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$Al(OTf)_3$-catalyzed one-pot synthesis of pyrrolo[3,2-*d*]pyrimidinedione derivatives

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ABSTRACT

A series of polysubstituted pyrrolo[3,2-*d*]pyrimidinedione derivatives have been synthesized in excellent yields. This prominent scaffold is obtained via an $Al(OTf)_3$-catalyzed tandem addition-annulation sequence between propargylic alcohols and aminopyrimidines. The process is simple, facile, inexpensive, and provides a diverse range of substituted pyrrolo [3,2-*d*]pyrimidinedione derivatives with short reaction times from readily obtainable starting materials.

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Introduction

Pyrrole and pyrimidine-containing compounds are important heterocycles in medicinal chemistry and organic synthesis which have stimulated extensive research [1,2]. Pyrrole and pyrimidine derivatives exhibit pharmacological properties such as antibacterial [3], antimicrobial [4], antitumor [4,5], antimalarial [6], anti-inflammatory [7,8], anti-oxidant [9] and immunosuppressant [10] activities. The combination of both pyrimidine and pyrrole units have also been proven to possess a broad range of biological activities [11–13]. As a result the synthesis of pyrrolo-pyrimidine derivatives from readily accessible precursors are of significant importance.

Metal triflates have gained significant interest because of their unique Lewis acidity, low toxicity, low cost, high stability, tolerance to various functional groups, ease of handling, and potential recovery from water [14]. Herein, we report a novel Lewis-acid assisted tandem cyclization reaction of propargylic alcohols with pyrimidines for the preparation of substituted pyrrolo-pyrimidine derivatives.

Results and discussion

Initially, the model reaction between 1,3-dimethyl-5-(methylamino)uracil (**1a**) and 1,3-di-phenylpropargyl alcohol (**2a**) was examined at reflux in the presence of $Al(OTf)_3$. Since acetonitrile has been reported to be the solvent of choice for $Al(OTf)_3$ catalysed reactions [15–17], it was selected for the current investigation. Based on previous results [15–17], substitution of the propargylic OH was envisaged to involve the soft carbon nucleophile of **1a** and the soft electrophilic 1-position of the propargylic alcohol to yield propargylated uracil derivative **3aa** (Scheme 1, Route A). Close inspection of the ^1H NMR spectrum of the isolated product, obtained in 70% yield, however, revealed the signature resonance of the benzylic C*H* unit, expected for **3aa** [δ_H *ca.* 5.5 (s)], to be absent [16,17]. Furthermore, the ^{13}C NMR spectrum indicated 18 resonances (2 carbonyl, 12 aromatic and 4 aliphatic) suggesting that coupling between the uracil (7 carbons) and propargylic alcohol (11 carbons) entities in fact did occur.

Upon consideration of the ambident nature of both the uracil (**1a**) and propargylic alcohol (**2a**) moieties a number of products could be postulated (Scheme 1). Although the uracil could be expected to follow enamine chemistry, which would suggest nucleophilic attack by the carbon nucleophile to give **3aa** (Scheme 1, Route A), the presence of the carbonyl renders this functional group also an unsaturated carbonyl system which may lead to the secondary amine acting as the preferred nucleophile and **5aa** to be the intermediate product (Scheme 1, Route B). Similarly, although substitution of the propargylic alcohol is expected, (Routes A and B), addition to the β-carbon is also possible, therefore **8aa** and/or **10aa** are also plausible intermediate products (Scheme 1, Routes C and D). Following initial substitution (Routes A and B) by the uracil, intramolecular cyclization of compounds

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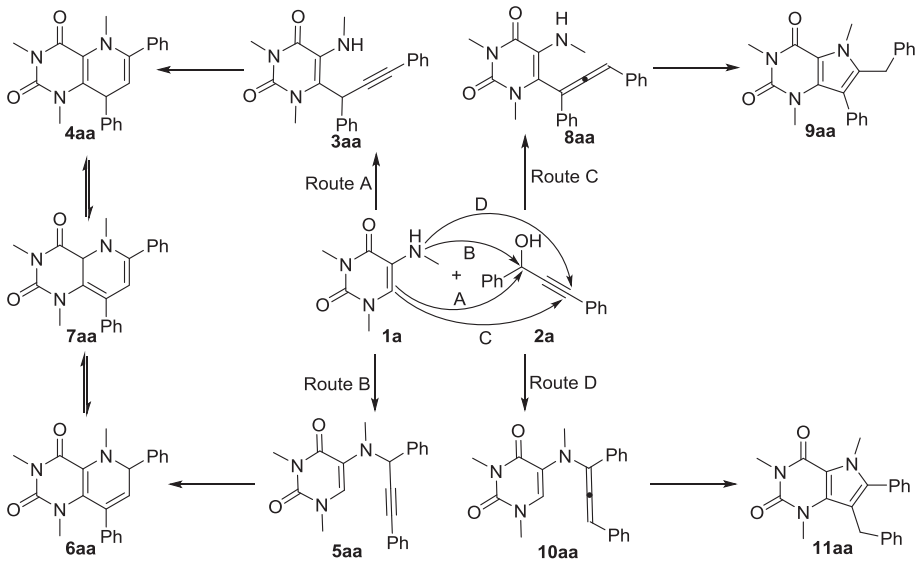


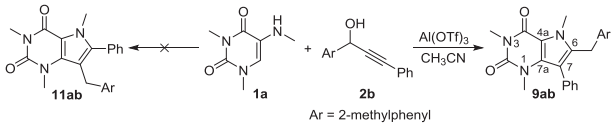
Scheme 1. Plausible products from the reaction between uracil **1a** and propargyl alcohol **2a**.

