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Investigations into a free radical-mediated 1,2-imino migration

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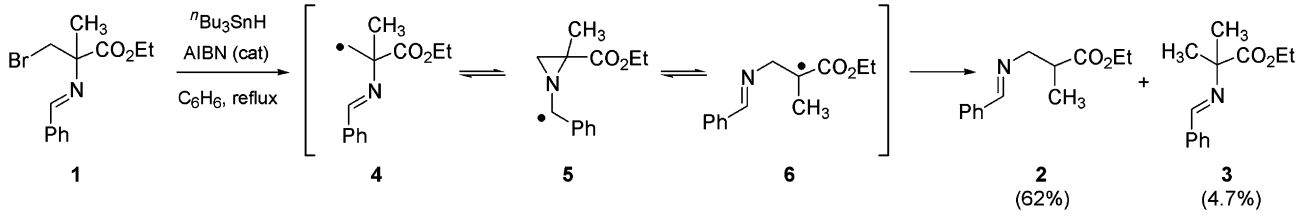
Abstract—The radical reactions of a series of bromides **9a–c** and selenides **12–15** have been investigated to determine the factors that are important for a successful radical-mediated 1,2-imino migration.

Enzyme catalysed 1,2-rearrangements involving radical intermediates play a vital role in biochemical processes and can often lead to transformations that are difficult to achieve in vitro. For example, the enzyme methylmalonyl-CoA mutase catalyses the interconversion of methylmalonyl-CoA and succinyl-CoA.[1] This reaction has been proposed to proceed via a radical pathway involving a 3-*exo*-trig cyclisation–fragmentation process resulting in intramolecular 1,2-migration of the thioester moiety. A number of attempts have been made to model this transformation in the laboratory and whilst reactions involving anionic intermediates have been successful,[2] those involving solely radical intermediates have only been achieved with poor efficiency.[3] Similarly, the aminomutases are a class of enzymes that are known to carry out the 1,2-shift of an amino group. For example, the enzyme lysine 2,3-aminomutase catalyses the interconversion of L-lysine with L-β-lysine via a mechanism thought to involve an analogous 3-*exo*-trig cyclisation of a radical onto a pyridoxal 5′-phosphate imine, followed by ring-opening of the resulting aziridine.[4] However, whilst this transformation has been computationally modelled,[5] there has only been a single report of a chemical model for this intriguing radical-mediated 1,2-imino migration[6] (although similar 1,2-[7] and 1,4-imino[8] group transfers have also recently been reported). Frey and Han have shown that the imine **1** undergoes a free radical-mediated rearrangement to give the β-imino ester **2** together with imine **3**, formed by direct reduction of the starting material, in a 13:1 ratio as shown (Scheme 1).[6] The reaction is thought to proceed via the cyclisation–ring opening sequence indicated (i.e., **4**→**5**→**6**) involving the intermediate azacyclopropyl carbinyl radical **5**. The lack of any further reports of radical-mediated 1,2-imino migrations has led us to explore this transformation further and this paper presents our initial results concerning the factors necessary for successful migration.

We initially chose to examine the radical migration of suitably functionalised *N*-benzylidene imines. However, although we were able to reproduce the results reported by Frey and Han[6] using the imine **1** we found that in general the hydrolytic instability of benzaldehyde



Scheme 1.

