Organic & Biomolecular Chemistry

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Synthesis of functionalised 4*H*-quinolizin-4-ones *via* tandem Horner–Wadsworth–Emmons olefination/cyclisation†

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 3337

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Received 22nd March 2013,
Accepted 25th March 2013

DOI: 10.1039/c3ob40578h

www.rsc.org/obc

4*H*-Quinolizin-4-ones are a unique class of heterocycle with valuable physicochemical properties and which are emerging as key pharmacophores for a range of biological targets. A tandem Horner–Wadsworth–Emmons olefination/cyclisation method has been developed to allow facile access to substituted 4*H*-quinolizin-4-ones encoded with a range of functional groups.

Heterocyclic compounds are of particular interest and significant importance in the search for new bioactive agents in both the agrochemical and pharmaceutical industries. Indeed, with particular reference to the pharmaceutical industry, heterocyclic motifs are especially prevalent with over 60% of the top retailing drugs containing at least one heterocyclic nucleus as part of the overall topography of the compound.[1]

In this regard, heteroaromatic rings are extensively used as scaffolds as (i) their structure and associated physicochemical properties often lead to efficient binding to a biological target and selectivity, (ii) derivatives are often readily available *via* common synthetic transformations, (iii) there are no complications due to stereochemistry, and (iv) a novel ring system or substitution pattern of an existing system can expand the intellectual property estate of a discovery programme.[2] Consequently, the identification of new heteroaromatic rings that (i) exhibit improved properties over existing frameworks (*e.g.*, improved metabolic stability, higher solubility, lower log *P*), (ii) new methods with which to access novel substitution patterns (improved synthetic tractability), or (iii) that provide access to new chemical space is of immense importance in the search for new bioactive agents.

Concurrently, in specific relation to the pharmaceutical industry, fragment-based drug discovery is of considerable interest in the search for new ligands for biological targets and offers an efficient method of identifying new hits or leads.[3] New or unusual heterocyclic fragments and derivatives are particularly valued in this area as they can offer many of the desirable attributes described above and provide good points on which to base further research and development.

As part of a programme aimed at the preparation of unusual heterocyclic structures, we have targeted the generation of libraries of novel heteroaromatic scaffolds. More specifically, we have been interested in the 4*H*-quinolizin-4-one ring system (Fig. 1) based on calculated desirable physicochemical properties and projected synthetic utility.[4] The 4*H*-quinolizin-4-one scaffold and the related partially- or fully-saturated systems have previously found broad use within medicinal chemistry programmes as ligands for a variety of receptor targets including as treatments for Alzheimer's disease,[5] Type 2 diabetes,[6] and HIV.[7] However, despite encouraging biological activity, there is a lack of a general method for the construction of this ring system. Existing methods tend to be bespoke for a particular target and lack flexibility rendering them unsuitable to the generation of a bank of analogues. Consequently, we became interested in pursuing a more general method for the assembly of this valuable ring system and one that may be amenable to

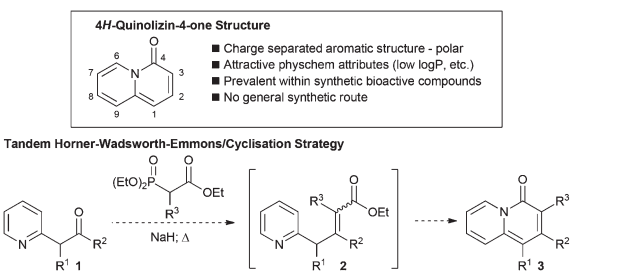

Fig. 1 The 4*H*-quinolizin-4-one ring system and proposed tandem HWE/cyclisation strategy.

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†Electronic supplementary information (ESI) available: Experimental procedures and characterisation data for all compounds, crystallographic data for compound **3a**. CCDC 915082. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob40578h

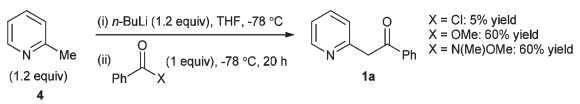
variation of substitution and functionality in order to improve synthetic tractability upon identification of a promising ligand.

Our synthetic strategy is shown in Fig. 1.[8] From a suitable β-carbonyl pyridine, the pyridone ring would be annulated *via* a tandem Horner–Wadsworth–Emmons olefination/cyclisation event with the cyclisation taking place under thermal promotion.[9] Use of functionalised β-carbonyl pyridines and/or phosphonates would potentially provide a range of functionality in the products around the pyridone ring.

