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Original article

Application of Ullmann and Ullmann–Finkelstein reactions for the synthesis of N-aryl-N-(1*H*-pyrazol-3-yl) acetamide or N-(1-aryl-1*H*-pyrazol-3-yl) acetamide derivatives and pharmacological evaluation

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ABSTRACT

Ullmann-type reactions are becoming a major tool in medicinal chemistry. In this article, we describe the use of these Copper-catalyzed reactions with various precursors, acyl-heteroarylamines or pyrazoles of interest for pharmacomodulation. To the medicinal chemist they offer new, usually untapped disconnection approaches to compounds of interest. They thus open the way to new original analogues of bioactive compounds possibly not patented, from common building-blocks. They also allow C to N bioisosteric replacements, which sometimes are synthetically challenging. We report for the first time the critical effect of acetylamino substituents on the regioselective arylation of unsymmetrical pyrazoles that are useful for medicinal chemists. Finally, we have applied this strategy to the design of novel AT_1 receptor antagonists. Though this family has been extensively investigated in the past 30 years, N-arylation and C to N replacement made possible by Ullmann chemistry, can produce original antagonists.

1. Introduction

Ullmann-type reactions are copper-catalyzed reactions that have paved the way to new synthetic schemes particularly useful for chemists [1]. Among many applications, they allow 1) N-arylation of pyrazoles and other acidic N-heterocycles; 2) N-arylation of anilines and more recently heteroarylamines and 3) N-arylation of amides [2]. Recently microwave conditions for this reaction were published [3]. Chemists in the field of natural product synthesis use thoroughly these Cu-catalyzed reactions [4]. Also, medicinal chemists use these reactions to access new templates for bioactive molecules. For example, it was used to synthesize Chk-1 Inhibitors based on the benzodiazepine scaffold (Fig. 1) [5]. Such reactions are also key steps in the synthesis of inhibitors of blood coagulation factor Xa apixaban, razaxaban [6,7] and derivatives (Fig. 1) [8]. Interestingly, these strategies allow developing new retrosynthetic pathways for known drugs or bioactive compounds allowing new disconnection approaches. For example, a new mild synthetic, side-product free protocol to SB214857, a potent GPIIb/IIIa receptor antagonist, makes use of Cu-mediated reactions (Fig. 1) [9]. Cost-effective copper sources provide alternative route for imatinib synthesis [10]. These reactions could be also investigated for other bioactive series bearing arylated pyrazoles like celecoxib derivatives, fipronil derivatives, rimonabant (Fig. 1)[11].

We wanted to apply these reactions to a well-known therapeutic class like sartans, in our continuing effort to provide valuable chemical paths for bioactive compounds [12]. Interestingly, many Angiotensin-2 Receptor Type 1 (AT1) antagonists display N-substituted heterocycles [13] and in particular pyrazoles. In these series, pyrazole is alkylated either with the canonical biphenylmethyl moiety [14] or with a propyl or butyl [15,16]. Other series display key pharmacophoric elements on the 3 carbons of pyrazoles [17,18] or benzopyrazoles [19] or aminopyrazoles [20,21]. Having previously explored the potential of Ullmann-type

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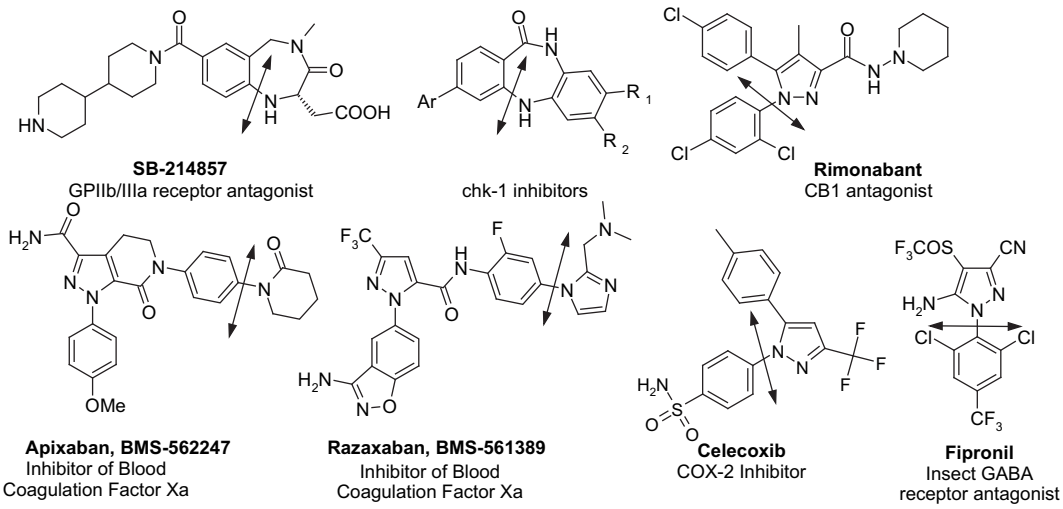