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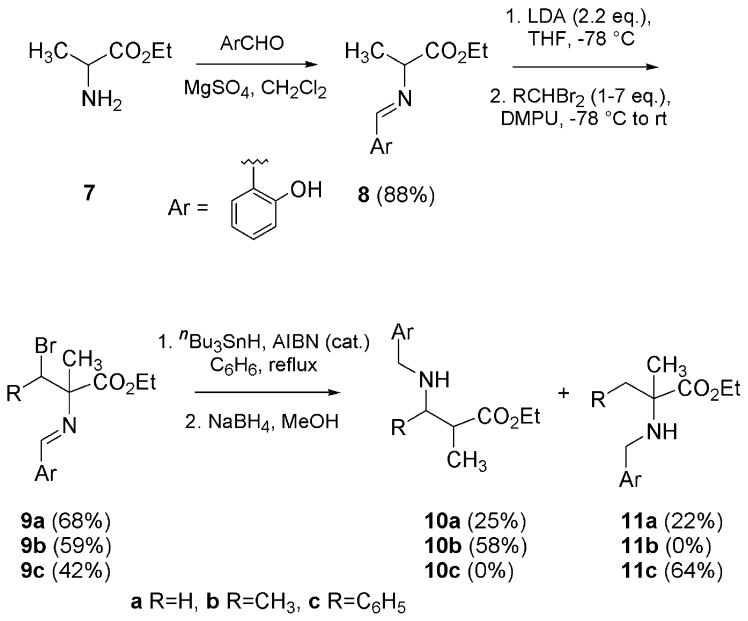


Scheme 2. Compounds **9b**, **9c** and **10b** were isolated as an approx 1:1 mixture of diasteroisomers.

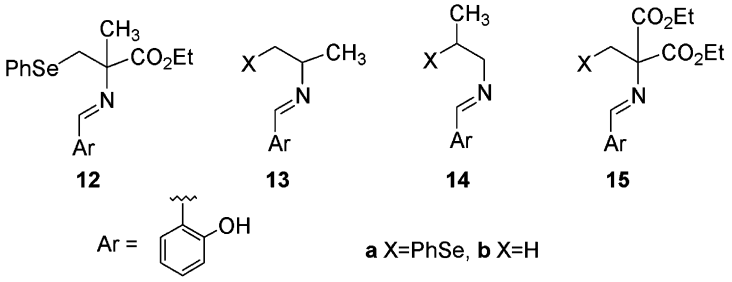
derived imines hindered their use as substrates. Consequently we turned our attention to working with the more stable salicylaldehyde derivatives. Three bromides were initially synthesised and their radical migration reactions investigated as shown (Scheme 2).

Thus initial conversion of DL-alanine ethyl ester **7** to the corresponding imine **8** proceeded in excellent yield.[9] Conversion of **8** to the corresponding dianion using 2.2 equiv of LDA allowed for successful α-alkylation with the three 1,1-dibromides indicated to give the radical precursors **9a**–**c** in good to moderate yields. It should be noted that, to the best of our knowledge, there is only a single report of an analogous α-alkylation of α-amino acid derived salicylaldehyde imines and that this required the use of excess (7–10 equiv) LDA.[10] We believe that the method presented here provides an excellent direct route to α,α-dialkyl imines of this type. Radical reactions of the bromides **9a**–**c** were carried out by the dropwise addition over 3 h of $^{n}Bu_3SnH$ (1.0 equiv) and AIBN (0.05 equiv) in benzene to a refluxing solution of **9a**–**c** (0.01 M in benzene) followed by an additional 2 h reflux. To avoid any losses due to imine hydrolysis the resulting reaction mixtures were treated with $NaBH_4$ in methanol and the products isolated as their salicylaldehyde-derived benzyl amines **10a**–**b**, **11a** and **11c**.[11]

Reaction of the bromide **9a** gave the β- and α-amino esters **10a** and **11a** in an approximately 1:1 ratio and 47% overall yield. The lower level of 1,2-imino migration seen with **9a** when compared to the corresponding benzylidiene imine **1** suggests that the *ortho*-hydroxyl substituent adversely affects the migration process. This result is in accord with the findings from computational studies, which have indicated that the presence of an *ortho*-hydroxyl group can raise the energy barrier for the initial 3-*exo*-trig cyclisation.[5] In contrast, reaction of the bromide **9b** gave only the migrated product **10b** in good yield. This observation is particularly interesting as the secondary radical initially formed from **9b** is predicted to be more stable than the corresponding primary radical produced from **9a**. Hence, these two results demonstrate that the relative stabilities of the two ring-opened radical intermediates involved in the reaction pathway are not solely responsible for determining the extent of imino migration. The lack of any migrated product observed in the reaction of **9c** suggests that in this case the initially formed benzyl radical is either too stable to undergo 3-*exo*-trig cyclisation, or that cyclisation occurs to give the corresponding azacyclopropyl carbinyl radical, which then simply ring opens to regenerate the stable benzyl radical.