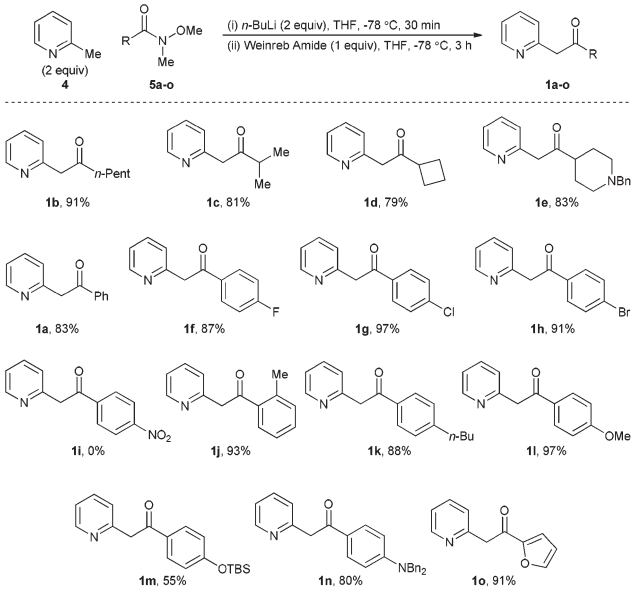
We were specifically interested in 2-substituted 4*H*-quinolizin-4-ones as routes to this specific substitution are exceedingly rare with only one example of a direct preparation which delivers a mixture of products.[8k] All other previous routes generate products with 1,2-, 2,3-, or 1,2,3-functionalisation.[8] However, in terms of bioactive agents, fine-tuning of the 2-substitution is key for potency and selectivity.[5–7] As such, to initiate our study we required access to β-ketopyridines of type **1** where R^1 and R^3 = H and R^2 = alkyl or aryl (Fig. 1). A convenient method of preparing these compounds was identified as being *via* the direct acylation of the 2-picoline anion, obtained *via* deprotonation using organolithium reagents (*e.g.*, LDA, *n*-BuLi).[10] In the event, we elected to employ *n*-BuLi as trial reactions revealed low reactivity with LDA. In addition, we surveyed three potential acylating agents: acyl chlorides, esters, and Weinreb amides (Scheme 1). While Weinreb amides were anticipated to be less problematic in terms of the potential for over-alkylation, we reasoned that the tetrahedral intermediate generated upon nucleophilic addition to acyl chlorides or esters may be stabilised by the presence of the pyridine nitrogen (*via* a 6-membered chelate) and thus may prevent collapse in the reaction vessel, enabling acylation with these more readily available (commercial) reagents.[11] Indeed, in preliminary reactions, esters were found to perform equally as well as Weinreb amides with acyl chlorides revealed as unsuited to the desired transformation.

However, subsequent optimisation steps demonstrated that the yields for ester-based acylation were consistently lower than those achievable using the corresponding Weinreb amides and as such, we moved forward with the latter as the acylation reagent of choice, with two equivalents of 2-picoline/*n*-BuLi proving optimal (83% yield of **1a**). Accordingly, a series of Weinreb amides, **5a–o**, were prepared using either acyl chlorides or an established i-PrMgCl-based ester amidation method[12] (for full details, see the ESI†) and used to prepare a range of functionalised β-ketopyridines (Scheme 2).

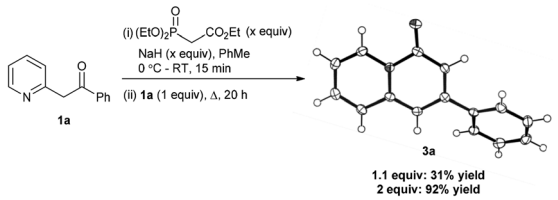
Pleasingly, the developed acylation conditions operated effectively for both alkyl and aryl Weinreb amides possessing a range of functionality in generally high yields with only two exceptions: the NO_2-substituted derivative **1i** could not be induced to follow the desired acylation pathway and, instead, generated a complex mixture of undesired products presumably through reaction pathways enabled by the NO_2 functionality. The OTBS substrate **1m** could be isolated but in somewhat moderate yield due to desilylation of the phenol under the basic reaction conditions.



