An Improved, Fully Heterogeneous, Diastereoselective Synthesis of (Z)-α-Bromonitroalkenes

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Abstract: α-Bromonitroalkenes are both key starting materials for the preparation of complex structures and possess antimicrobial activity. In this context, we disclose a simple, fully heterogeneous synthetic approach for their preparation in good overall yields.

Key words: Henry reaction, dehydronitroalcohol, α-bromonitroalkenes, heterogeneous catalysis

Unsaturated nitro compounds are an important class of valuable precursors to a wide variety of target molecules. The utility of conjugated nitroalkenes in organic synthesis is largely due to their versatile reactivity as Michael acceptors, dipolarophiles, 1,3-dipoles, dienophiles, and heterodienes. Nitroalkenes are also distinguished by their diverse biological activities. In this respect, of particular interest are the α-bromonitroalkenes since they have shown important antimicrobial activities as well as being key intermediates.

Due to the importance of these compounds, their easy availability is strategically important and simpler synthetic procedures for their preparation would increase the importance of these bifunctionalized alkenes. The general synthetic method for the preparation of α-bromonitroalkenes involves bromination–debromination of nitroalkenes 3 (Scheme 1). However, since nitroalkanes 3 are generated by Henry reaction followed by elimination, it is clear that the preparation of α-bromonitroalkenes 5 starting from their ultimate precursors (nitromethane and aldehydes) involves a complex multistep sequence.

Some decades ago, a direct procedure involving the nitroaldol condensation of aldehydes with bromonitromethane in the presence of tributylarsine was described. However, the method appears to work just with aromatic aldehydes, and requires a large excess of bromonitromethane, a dry atmosphere, and high temperatures. Moreover, the reaction must be manipulated with attention in order to avoid possible explosion, probably due to the use of tributylarsine. Thus, a simpler method would be valuable. In this context, based on our previous experience in the nitroaldol (Henry) reaction, we have developed a new, simple, mild, and fully heterogeneous approach for the synthesis of α-bromonitroalkenes 5 starting from the Henry reaction between aldehydes 1 and bromonitromethane 6, followed by the dehydration of the obtained crude nitroalkanols (Scheme 2).

We chose, as a model system, the reaction of 6 with hexanal (1a) under basic and solvent-free conditions (carbonate on silica), in which the crude nitroalkanol 7a can be directly dehydrated, by Amberlyst 15/Ac2O into the target compound 5a avoiding any intermediate purification step.

As reported in Table 1, the optimal result was obtained by employing 0.3 equivalents of carbonate on silica, coupled with 500 mg/mmol of Amberlyst 15 and three equivalents of Ac2O.

In order to assess the generality of our procedure we investigated a variety of substrates and, as reported in Table 2, satisfactory to good yields (55–85%) were achieved with aromatic and aliphatic aldehydes, including functionalized substrates. Only 5-bromo-2-furfural 1k (Table 2, entry 11) afforded a low yield (31%) of alkene 5k, probably due to the chemical frailty of the furan ring.

Furthermore, all the obtained α-bromonitroalkenes were isolated as a single Z-diastereomer. The configuration was established by comparison with the literature data.
In conclusion, our procedure offers important advantages with respect to the previous reported approaches since it gives access to the target compounds, without the need for excess bromonitromethane, under mild reaction conditions (room temperature) and short reaction times, with evident economical and environmental benefits. Moreover, a variety of other important functionalities can be tolerated giving access to polyfunctionalized α-bromonirotolkeines that could be of interest as targets with potential biological activities.

Finally, it is important to point out that our method employs a fully heterogeneous procedure and that the final dehydration of nitroalkanol proceeds under acidic conditions, contrary to the standard procedures that usually employ basic conditions.

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References and Notes


Typical Procedure for the Synthesis of Compounds 5


(9) Usually, the dehydration of bromonitroalkanols is performed under basic conditions, see ref. 6.

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