results. © 2002 Elsevier Science Ltd. All rights reserved.

Combinatorial chemistry has emerged during the last decade as an important tool for the rapid synthesis of compound libraries. Solid-phase chemistry, originally only applied to the synthesis of oligonucleotides and peptides, has been extended to the synthesis of libraries of small molecules with huge structural diversity. Nevertheless, a few problems with solid-phase synthesis have been encountered. Adaptation of solution chemistry to a solid-phase strategy is not always straightforward. In addition, synthesis on solid support is difficult to follow and characterization of solid-phase bound compounds is not simple. Furthermore, appropriate linker entities are needed for the attachment of starting materials, intermediates and final products to the solid phase. However, after synthesis, it should be possible to cleave the desired compounds from the support material in high yields.

Thus, alternative techniques, based on solution chemistry, are becoming more prominent for the synthesis of compound libraries. These alternative methods comprise, in essence, polymer-supported reagents,[1] polymer-based scavenger entities[2] and synthesis in fluorous biphasic systems (FBS).

Synthesis in fluorous biphasic systems was first reported by Horváth and Rábai for the recycling of catalysts[3] and was developed later, mainly by Curran, for combinatorial approaches.[4–7]

Fluorous techniques allow for the separation of perfluoro-tagged compounds from standard organic compounds by simple work-up procedures, such as liquid–liquid extraction between perfluorinated solvents and organic solvents. Alternatively, solid-phase extraction protocols using fluorous reversed phase silica gels can be applied.[8] In both procedures, time-consuming chromatographic separations can be omitted. These facts make the FBS strategy especially suitable for the preparation of combinatorial libraries by parallel synthesis in solution and for the recycling of perfluoro-tagged catalysts.

Recently, we have reported on the synthesis of perfluoroalkyl-tagged triphenylphosphines. We have used these phosphines as ligands for Pd complexes, which we have applied to Stille and Suzuki CC-couplings.[9,10] High coupling yields were obtained and, due to the perfluoro-tags, the catalysts could be recycled several times by liquid–liquid extraction without significant loss of activity.

Herein we report for the first time on the use of a perfluoroalkyl-tagged phosphine as a fluorous reagent. Phosphine **1** was applied to an intramolecular Aza-Wittig reaction generating a quinazoline core. Quinazolines are important pharmacophores present in a great number of biologically active compounds.[11–14]

Keywords: fluorous biphasic system; Aza-Wittig; perfluoro-tagged phosphine; 3*H*-quinazolin-4-ones.

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Generally, due to the formation of CN-double bonds, Aza-Wittig reactions have attracted a great deal of interest, since they allow to access different types of heterocyclic structures.[15] Thus, the strategy presented here is not limited to quinazolines and can be extended to other types of heterocycles as well.

The actual synthesis is outlined in Scheme 1.

In a Staudinger reaction the starting materials of type **2** reacted quantitatively with the perfluoro-tagged phosphine **1** leading to the iminophosphoranes **3**.[16] These intermediates were not isolated but converted directly by an intramolecular Aza-Wittig reaction to the desired quinazoline derivatives. The reactions were carried out in toluene with $C_6H_5CF_3$ as the co-solvent. After the reaction, separation and isolation of the products of type **4** was achieved by solid-phase extraction on fluorous reversed phase silica gel.[17] Since the unreacted iminophosphoranes **3** and the phosphane oxide **5** are equipped with the perfluoro-tag, they are retained on this material, whereas the products can be washed off efficiently. In this way, easy isolation of quinazolin-4-ones **4** is possible even if the cyclization does not proceed quantitatively.