3aa and **5aa** should lead to **4aa** and **6aa**, respectively, which may both isomerize to **7aa**. These 6-membered products are to be expected as possible pi-bond activation by the $Al(OTf)_3$ would render the benzylic carbons of **3aa** or **5aa** the more stable incipient carbocations and thus the more favorable centers for electrophilic attack. If addition is the preferred process (Routes C and D), the allene intermediates (**8aa** or **10aa**) would be produced in a process similar to the Meyer-Schuster rearrangement [18,19]. The presence of phenyl substituents around the allene system (or *via* Lewis acid activation), may lead to the generation of an electrophilic center at the central allene carbon, which would afford a 5-membered cyclic product (**9aa** or **11aa**) after cyclization.

Since the ^1H NMR spectrum of the isolated product, apart from aromatic and methyl resonances, displayed only a two-proton singlet at δ_H 3.76, it could be concluded that the product from the reaction could either be **9aa** or **11aa**. The equivalence of the two phenyl substituents, however, rendered differentiation between the products impossible by all NMR techniques; therefore it was decided to prepare an analogue of **9aa** or **11aa** with two different aromatic entities in order to be able to use 2D NMR to distinguish between the two possible structures. An *ortho*-methyl group was introduced into the phenyl ring adjacent to the alcohol function and the reaction repeated with propargylic alcohol **2b** and the isolated product (**9ab**) subjected to ^1H and ^{13}C NMR analysis (Scheme 2).

By utilizing proton decoupled DEPT and HSQC experiments the resonances of the CH_2 unit were identified at δ_H 3.73 (s) and δ_C 28.01. In this regard, in accordance with observable HMBC correlations between the carbonyl (δ_C 152.2 and 156.1) and aromatic carbons (δ_C 135.8 and 130.3), the protons of the two amide groups and the toluyl methyl group could be assigned to the resonances at δ_H 3.44, 3.11 and 2.21, respectively; the remaining pyrrole methyl group is therefore located at δ_H 3.80. Due to HMBC correlations with the pyrrole methyl group, C-4a and C-6 could be identified as resonating at δ_C 139.1 and 110.5, respectively, while the resonance at δ_C 132.5 could be assigned to C-7a through a cross peak with the amide methyl group at δ_H 3.11 in the HMBC spectrum. HMBC analysis revealed further correlations between the CH_2 (δ_H 3.73) and four aromatic carbon atoms at δ_C 111.24 (C-7), 126.9 (C-6′), 135.8 (C-2′) and 139.13 (C-6), whereas the CH_2 carbon (δ_C 28.01) exhibited coupling to only one proton at δ_H 6.67 (d). The chemical shift and multiplicity of the doublet at δ_H 6.67 suggested this resonance to represent either proton 3′ or 6′ of the substituted phenyl ring. As HMBC generally reveals coupling 2/3 bonds away this established the resonance at δ_H 6.67 as originating from H-6 on the toluyl ring. This observation proved the 2-methylphenyl unit to be the benzyl moiety of the molecule. In addition to the correlation to δ_H 3.80 (pyrrole methyl), the resonance at δ_C 139.13 also exhibited correlation to δ_H 3.73 (CH_2) suggesting the benzyl moiety to reside in close proximity of the pyrrole methyl unit. These observations thus supported **9ab** to be the isolated product and thus Route C to be the most likely reaction pathway. A single crystal of **9ad** subjected to XRD analysis (Fig. 1) [20] unequivocally proved the structures of the products obtained.

In order to determine if the process is indeed catalysed by aluminium triflate, the reaction was repeated in CH_3CN without the



Scheme 2. Aluminium triflate catalyzed reaction between uracil **1a** and alkynol **2b**.

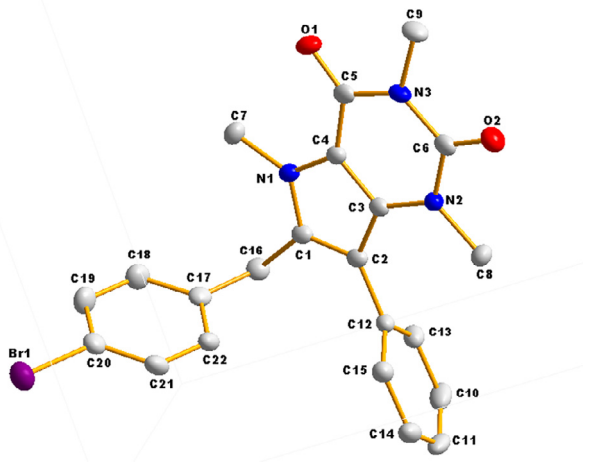


Fig. 1. ORTEP diagram of **9ad**.

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