chemistry proceedings

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Catalytic Synthesis of Versatile Chiral Heterocycles: En Route to g-Amino Acid Derivatives †

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† Presented at the 29th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-29); Available online: https://sciforum.net/event/ecsoc-29.

Abstract

The synthesis and application of new chiral amino acids (AAs) and peptides derived thereof is research topic of major importance. The introduction of g-AA as building blocks is useful for the development of original chiral small molecules and heterocycles, enabling exploration of 3D chemical space in search of selectivity in biological properties. 4.5-Dihydro-2H-pyridazin-3-ones (DHPDOs) are 6-membered *aza*-heterocycles considered as masked g-AA analogues. We herein report on the synthesis of various a-monosubstituted DHPDOs as platform-molecules using Meldrum's acid chemistry and the a-functionalization approach upon the asymmetric Michael addition using the Phase-Transfer Catalysis (PTC).

Keywords: organic chemistry; Meldrum's acid; asymmetric synthesis; phase-transfer catalysis; gamma amino acids

1. Introduction

Compared to classical a-amino acids (a-Aas), the introduction of g-AA derivatives into the corresponding peptidomimetics leads different secondary structures and improved hydrolytic stability towards peptidases, thus providing altered and sometimes better biological properties/activities [1].

For example, γ-aminobutyric acid (GABA) is the simplest g-AA and the main inhibitory neurotransmitter in the mammalian central nervous system, which is involved in several brain disorders such as neuropathic pain, Alzheimer's disease, Parkinson's disease. For these reasons, the signaling modulation of GABA is the basis of many pharmacologic treatments [2]. The therapeutic properties of g-AA derivatives in enantiomerically pure form have encouraged organic chemists to develop several procedures for their enantioselective synthesis. The construction of a-disubstituted g-AA derivatives remain challenging and furthermore the elaboration of g-AA with a tetra-substituted stereocenter is not a trivial task [3]. Moreover, a-disubstituted g-AA derivatives are also useful building blocks for the elaboration of original chiral small molecules and heterocycles allowing the exploration of the 3D-chemical space in search of selectivity in biological properties and prevent any racemization event [1,4,5]. 4,5-Dihydro-2H-pyridazin-3-one (DHPDO) scaffolds are important 6-membered *aza*-heterocycles and are widely used as key building

Academic Editor(s): Name

Published: date

Citation: Henry, P.J.; Burel, G.; Nzegge, W.; Waser, M.; Brière, J.-F. Catalytic Synthesis of Versatile Chiral Heterocycles: En Route to g-Amino Acid Derivatives. *Chem. Proc.* **2025**, *volume number*, x. https://doi.org/10.3390/xxxxx

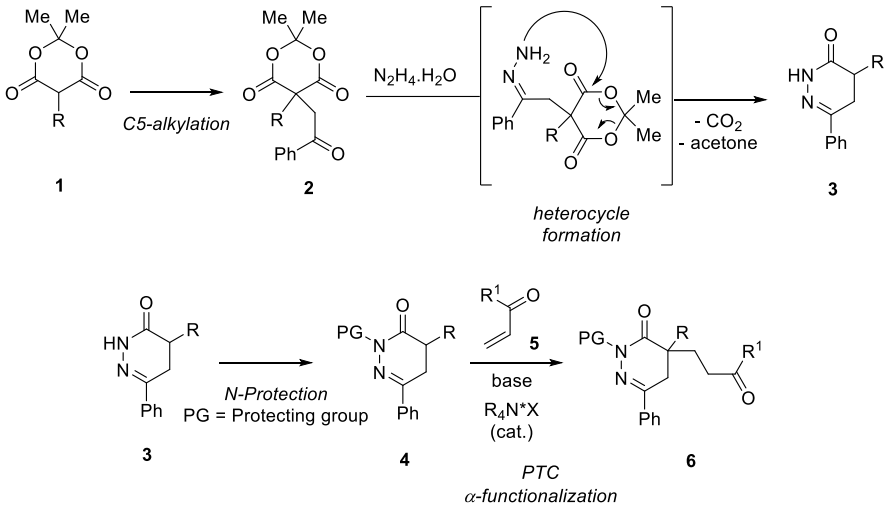
blocks in many biologically active molecules and therapeutic agents, with a wide range of pharmacological and medicinal properties. Some of them have been used in commercial pharmaceuticals and agrochemicals [6,7].

