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A novel substrate controlled chemoselective synthesis of aryl bis (thiazole-2-imine)methanes from 2-aminothiazoles and aldehydes

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ABSTRACT

Aryl bis(thiazole-2-imine)methanes have been synthesized chemoselectively for the first time by an unusual reaction between 5-aryl substituted 2-aminothiazoles and aromatic aldehydes with excellent yield using inexpensive and easy available acetic acid as a catalyst under mild conditions. The present protocol was constructed through N-C bond formation by the condensation and nucleophilic addition reactions.

Introduction

The development of efficient and novel chemical reactions that allows a rapid and direct construction of complex and diversified molecules from available and inexpensive starting materials stands at the forefront of synthetic chemistry and it also has impressive significance in industrial processes.[1] Nitrogen and sulphur containing privileged heterocyclic compounds such as thiazoles play an important role in the modern synthetic and medicinal chemistry due to their C-N and C-S bonds present in the ring structure which are found in many applications of chemistry.[2] Aminothiazoles are useful for drug design processes in medicinal chemistry due to their thiourea-like properties and tendency to modulate biological targets.[3] Also they have supramolecular properties and can act as hosts.[4] There are several possibilities to cause slight structural modifications in aminothiazoles. Structural changes can be made as a result of amine-imine tautomerism, salt formation and binding to metal ions.[5] Particularly, thiazole-2-imine derivatives have shown considerable biological attention as demonstrated by a broad pharmacological activities such as anti inflammatory, analgesic, kinase inhibition activities[6] anti fungal,[7] anti bacterial,[8] melanin reducing activity,[9] anti viral,[10] anti convulsant[11] and anti parasitic.[12]

Pifithrin (Fig. 1), for example, with 2-iminothiazoline scaffold acts as a potential therapeutic agent for the treatment of neurodegenerative disorders such as Alzheimer's disease, Parkinsons disease, stroke, cancer therapy, and other pathologies related to various signalling pathways.[13–15]

Because of their wide biological applications, the development of novel synthetic approaches for the preparation of thiazole-2-imine derivatives has gained significant attention and as a result, a few synthetic routes for this valuable scaffold have been reported in the literature.[16–19] Amongst them, a few important methodologies which have been recently developed are illustrated in Fig. 2.

D. H. De the and co-workers have reported a synthesis of thiazolidine-2-imines by multicomponent reaction of imine, terminal alkyne and isothiocyanate in the presence of chiral copper-pybox complex as a catalyst (Fig. 2a).[17] Chung-Ming Sun et al. have developed a one-pot synthesis of 2-imino-1,3-thiazolidines and 2-imino-1,3-thiazolines on the soluble support using ionic liquid tethered 2-aminobenzimidazoles, isothiocyanates and 1,2-dichloroethane (Fig. 2b).[18] Very recently, Yiqun Li et al. have developed a synthetic route for thiazole-2-imine involving phenacyl bromide, amine and phenyl isothiocynate with trypsin as a biocatalyst (Fig. 2c).[19] However, all these methods suffer from a few drawbacks such as the handling of toxic isocyanides and bromine sources, harsh reaction conditions, longer reaction times and tedious separation procedures. Whereas the switchable formation of benzylidenediamines or azomethines by condensation of 2-aminothiazoles (or 2-aminothiadiazoles) with aromatic aldehydes is already known and the chemoselectivity of the reaction has also been evaluated,[20] the present transformation leading to the forma-

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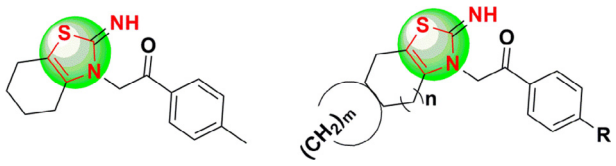

Fig. 1. Biological active pifithrin.

tion of bis(thiazole-2-imine)methanes has not at all been exploited.

Bis(heterocycle)methanes have a numerous applications in organic synthesis, optics, agrochemistry and medicinal chemistry.[21] In 2016, G. E. Kostakis group discovered a synthesis of bis(indolyl)methanes *via* C—C bond formation by nucleophilic addition of aldehydes or ketones to indoles using tetranuclear 3d/4f coordination clusters, (Fig. 2d)[22] but the reaction was limited to the transition metal cluster. In past years, there are no reports in the literature for the synthesis of bis-heterocycles based on thiazole-2-imine derivatives. Keeping this fact in mind that the current protocol deals with the chemoselective synthesis of bis(thiazole-2-imine)methane starting from aryl substituted 2-aminothiazoles and aldehydes precursors (Scheme 1). Notably this newly developed protocol was constructed through N-C bond formation by the condensation and nucleophilic addition reactions. More surprisingly, here the condensation reaction takes place on N-3 position of 2-aminothiazole with aldehyde and not in the second position of primary amine of 2-aminothiazole because of the tautomerism. In addition, the present type of scaffolds play a more significant role in many fields such as metal complexation, sensors and pharmaceutical preparations,[23] which is depicted in Fig. 3.