Fig. 1. Bioactive compounds that can be synthesized through Copper-catalyzed reactions.

reactions, it appeared to us that they could be useful for the synthesis of the target compounds in Figs. 2 and 3 [2,22,23] These compounds differ from the previously described pyrazoles by the connection of the pyrazole to the biphenyl ring system. We show that these reactions allow (i) the synthesis of new original analogues of bioactive compounds from common building-blocks, (ii) the validation of a key pharmacophore element and (iii) the C- to N- bioisosteric replacements, which sometimes are synthetically challenging. In all, these results show the utility of such reactions in pharmacomodulation and also as far as arylation of pyrazoles is concerned, show the impact of the –NHAc substituent in the regioselectivity of the reaction.

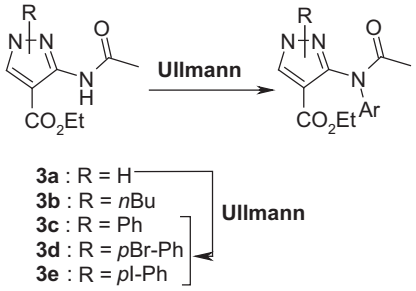


Fig. 2. Aminopyrazole precursors.

2. Results and discussion

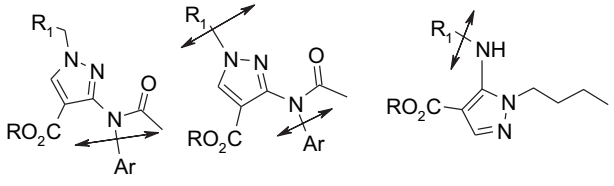
2.1. Chemistry

2.1.1. Synthesis of precursors *3a–e*

The key chemical precursors ethyl 3-acetylamino-*1H*-pyrazole-4-carboxylate **3a** or N-substituted derivatives of the pyrazole by n-butyl or phenyl groups **3b–d** were synthesized by construction of the pyrazole ring from the corresponding hydrazine to give **2a–d** (Scheme 1). Acylation of the exocyclic nitrogen to give **3a–d** prevents alkylation of the exocyclic nitrogen later in the synthesis [24], though this potential side-reaction is not always observed [25].

The synthesis of **3a–b** proceeds in two steps from ethoxymethylenecyanoacetic acid ethyl ester and **1a–b** using previously published conditions (Scheme 1), to give the aminopyrazoles **2a–b** that are further quantitatively acylated into **3a–3b** (**3b** is obtained directly from **1b** without isolating **2b**) [26]

As for **2a–b**, N-arylated pyrazoles **2c–d** can be synthesized from the corresponding hydrazines in variable yield (Scheme 1) [25]. To induce the synthesis of the desired regioisomer, hydrazine is first reacted with benzaldehyde to give the corresponding phenylhydrazone [27]. This hydrazone further reacts with ethoxymethylenecyanoacetic acid ethyl ester to give the desired N-arylated pyrazole [28]. The brominated derivative **3d**, was obtained with a low overall yield of 12% due to side-products at the nucleophilic substitution of ethoxymethylenecyanoacetic acid ethyl ester, and to the absence of precipitation of the intermediate in xylene. Given this low yield, another retrosynthetic pathway



[a] R_1 = 4-(2-(2H-tetrazol-5-yl)phenyl)-phenyl; Possible Copper-catalyzed N-arylations either of heteroaryl amides or pyrazoles are shown by arrows.

Fig. 3. Investigated compounds. [a]R_1 = 4-(2-(2H-tetrazol-5-yl)phenyl)-phenyl; Possible Copper-catalyzed N-arylations either of heteroaryl amides or pyrazoles are shown by arrows.