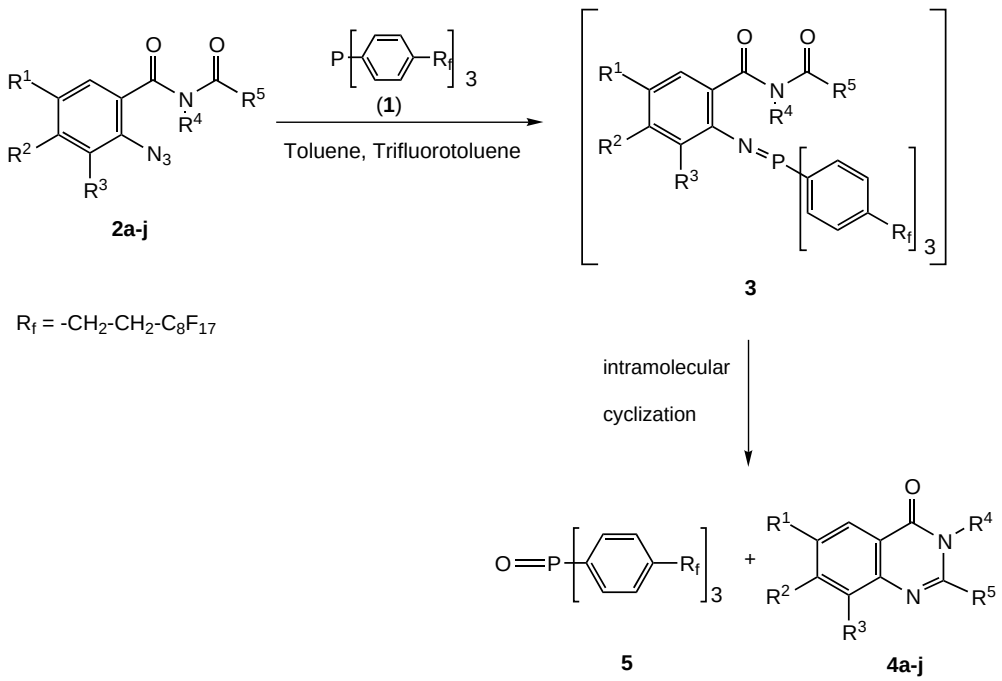
To demonstrate the feasibility of this approach we have synthesized a small library of representative quinazolin-4-ones by parallel synthesis (Table 1). The desired target molecules **4a–j** were obtained in good yields and high purity.[18] All compounds were characterized unambiguously by spectroscopic means.

For comparison, we have also employed the solid-phase bound triphenylphosphine **6**, which was prepared according to Scheme 2.[19] As can be seen in Scheme 2, compound **6** is easy to prepare and represents a cheap alternative to the commercially available solid-phase bound triphenylphosphine. After the cyclization step shown in Scheme 1, which was carried out with the solid-phase bound phosphine **6** instead of **1**, a simple filtration step was performed to separate the desired quinazolin-4-ones **4** from the solid-phase bound triphenylphosphine oxide and any possibly unreacted solid-phase bound iminophosphorane. As shown in Table 1, the yields obtained with the solid-phase bound phosphine **6** were comparable with the ones obtained with **1**.[20] In this way, we have established two alternative ways of synthesizing pure products without the use of time-consuming chromatographic steps.

For further comparison, we have carried out the cyclization step with $P(Ph)_3$ (compounds **4a–d**). In contrast to the straightforward isolations mentioned above, the desired compounds were obtained in pure form only after a tedious silica gel chromatography.

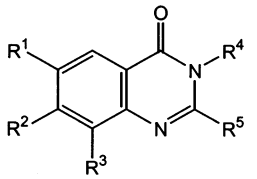
The starting materials for the Aza-Wittig reactions were prepared according to Scheme 3. The anthranilic acid derivatives **7** were transformed with $NaNO_2$/HCl followed by NaN_3 into the corresponding *o*-azido benzoic acid derivatives **8** which were isolated in yields of 30–84%. Reaction with $SOCl_2$ yielded the corresponding acid chlorides **8**, which reacted with the anions of the amides, obtained from **9**, and LDA. The desired starting materials **2a–j** for the Aza-Wittig reactions were obtained in isolated yields of 19–54%.

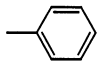
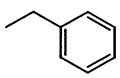
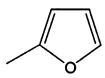
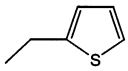
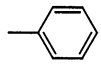
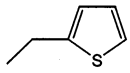
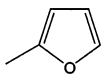
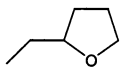
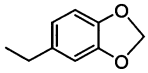
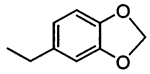
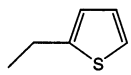
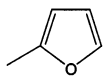
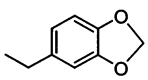
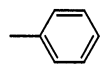
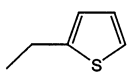
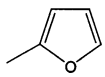
The perfluoro-tagged triphenylphosphine oxide **5**, formed as a side product of the reaction shown in Scheme 1 could be reduced with Cl_3SiH to the phoshine **1** and, thus, we were able to recycle it for further reactions in an isolated yield of 88.5%.[21]

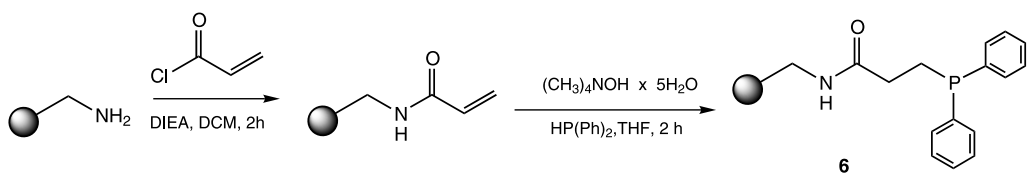


Scheme 1.