Results and discussion

Generally, 2-aminothiazole can exist as the amino and the imino tautomers.[24] Therefore we tried to study the substrate scope by reacting 5-(4-methoxyphenyl)thiazol-2-amine (1a) and 3,4,5-trimethoxybenzaldehyde (2a) under 70 °C reflux for 12 h without any catalyst. Pleasingly, we obtained the desired bis(thiazole-2-imine)methane (3a) as the sole product in low yield (34%). Worth mentioning here is that the corresponding imine (schiff base) (4a) was never detected (Scheme 1). The structure of aryl substituted bis(thiazole-2-imine)methane (3a) was well characterized using spectroscopy techniques (IR, NMR, HRMS and CHN-Analysis). Since this reaction represents a novel chemoselective synthesis of bis(thiazole-2-imine)methane, we carried out an extensive optimization of the reaction conditions (Table 1) for the furtherance of discovery of new set of compounds.

At this stage under these conditions, we presumed that, 5-aryl substituted 2-aminothiazole (1a) might be in one of its tautomeric forms which could condense with aldehyde to provide an intermediate. Again the other tautomeric form of 2-aminothiazole by attacking the intermediate might give a new aryl substituted bis(thiazole-2-imine)methane (vide Scheme 3). As shown in Table 1, when the reaction was carried out in the presence of acetic acid (1 mol%), the yield of 3a improved up to 53% (Table 1, entry 2)

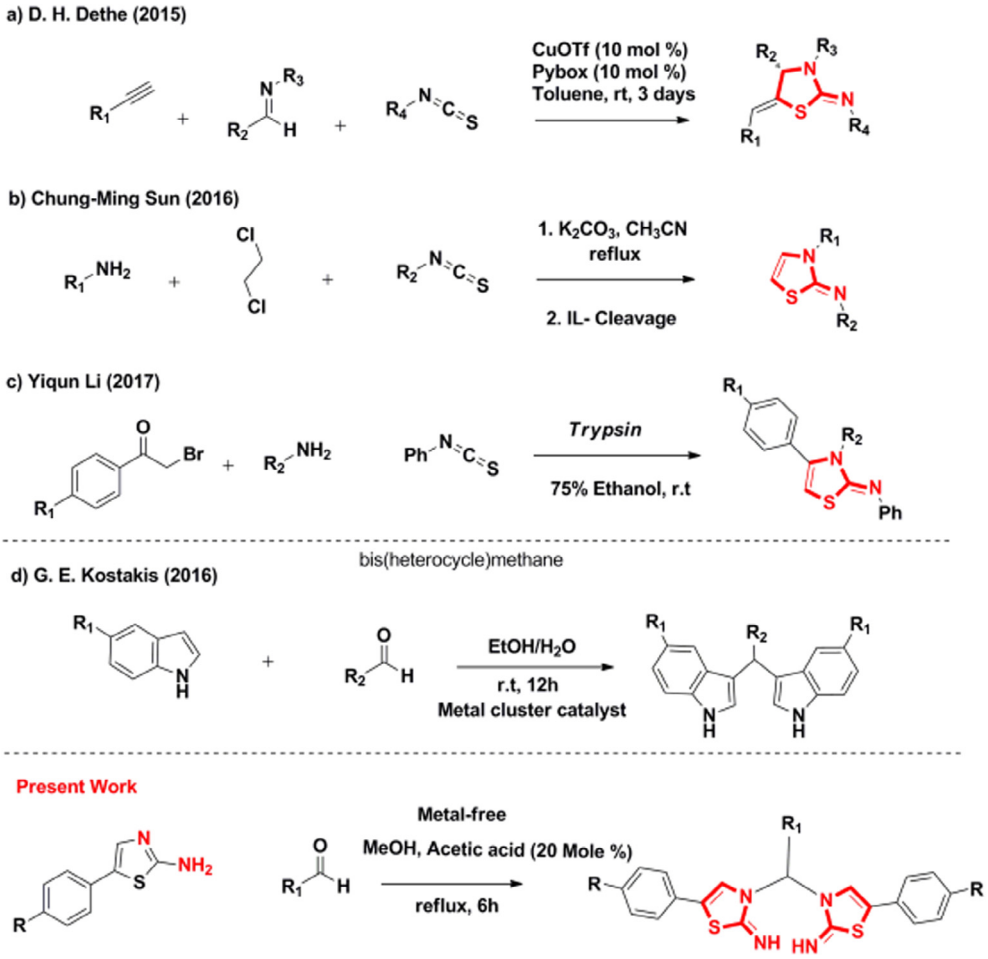

Fig. 2. Current state of the related works and proposed bis(thiazole-2-imine)methane scaffold.