Scheme 1 Evaluation of potential acylating agents.



Scheme 2 Synthesis of β-ketopyridines.

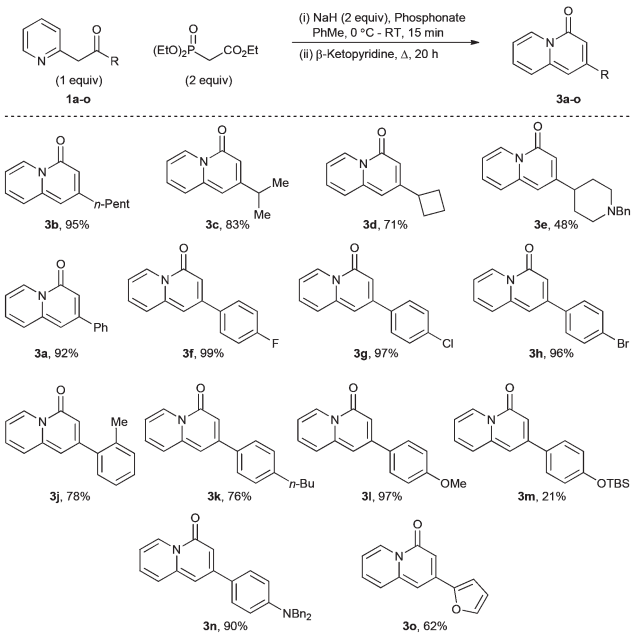


Scheme 3 Tandem synthesis of 4*H*-quinolizin-4-one **3a** from β-ketopyridine **1a**. Thermal ellipsoids are drawn at 50% probability.

It should be noted that β-ketopyridines **1a–o** exist as a mixture of enol–keto tautomers, with the ratio dependent on the carbonyl substitution. These compounds may find further use as synthetic intermediates or, based on the proximity of the heteroatoms, as ligands for metal systems.

With these β-ketopyridines in hand, our attention moved to the pivotal tandem HWE/cyclisation process. Exposing β-ketopyridine **1a** to a mixture of triethylphosphonoacetate and NaH in toluene at 0 °C followed by warming to reflux for 20 h delivered the 4*H*-quinolizin-4-one **3a** in 31% yield (Scheme 3). Simply increasing the ratio of triethylphosphonoacetate and NaH to 2 equivalents delivered **3a** in a synthetically useful yield of 92%. Structural confirmation was achieved by NMR as well as X-ray crystallography (Scheme 3).

We proceeded to apply these conditions to the range of β-ketopyridines to provide a small array of 4*H*-quinolizin-4-ones in generally good yields (Scheme 4). Once again, the TBS-protected phenol substrate **3m** was isolated in low yield



Scheme 4 Tandem HWE/cyclisation 4*H*-quinolizin-4-one synthesis.

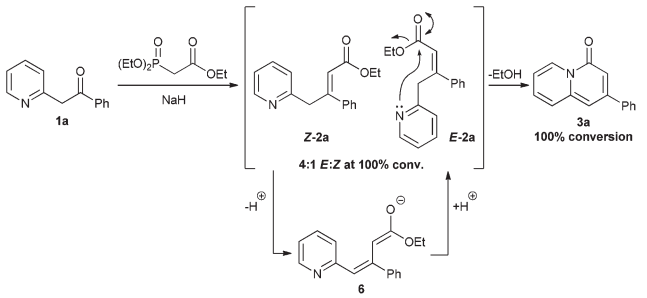
due to desilylation under the basic reaction conditions as previously observed during preparation of the β-ketopyridine **1m**.

From a mechanistic perspective, the tandem process proceeds *via* HWE olefination of the carbonyl unit followed by straightforward intramolecular *N*-acylation of the pyridine, proton loss, and electronic reorganisation to provide the annulated product. The *E*/*Z* selectivity of the HWE olefination was unknown at this stage although this was assumed to be *E*-selective based on the generally high yields of 4*H*-quinolizin-4-one product and the assumption that only the *E*-olefin would be able to be converted to the annulated product. To validate this, we decided to probe the selectivity of the olefination by analysis of an aliquot of the reaction of **1a** prior to the reflux step. We found that the selectivity of the olefination is actually rather modest at only 4 : 1 in favour of ***E*-2a** suggesting a maximum expected yield of approximately 80%.‡ However, we observed 100% conversion to **3a** suggesting that ***Z*-2a** must be converted to ***E*-2a** prior to cyclisation. We believe this is a base-assisted process proceeding through the enolate **6** which allows for olefin isomerisation and subsequent cyclisation to **3a** (Scheme 5).

