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Thesis abstract

Divergent synthesis of heterocycles using dinitrobenzyl chloride analogues

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Often prized for their bioactivity, heterocycles are present throughout chemical industries and research. The development of new heterocycles and novel methods to synthesise them are central pursuits of small-molecule chemistry and serve as the overarching ambition of this thesis. The following dissertation is divided into two parts, detailing the alternate reactivity of electron-deficient di-substituted benzyl chloride analogues and the synthetic utility of their respective heterocyclic products.

Part I exploits the electrophilic reactivity of 3,5-dinitrobenzyl chloride in a multi-step process to synthesise benzoazepine-fused isoindole atropisomers. Recent developments in the study and synthesis of medium-ring benzo-fused N-heterocycles are reviewed in Chapter 1. The protocol developed for the synthesis of atropo-enantiomeric benzoazepine-fused isoindoles is detailed in Chapter 2. Based on previous work by our research group, 2-aminobenzaldehydes are benzylated with 3,5-dinitrobenzyl chloride to generate a tethered species which can form azomethine ylides *in situ* that undergo an intramolecular (3 + 2) cycloaddition-elimination sequence to benzoazepine-fused isoindolines. In this work, a procedure to oxidise the isoindoline systems to the respective isoindoles is developed, provoking dramatic conformational changes and enantio-atropisomerism. Through kinetic HPLC experiments and X-ray crystal structure analysis, the source of this atropisomerism and the relative enantiostability of analogous compounds was determined, with restricted rotation around the C_{aryl}–$N_{sulfonamide}$ axis identified as a key factor in regulating the rate of racemisation. In Chapter 3, this work is extended to atropo-diastereomeric systems through the addition of a pendent stereocentre, installed during formation of the azomethine ylide. With the diastereomers distinguishable using NMR spectroscopy, oxidation of the isoindolines was revealed as a stereoselective process dictated by central-to-axial chirality conversion. Further, the folded conformation of the oxidised system was shown to induce facial selectivity during Diels–Alder cycloaddition of the isoindole. This process thus allows for the selective generation of complex three-dimensional structures in high yields.

Part II of this thesis discusses the bifunctional reactivity of benzyl chlorides substituted with electron-withdrawing groups in the 2- and 4-positions. In addition to reacting as electrophiles, 2,4-substituted benzyl chlorides have been shown to undergo benzylic deprotonation to form a resonance and inductively stabilised anion, enabling them to function as carbene-like nucleophiles.

In Chapter 4, work is discussed where this dual reactivity is harnessed through the development of a two-step (4 + 1) annulation-dehydration protocol to synthesise C2-arylated indoles and benzofurans. Using 2,4-dinitrobenzyl chloride as a model, a substrate scope of the 4-atom component found that variation of the aryl substituents was broadly tolerated, with subsequent dehydration to the desired indole or benzofuran product proceeding smoothly (33–98% yield). A probe into the limitations of the benzyl chloride reagent revealed that the protocol proceeds successfully with different *para* electron-withdrawing substituents (18–77% yield). The singly-activated 2-nitrobenzyl chloride however, was not sufficiently nucleophilic to undergo (4 + 1) cycloaddition, instead participating in electrophilic benzylation. Side-products generated from 2,4-dinitrobenzyl chloride under the reaction conditions were also investigated, revealing multi-nitrated, ring-strained compounds of potential interest as high energy density materials.

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