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Intramolecular inverse electron-demand [4+2] cycloadditions of ynamidyl-tethered pyrimidines: Comparative studies in trifluorotoluene and sulfolane

Cycloaddition [4+2] intramoléculaire à demande électronique inverse d'ynamidyl pyrimidine : études comparatives dans le trifluorotoluène et le sulfolane

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ABSTRACT

Three representative 6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-4-amines were synthesized using an intramolecular inverse electron demand hetero–Diels–Alder/retro–Diels–Alder sequence between pyrimidines (acting as azadienes) and ynamides (acting as dienophiles). Two solvents of this reaction, sulfolane and trifluorotoluene, were compared at 210 °C and the former consistently led to higher yields. In addition, these studies confirmed the importance of the steric bulk of the C5-position of the pyrimidinyl cycloaddition precursor.

RÉSUMÉ

Trois 6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-4-amines representatives ont été synthétisées par une réaction d'hétérocycloaddition [4+2] intramoléculaire à demande électronique inverse (*ih*DA)/rétro-Diels–Alder (*r*DA) entre des pyrimidines (jouant le rôle d'azadiènes) et des ynamides (jouant le rôle de diénophiles). Deux solvants de cette transformation, le sulfolane et le trifluorotoluène, ont été comparés à 210 °C; le premier des deux a conduit systématiquement à de meilleurs rendements. De plus, ces études confirment l'importance de l'encombrement stérique de la position C5 du précurseur de cycloaddition de type pyrimidinyl.

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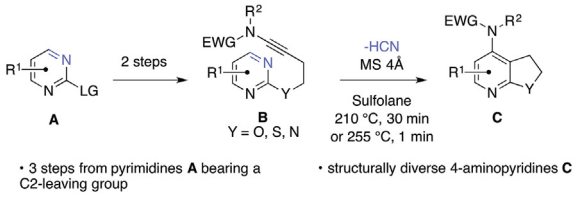
1. Introduction

The rapid access to polysubstituted 4-amino pyridines is a central endeavor in chemical sciences, owing to the importance of these nitrogenated heterocycles as building blocks or lead compounds in medicinal and agrochemical chemistries [1], as ligands in organometallic complexes [2] or as efficient catalysts [3]. Among the strategies leading to pyridines, cycloaddition reactions proceed under neutral conditions and have been used as key steps in numerous syntheses of biologically relevant organic compounds [4]. In line with our interest in alkyne [5] and heterosubstituted alkyne chemistry, we have recently reported that polysubstituted 4-aminopyridines **C** could be synthesized in three simple steps from **A** (Scheme 1) via an inverse electron demand hetero–Diels–Alder (*ih*DA)/retro–Diels–Alder (*r*DA) cycloaddition between a pyrimidine and a ynamide, the latter acting as the electron-rich 2π partner [6].

This intramolecular cycloaddition/cycloreversion of **B** is general and tolerates various electron-withdrawing groups on the nitrogen atom (such as oxazolidinone, azetidinone, sultame, sulfonamide, and indole). We also demonstrated that various types of tethers between the pyrimidine and the ynamide could be successfully used in this *ih*DA/*r*DA sequence, such as ethyloxy, ethylamino, and ethylthio linkers. The corresponding cycloadducts **C** were pyridines fused to oxygen-, sulfur-, and nitrogen-containing five-membered heterocycles.

In the late 1980s, the pioneering work of van der Plas [7] has demonstrated that a fully carbon-substituted tether between an alkyne and a pyrimidine was tolerated in the *ih*DA/*r*DA sequence, leading to 6,7-dihydro-5*H*-cyclopenta[*b*]pyridine in moderate yields. In continuation of our investigations of this *ih*DA/*r*DA sequence between ynamides and pyrimidines, we were keen to study if a carbon tether, such as a propyl unit, was also tolerated in this reaction. This would constitute a novel approach to biologically important 6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-4-amines that are found, for example, in some tacrine–rhein hybrids [8] and some fructose-1,6-bisphosphate inhibitors [9] (Fig. 1). We report therein that such fused pyridines are indeed attainable using the intramolecular *ih*DA/*r*DA sequence between pyrimidines and ynamides, and that sulfolane performs better as a solvent compared to trifluorotoluene.



Scheme 1. A three-step synthesis of pyridines **C** via the first *ih*DA/*r*DA of ynamides and pyrimidines [6].

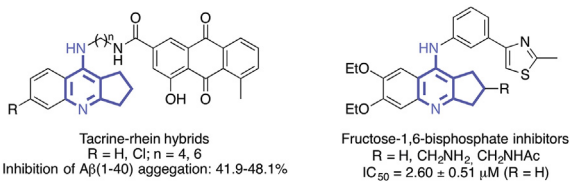
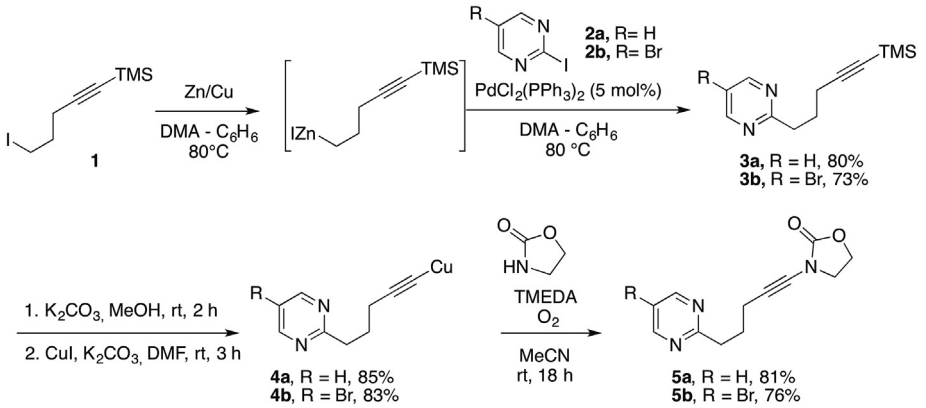


Fig. 1. Selected biologically relevant compounds possessing the 4-aminopyridine motif (in light blue) [8,9].

2. Results and discussion

To investigate the relevance of a carbon-tether between the pyrimidine (4π component) and the ynamide (2π component), we synthesized a small subset of representative cycloaddition precursors **5** that differ only by the nature of the C5-substituent of the pyrimidine (**5a**, C5–H; **5b**, C5–Br; and **5c**, C5–Cl), according to two different strategies (Schemes 2 and 3). In a first approach, the bis-homopropargyl derivative **1** [10] was converted into the corresponding organozinc iodide using the zinc/copper amalgam [11] in a dimethylacetamide (DMA)-benzene (1:15) mixture at 80 °C. 2-Iodo pyrimidines **2a** and **2b** were added, followed by $PdCl_2(PPh_3)_2$ (5 mol %). This Negishi cross-coupling reaction delivered the expected C2-alkylated pyrimidines **3a** and **3b** in 80% and 73% yields, respectively [12]. The latter were then treated with potassium carbonate in methanol, and the intermediate terminal



Scheme 2. Synthesis of *ih*DA/*r*DA precursors **5a** and **5b**.