Table 1.



Compound	R1	R2	R3	R4	R5	Yield (%) 1	6	$P(Ph)_3$
4a	H	H	H	iPr		95	91	92
4b	H	H	H			72	56	69
4c	H	H	H			93	69	70
4d	H	H	H			93	89	82
4e	H	H	H			93	93	
4f	H	H	H			81	89	
4g	I	H	H			90	83	
4h	I	H	H			77	70	
4i	H	H	Me			78	73	
4j	OMe	OMe	H			92	94	



Scheme 2.

In summary, we have demonstrated that the application of a perfluoroalkyl-tagged phosphine **1** in intramolecular Aza-Wittig reactions leads to a simple work-up procedure for the isolation of the products, which has been demonstrated for a small library of quinazolin-4-ones. We have also applied a solid-phase bound phosphine **6**, which is easy to prepare and yields the desired products after a filtration step, therefore omitting time-consuming chromatographic procedures. The methods outlined above are of general value for the parallel synthesis of heterocycles by intramolecular Aza-Wittig reactions.

Acknowledgements

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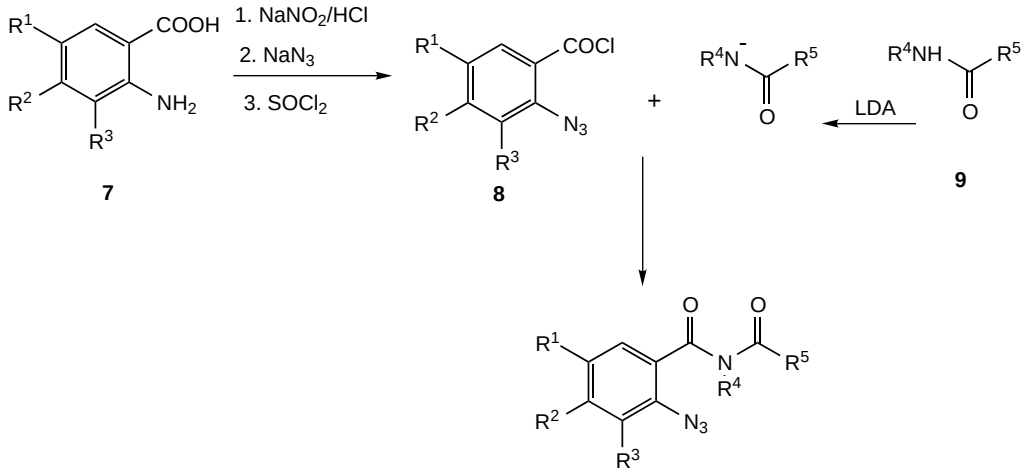

Scheme 3.

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18. General procedure: Under argon, 71 mg (0.20 mmol) of **2d** were dissolved in a mixture of 8 ml of toluene and 4 ml of BTF. After addition of 420 mg (0.26 mmol) of **1** it was heated to 80°C until the conversion was complete, as judged by TLC (5 h). The solvents were evaporated and the residue was taken up in acetonitrile and applied directly onto a plug of fluorous reversed phase silica gel (4 g). Elution with acetonitrile and evaporation yielded 57 mg (93%) of **4d**. Elution with diethylether yielded the triphenylphosphine oxide.
19. To a suspension of 5 g aminomethyl polystyrene resin (0.54 mmol/g) in DCM were added 0.924 ml (5.4 mmol) of DIEA and 0.438 ml (5.4 mmol) of acryloyl chloride. After shaking for 2 h at rt the resin was filtered, washed with DCM and ether and dried under high vacuum. The Kaiser test indicated complete conversion of the amino functions.
    Of this resin, 3 g were taken up in 35 ml of THF and 440 mg (2.4 mmol) of tetraethylammonium hydroxide and 0.42 ml (2.4 mmol) of diphenylphospine were added. After shaking for 2 h at rt it was filtered and washed with DMF/H_2O (1:1), DMF, DCM and ether and dried under high vacuum to yield **6**, which was used as such for the Aza-Wittig reactions.
20. General procedure: Under argon, 71 mg (0.20 mmol) of **2d** was dissolved in 12 ml of toluene. To this solution were added 1.5 g of solid-phase bound triphenylphosphine **6** (0.60 mmol). The solution was heated to 80°C for 2 h. It was filtered off the resin, the resin was washed with toluene and evaporation of the combined touene filtrates yielded 55 mg (89%) of **4d**.
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