Conclusions

In summary, we have developed a tandem Horner–Wadsworth–Emmons/cyclisation approach for the synthesis of the 4*H*-quinolizin-4-one architecture. The developed route enables effective synthesis of 2-substituted 4*H*-quinolizin-2-ones and proceeds in good to excellent yield. Based on the highly effective use of 2-substituted 4*H*-quinolizin-4-one scaffolds

‡The *E* : *Z* ratio was determined by nOe ^{1}H NMR spectroscopy.



Scheme 5 Proposed mechanism for the tandem reaction.

within bioactive agents and the significance of this particular ring substitution in the context of target potency and selectivity, we believe this new synthetic approach will be of broad utility in the design and synthesis of new biologically active compounds. Translation of this process in order to realise alternative substitution patterns and novel heterocyclic ring constructs is currently underway.

Experimental section

General experimental procedure for the deprotonation of 2-picoline and nucleophilic addition to Weinreb amides

For example, for compound **1a**. An oven-dried flask equipped with a stirrer bar and fitted with a septum was purged with N_2. The flask was cooled to −78 °C by submerging in a bath of dry ice/acetone. The flask was then charged with dry THF (11 mL) and 2-picoline (2 equiv., 4 mmol, 372.5 mg, 0.395 mL) and stirred. *n*-Butyllithium (1.6 M in hexanes, 2 equiv., 4 mmol, 2.5 mL) was added to the flask dropwise over 5 minutes. Concurrently, an additional oven-dried flask equipped with a stirrer bar and fitted with a septum was purged with N_2. The flask was cooled to −78 °C by submerging in dry a dry ice/acetone bath. The flask was then charged with dry THF (5 mL) and *N*-methoxy-*N*-methylbenzamide (1 equiv., 2 mmol, 330.4 mg, 0.304 mL) and stirred. After 30 min, the deprotonated picoline solution was added to the Weinreb amide solution by dropwise addition *via* syringe over 10 minutes. The reaction was allowed to proceed for 3 hours before quenching with water. EtOAc (5 mL) was added and the phases were separated. The aqueous layer was then re-extracted with EtOAc (5 × 5 mL). The combined organic phases were dried ($MgSO_4$), passed through a hydrophobic frit, and concentrated under reduced pressure to afford a residue that was purified by flash column chromatography (1 : 2 EtOAc–petroleum ether 40–60°) to afford the title compound (327 mg, 83% yield).

General experimental procedure for the synthesis of quinolizinones *via* tandem Horner–Wadsworth–Emmons olefination/intramolecular cyclisation

For example, for compound **3a**. An oven-dried flask equipped with stirrer bar was purged with N_2 and cooled to 0 °C by submerging in an ice/water bath. The flask was charged with dry toluene (5 mL), triethyl phosphonoacetate (2 equiv., 2 mmol,

448.4 mg, 0.398 mL), and NaH (60% dispersion in mineral oil, 2 equiv., 2 mmol, 83.0 mg). The mixture was stirred for 15 min before removing from the cooling bath and warming to room temperature. 1-Phenyl-2-(pyridin-2-yl)ethanone (**1a**, 1 equiv., 1 mmol, 197.1 mg) was added and the reaction mixture was heated to reflux for 20 hours. The reaction was then treated with Et_2O (5 mL), concentrated under reduced pressure to a residue that was purified by flash column chromatography (1 : 1 EtOAc–petroleum ether 40–60°) to afford the title compound (203.5 mg, 92% yield).

Acknowledgements

We thank the EPSRC National Mass Spectrometry Service Centre, Swansea University, and Dr David Watson, Dr Gavin Blackburn, and Tong Zhang at the Strathclyde Institute of Pharmacy and Biomedical Sciences for analyses. We are grateful to GlaxoSmithKline for the kind donation of consumables and equipment. Dr Simon MacDonald (GSK), Dr Craig Jamieson (University of Strathclyde), and Pat Keating (University of Strathclyde) are thanked for helpful discussions.

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