Unsurprisingly, many research groups have developed asymmetric catalytic syntheses of DHPDO derivatives that are either mono-substituted at the C5- or the C4-position (a-position of the carbonyl functionality) [8,9]. In this respect, several of these heterocycles of potential medical interest contain one or two substituents at the C4-position [10]. However, to our knowledge, the asymmetric catalytic synthesis of a,a-disubstituted DHPDO derivatives containing a quaternary stereogenic center has not yet been addressed [12]. Thus, the development of reliable strategies that provide easy access to different a-functionalized DHPDOs, even asymmetrically, is a laudable goal.

In accordance with the value mentioned above for chiral 4,5-dihydro-2H-pyridazin-3-ones, we have now set ourselves the goal of establishing a robust synthetic pathway for obtaining various a-functionalized DHPDOs. We also present a strategy that involves the asymmetric quaternary ammonium salt phase-transfer catalyzed Michael addition reaction of a-monosubstituted DHPDOs.

2. Results and Discussion

Our synthetic plan was based on the elaboration of various a-functionalized DHPDOs **3** from hydrazine and Meldrum's acid chemistry, i.e., making use of derivatives **1**. The readily accessible compounds **1** were expected to enable the construction of appropriately C5-disubstituted Meldrum's acid derivatives **2**, precursors for the synthesis of DHPDOs **3–4** after treatment with hydrazine. Finally, after a suited *N*-protection to modulate the reactivity of DHPDO compound **4**, we investigated the asymmetric organocatalytic a-functionalization with different Michael acceptors under chiral ammonium salt phase transfer conditions for the construction of new heterocyclic derivatives **6** (Scheme 1).



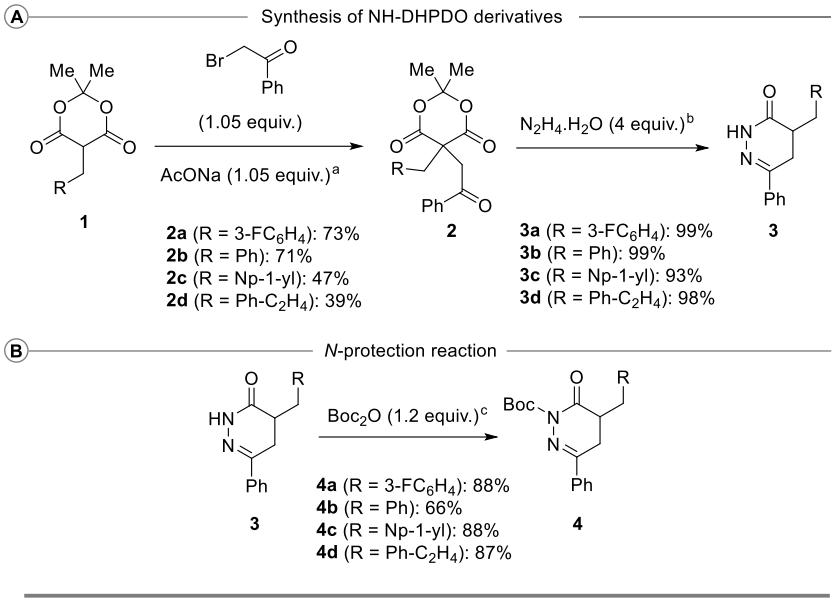
Scheme 1. Synthetic route enabling the obtention of new a-disubstituted heterocyclic derivatives.

2.1. Synthesis of N-Boc DHPDO Derivatives **4**

The synthesis of the C5-alkyl Meldrum's acid derivatives **1a–d** was easily achieved following the methodology of Ramachary and collaborators [12].

For the elaboration of NH-DHPDO derivatives **3**, we based our methodology on the contribution of Tóth and collaborators, starting from the monosubstituted Meldrum's acid derivatives **1** (Scheme 2A) [13]. First, the C5-disubstituted Meldrum's acid derivatives **2** are obtained by alkylating **1** using 2-bromoacetophenone under basic conditions. Then,

the NH-DHPDO derivatives **3** were obtained by the condensation of hydrazine at room temperature. Finally, the free NH-DHPDO derivatives **3** were *N*-protected using *tert*-butoxycarbonyl anhydride (Scheme 2B).

