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2-Bromo-1-(1*H*-pyrazol-4-yl)ethanone: versatile precursors for novel mono-, bis- and poly{6-(1*H*-pyrazol-4-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines}

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ABSTRACT

A simple synthesis of novel mono-, bis- and poly{6-(1*H*-pyrazol-4-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines} is reported. The formation of the target compounds was achieved by the reaction of 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone with the appropriate aminotriazolethiol or by the reaction of 6-pyrazolyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-3-thiol with the appropriate di- and poly(bromo) compounds. The structures of the newly synthesized compounds were established by spectroscopy and elemental analyses.

1. Introduction

Pyrazole derivatives are an important class of heterocyclic compound for being key substructures in a variety of compounds with important biological properties.[1] They are known to possess a wide spectrum of activities such as antimicrobial,[2,3] antiinflammatory,[4,5] antiparasitic,[6] antidepressant,[7] antiviral,[8] antifungal,[9] and antitumour activities.[10,11] Moreover, the pyrazole nucleus represent the core unit in a variety of drugs such as celecobix (Celebrex),[12] sildenafil (Viagra),[13] and rimonabant (Acomplia).[14]

Moreover, much attention has been paid over the past decade for the synthesis of 1,2,4-triazoles and their heterocyclic fused analogues, triazolothiadiazines, for their therapeutically importance. They are reported to possess a wide spread of medical applications such as antibacterial, antifungal, anticancer, antitumour, anticonvulsant, anti-inflammatory, antimicrobial activity and analgesic properties.[15–19]

In addition, compounds including bis-heterocyclic moieties were encountered in many bioactive natural products.[20] Recent reports showed that among libraries of derivatized heterocycles, the most active library compounds have a bis-heterocyclic structure.[21–24] Bis-heterocycles in which two bioactive heterocycles are tethered *via* a flexible linker were reported to be anticancer[25–28] and as antimicrobial agents.[29] Along with these activities, some bis-heterocyclic derivatives also exhibited potent antialzheimer and antiprion activity.[30]

In addition, bis-heterocyclic compounds separated by a carbon chain or other functional group have also been recently reported as corrosion inhibitors.[31]

Furthermore, over recent years there have been an increasing number of reports of so-called 'multi-armed' molecules.[32] For example, benzene cores appended by six flexible arms, each terminated by an anionic group, have recently been shown to form micelles in aqueous solution.[32a,b] Multi-armed molecules, in which a combination of an aromatic core and aromatic side chains find uses as discotic liquid crystals.[32q] Some multi-armed derivatives with arms containing donor atoms have been utilized as metal ion ligands.[33] Multi-armed compounds have also been used as building units for dendrimers.[34] Some conjugated multi-armed compounds exhibit interesting properties in materials science.[35,36]

Motivated by these findings, we report herein on the synthesis of some novel mono-, bis- and poly heterocyclic compounds incorporating a combination of pyrazole and [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine pharmacophores for the first time. The combination of two pharmacophores into a single molecular skeleton is a well-established approach for designing more potent drugs with significant increase in activity.

The strategy used for the synthesis of the target {6-(1*H*-pyrazol-4-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine} depends mainly on the initial formation of 2-bromo-1-(5-methyl-1-phenyl-1*H*-

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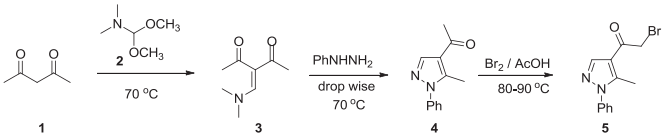
pyrazol-4-yl)ethanone (**5**) as a key intermediate and subsequent reaction with the appropriate aminotriazolethiol. The amino and mercapto groups in these compounds serve thereby as readily accessible nucleophilic centres for the preparation of *N*-bridged heterocycles.

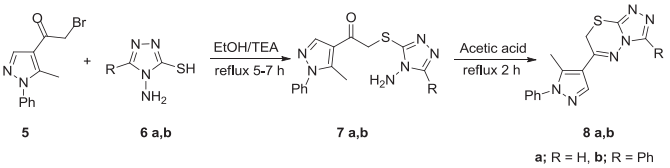
2. Results and discussion

The desired 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl) ethanone (**5**) was synthesized by the reaction of phenylhydrazine with ((dimethylamino)methylene)pentane-2,4-dione (**3**), obtained upon treatment of acetylacetone with dimethylformamide dimethylacetal (DMFDMA), to give 1-phenyl-5-methyl-4-acetypyrazole (**4**)[37] followed by bromination upon treatment with Br_2 in AcOH to give **5**[38] (Scheme 1).



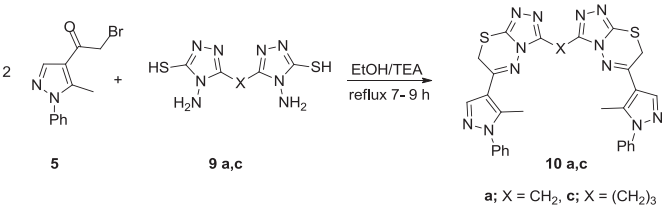
Scheme 1. Synthesis of 2-bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone.