The results observed with bromides **9a**–**c** suggest that the relative stability of the radical intermediates involved in the reaction pathway is not the sole factor responsible for determining whether a successful 1,2-imino migration occurs. To explore, which other variables are also important the four phenyl selenides **12** and **13a**–**15a** were synthesised and their radical reactions examined.[12]

Reaction of **12** under our standard radical conditions gave the expected β- and α-amines **10a** and **11a** in a 3:1 ratio (overall yield 54%). The only difference in the reactions of selenide **12** and bromide **9a** will be the greater rate of S_H2 reaction of the former with the tributyl tin radical.[13] Thus the increased proportion of the β-amine **10a** produced from the selenide **12** compared to that observed with the bromide **9a** suggests that the rate of radical propagation also has a vital influence in determining the extent of 1,2-migration. The three precursors **13a**–**15a** were synthesised to examine the influence of the ester group on the migration reaction. Reaction of the three selenides **13a**–**15a** under our standard radical



conditions, however, failed to give any of the anticipated products resulting from 1,2-imino migration. Only the directly reduced products **13b**–**15b** (isolated, after reaction with $NaBH_4$, as the corresponding salicylaldehyde-derived benzyl amines) were formed in these reactions. Any 3-*exo*-trig cyclisation of the radicals generated from the selenides **13a** and **14a** would produce the same azacyclopropyl carbinyl radical intermediate, which would be expected to give the same reaction products in either case. The absence of any product **13b** from the reaction of **14a** (and of **14b** from **13a**) therefore indicates that the 3-*exo*-trig cyclisation step is not occurring in either of these reactions and suggests that the presence of an α-carboxyl ester may be necessary to facilitate azacyclopropyl formation. The influence of imine polarisation in radical cyclisation reactions has been documented.[14,15] Thus, nucleophilic alkyl radicals have a strong preference for attack on the electrophilic imine C-atom and consequently there are only a few reports of alkyl radical addition onto the electronegative N-atom of imines.[15] The failure of both **13a** and **14a** to undergo 3-*exo*-trig cyclisation onto the imine N-atom suggests that the electron withdrawing ester group in **9a**, **9b** and **12** may be necessary to activate the imine to attack at the 'wrong' end.

The absence of any 1,2-imino migration products from the reaction of **15a** is intriguing as this system seems particularly favourable for the reaction. The two ester moieties would expected to increase the rate of 3-*exo*-trig cyclisation (by increasing the electropositive nature of the imine N-atom) and would also favour ring opening of the resulting azacyclopropyl carbinyl radical in the forward sense, due to the stabilised tertiary α-malonate radical thus produced. This second point suggests that the 3-*exo*-trig cyclisation does not take place despite the activating effect of the two esters. However, there is another possible explanation for this result. Newcomb et al. have shown that the rate of hydrogen abstraction from $^{n}Bu_3SnH$ by tertiary α-carboethoxy radicals is an order of magnitude slower than for the reaction of tertiary alkyl radicals, which they attribute to steric effects due to enforced planarity at the radical centre.[16] Such effects would also be expected with the tertiary α-malonate radical formed in the migration pathway from **15a** and we cannot rule out that the slow rate of H-abstraction by this radical, coupled with the low concentration of tin hydride used in the reaction, is determining the products observed. Unfortunately, the results presented here do not let us distinguish between these two possibilities.

In summary we have begun to discover some of the factors that are important for a successful free radical-mediated 1,2-imino migration. We are currently investigating this intriguing transformation for the synthesis of β-amino acid derivatives.

Acknowledgements

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