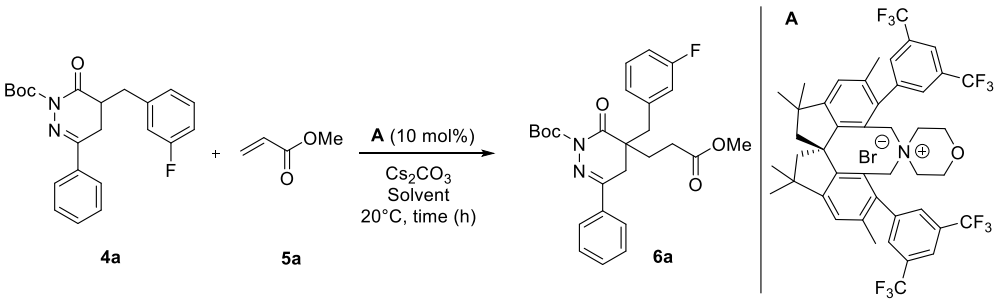


Scheme 2. Synthesis of *N*-Boc DHPDO derivatives.

2.2. α-Functionalization of N-Boc DHPDO Derivatives **4**

We were next interested in the asymmetric α-functionalization of *N*-Boc DHPDO derivatives **4** using the spirobiindane-based salt **A** [14]. The optimization was performed using the heterocycle **4a**, methyl acrylate **5a** as an acceptor and cesium carbonate as a simple inorganic base (Table 1).

Table 1. Optimization of ammonium salt (A)-catalyzed Michael addition of *N*-Boc DHPDO **4a** to methyl acrylate **5a** [1].



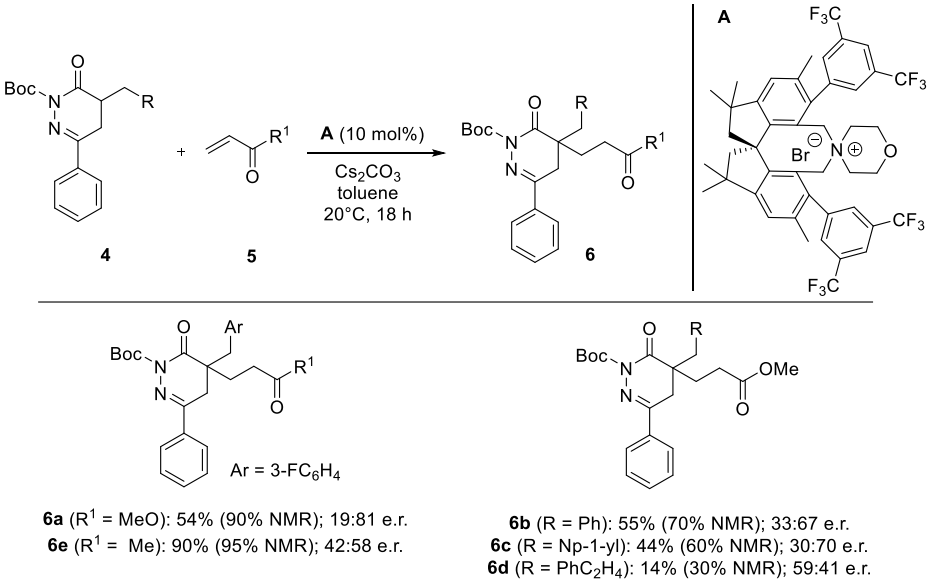
Entry	Solvent	Cs_2CO_3 (eq.)	Time (h)	Conv. (%) [2]	6a (%) [3]	e.r. [4]
1	CH_2Cl_2	1.5	3	90	85	36:64
2	THF	1.5	3	95	50	42:58
3	toluene	1.5	3	30	25	10:90
4	toluene	1.5	18	80	75	15:85
5	toluene	1.5	40	100	95	18:82
6	toluene	3	18	100	95 (54)	19:81

[1] All reactions were run using 0.1 mmol **4a**, 0.3 mmol **5**, the indicated base in the given solvent (0.1 M) at room temperature unless otherwise stated. [2] Based on remaining **4a** calculated from the ^1H NMR spectrum of the crude product using nitromethane as an internal standard (rounded in

increments of 5%). [3] NMR yields using nitromethane as an internal standard (rounded in increments of 5%)—isolated yields given in brackets. [4] Determined by HPLC using a chiral stationary phase, given in order of retention.

