

QUATERNARY AMMONIUM SALTS AS ALKYLATING REAGENTS IN C-H ACTIVATION CHEMISTRY

Manuel Spettel, Michael Schnürch

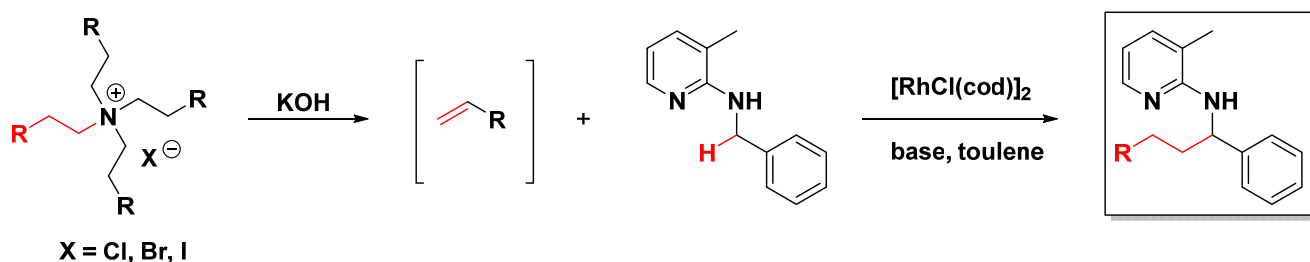
E163 - Institute of Applied Synthetic Chemistry, TU Wien, Vienna, Austria

INTRODUCTION

Selective C-C bond-forming reactions are very fundamental and often used reactions in organic chemistry. Yet, such reactions often require functionalized starting materials. Therefore, in recent years, transition-metal-catalyzed C-H activation reactions have gained lots of attraction and are an important tool in organic chemistry.^[1-3] These reactions generally use less functionalized starting materials, and are therefore more step- and atom efficient.^[4, 5] Also, they tolerate a wide area of functional groups. Thus, in recent years, C-H activation processes for assembly and functionalization of organic molecules could greatly simplify the synthesis of pharmaceuticals, natural products and general feedstock chemicals.^[6-8] Amongst the transformations which can be carried out via C-H activation methods, alkylation reactions are tremendously important and frequently used in the organic lab. Conventional approaches use primarily either alkyl halides or olefins as alkylation agents, whereas both alkyl sources have their advantages and disadvantages. The goal of the present work was to find an alternative alkyl source which combines the best features of the two aforementioned reagents.

FUNDAMENTAL OF THE PROBLEM

Sideproduct formation is a major drawback when using alkyl halides. On the other hand, transition-metal-catalyzed C-H activation reactions using olefins as alkylating reagents are highly potent C-C bond-forming reactions and have been used successfully in numerous examples in the last two decades.^[9, 10] However, short chained olefins such as ethylene, propylene or butylene are gaseous at room temperature and highly flammable, therefore not a desired alkylating agent in the lab. Thus, herein we tried to overcome the disadvantages of using gaseous olefins, by using solid quaternary ammonium salts as alkylating agents. An *in-situ* Hofmann elimination delivers the olefin which is then used by a Rh(I)-catalyzed reaction towards the desired alkylated product.



Scheme 1: Reaction scheme for C-H alkylation with quaternary ammonium salts

We started the development of direct alkylation of benzylic amines using the conditions optimized for our direct alkylation reactions with olefins^[10], but employing quaternary ammonium salts as alkyl source. Initial experiments using potassium carbonate as base showed only good results for the ethylation protocol but were quite slow (28h). Longer alkyl chains dropped to nearly no conversion immediately. We realized that the rate limiting step for the reaction seems to be the formation of the olefin *via* Hofmann elimination. After intensively screening for optimal conditions

to accelerate the elimination step, potassium hydroxide was found as crucial reagent for this reaction. With optimized conditions in hand, also longer alkyl chains could be introduced with good efficiency.

RESULTS AND DISCUSSION

With the optimized protocol in hand, we performed alkylation reactions with different quaternary ammonium salts on a number of different substrate to demonstrate the scope of the present transformation. We used different quaternary ammonium salts in order to obtain products with alkyl chains up to C8. Also we changed substitution patterns at our starting material leading us to a variation of products with different moieties.

CONCLUSION

Benzylic amines were alkylated using quaternary ammonium salts as alkyl source. The Hofmann elimination was found to be the crucial step in order to obtain effective conversion to the product. Kinetic studies towards a fast Hofmann elimination have led to a universal and handy protocol for alkylating C-H activation reactions, especially since gaseous olefins can be substituted for solid quaternary ammonium salts.

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