Thus, reaction of **5** with 4-amino-3-mercapto-1,2,4-triazole derivatives **6a**,**b**[39] in refluxing ethanol in the presence of a few drops of triethylamine as catalyst, afforded the novel pyrazolyl(5,6-dihydro-*s*-triazolo[3,4-*b*]thiadiazines) **8a** and **8b** in 70 and 75% yields, respectively, *via* initial formation of 2-(4-amino-5-methyl-4*H*-1,2,4-triazol-3-ylthio)-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl) ethanone, followed by cyclocondensation in refluxing acetic acid (Scheme 2).



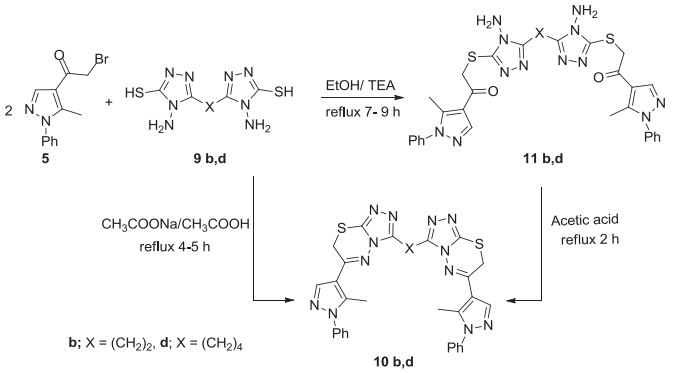
Scheme 2. Synthesis of pyrazolyl(5,6-dihydro-*s*-triazolo[3,4-*b*]thiadiazines).

In continuation of this work, we also describe simple and efficient routes for the synthesis of novel bis(6-pyrazolyl-*s*-triazolo [3,4-*b*][1,3,4]thiadiazines) **10a**–**d** in which the pyrazolyl-triazolothiadiazine is linked to the alkyl spacer through the triazole ring (Schemes 3 and 4).



Scheme 3. Synthesis of bis(6-pyrazolyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines) linked to methylene or propylene spacer.

The synthetic approach used for the synthesis of the target bis-compounds **10a**,**c** includes the initial formation of the appropriate bis(4-amino-5-mercapto-1,2,4-triazol-3-yl)alkanes **9a**,**c** as precursors, which upon treatment with two equivalents of **5** in refluxing EtOH, containing few drops of triethylamine, afforded the corresponding bis(6-pyrazolyl triazolothiadiazines) **10a** and **10c** in 73 and 70% yields, respectively.

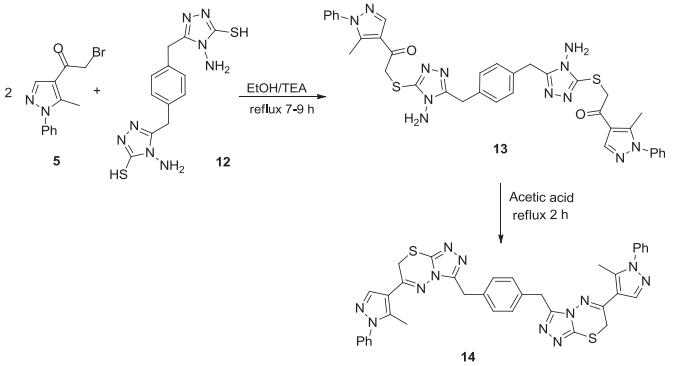


Scheme 4. Synthesis of bis(6-pyrazolyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines) linked to ethyl or butyl spacer.

The bis(triazoles) **9a**–**d** can be obtained by a one-step reaction between aliphatic dicarboxylic acids and two molar equivalents of thiocarbohydrazide at the melting temperature for 30 min according to the method described by Xu *et al.*[40]

The reaction pathway is assumed to involve S-alkylation to give the corresponding bis(aminotriazole) intermediates, followed by intramolecular cyclocondensation to give **10**. The proposed mechanism was confirmed by the possible isolation of the corresponding bis(triazolyl)bis(sulfanediyl)bis(1*H*-pyrazol-4-yl)ethanone **11b** and **11d** upon treatment of **9b**,**d** with two equivalents of **5** in refluxing EtOH containing a few drops of triethylamine. The latter compounds underwent cyclocondensation in refluxing acetic acid to give **10b** and **10d**, respectively (Scheme 4). Compounds **10b**,**d** can also be alternatively obtained in 79, 80% yield in a one step reaction of **9b**,**d** with **5** in refluxing acetic acid containing sodium acetate.

The same methodology was extended to the preparation of bis(*s*-triazolo[3,4-*b*][1,3,4]thiadiazines) **14** in which the pyrazolyl-triazolothiadiazine is linked to a benzene core *via* an alkyl linkage as depicted in Scheme 4. Thus, treatment of 5,5′-(1,4-phenylenebis(methylene))bis(4-amino-4*H*-1,2,4-triazole-3-thiol) **12** with two equivalents of **5** in refluxing EtOH containing a few drops of triethylamine afforded the corresponding bis(amino-triazoles) **13**. The latter compound underwent cyclocondensation in refluxing acetic acid to give **14** (Scheme 5). Compound **12** was obtained by the reaction of one mole of 2,2′-(1,4-phenylene)diacetic acid with two moles of thiocarbohydrazide under fusion conditions.[41]



Scheme 5. Synthesis of bis(6-pyrazolyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazines) linked to xylyl spacer.

We also studied the synthesis of novel twofold branched pyrazolyltriazolothiadiazines **18a**–**c** which are linked to an alkyl spacer *via* a thioether group as outlined in Scheme 6.

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