The use of toluene as solvent allowed us to achieve a good enantioselectivity (90:10 e.r.) but with a low conversion of 30% (entry 3). Preliminary investigation showed that these conditions surpassed the outcomes in THF and CH_2Cl_2 (entries 1–2). Then, by increasing the time of reaction to 18 and 40 h, we obtained better conversion but with a decrease in enantioselectivity as low as 18:82 e.r. (entry 4–5). This observation could be interpreted by counter-cation exchange or a catalyst degradation. Using a larger excess of base, product **5a** was obtained with a high NMR yield of 95% and a moderate enantioselectivity (19:81 e.r., entry 6). Worthy of note, a lower isolated yield than that forecast based on the NMR yield was obtained. It can be explained by a partial retro-Michael addition after the purification by normal-phase silica gel column chromatography (a notable amount of starting material **4a** was recovered).

The conditions depicted in entry 6 represent a fair compromise between conversion and enantioselectivity. Then, we tackled the exemplification of this method testing various a-substituted *N*-Boc DHPDOs and methyl vinylketone **5b** as an acceptor (Scheme 3).



6a (R^1 = MeO): 54% (90% NMR); 19:81 e.r.
6e (R^1 = Me): 90% (95% NMR); 42:58 e.r.

6b (R = Ph): 55% (70% NMR); 33:67 e.r.
6c (R = Np-1-yl): 44% (60% NMR); 30:70 e.r.
6d (R = PhC_2H_4): 14% (30% NMR); 59:41 e.r.

Scheme 3. Application scope for the asymmetric 1,4-addition of *N*-Boc DHPDOs **4** to Michael acceptors **5**.

The use of acceptor **5b** (R^1 = Me) gave the product **6e** with a low enantioselectivity (42:58 e.r.) despite a high yield of 90%. Then, a-substituted *N*-Boc DHPDO derivatives were investigated using methyl acrylate **5a** as acceptors giving products **6b–c**, having benzylated pendants, with yields ranging from 44% to 55% and up to 30:70 e.r. Unfortunately, we obtained modest enantioselectivities (59:41 e.r.) combined with a lower yield (14%) for compound **6d** having a longer alkyl chain (R = PhC_2H_4).

3. Conclusions

We successfully developed a methodology to access α-functionalized 4,5-dihydro-2H-pyridazin-3-ones using Meldrum's acid chemistry. Subsequently, we developed a new methodology based on asymmetric Michael addition reaction employing Phase-Transfer Catalysis. This resulted in the formation of novel α,α-disubstituted pyridazinone

derivatives, which contain a quaternary stereocenter and had not been previously addressed.

Author Contributions: Conceptualization, M.W. and J.-F.B.; methodology, M.W. and J.-F.B.; investigation, P.J.H., G.B. and W.N.; resources, M.W. and J.-F.B.; data curation, P.J.H. and W.N.; writing—original draft preparation, P.J.H. and W.N.; writing—review and editing, P.J.H., W.N., M.W. and J.-F.B.; visualization, M.W. and J.-F.B.; supervision, M.W. and J.-F.B.; project administration, M.W. and J.-F.B.; funding acquisition, M.W. and J.-F.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by AUSTRIAN SCIENCE FUNDS (FWF) through project No. P36004.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

Acknowledgments: Austrian Science Funds (FWF) is gratefully acknowledged. This work has been partially supported by Université Rouen Normandie, INSA Rouen Normandie, Centre National de la Recherche Scientifique (CNRS), European Regional Development Fund (ERDF), Région Normandie, Labex SynOrg (ANR-11-LABX-0029), Carnot Institute I2C, and the graduate school for research XL-Chem (ANR-18-EUR-0020 XL CHEM).

Conflicts of Interest: The authors declare no conflicts of interest.

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