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An efficient one-pot multicomponent approach to 5-amino-7-aryl-8-nitrothiazolo[3,2-*a*]pyridines

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ABSTRACT

A series of thiazolo[3,2-*a*]pyridines have been prepared using a multicomponent reaction between aromatic aldehydes, 2-nitromethylenethiazolidine and nitriles containing an active methylene group (malononitrile, ethyl 2-cyanoacetate and 2-phenylsulfonylacetonitrile) in the presence of Et_3N under mild conditions with high yields. One of the compounds shows promising anticancer activity across a range of cancer cell lines.

1. Introduction

Multicomponent reactions (MCRs) have found increasing application for the synthesis of libraries of complex pharmacologically important structures with multiple points of diversity in a small number of steps.[1] Among these structures, thiazolopyridine compounds have been studied[2] due to their importance in a number of biologically relevant areas, including cytotoxicity,[3] antimicrobial activity,[4] α-glucosidase inhibition[5] and hypolipemic activity.[6]

Heterocyclic enamines, including 2-methylenethiazolines, have a great deal of synthetic utility, particularly as bis-nucleophiles for the construction of more complex heterocyclic arrays.[7] However, while such compounds containing electron-withdrawing groups such as esters are common, the reactions of 2-nitromethylenethiazolidine have rarely been investigated.[8–10]

We now report that the reaction of 2-nitromethylenethiazolidine[11] with a range of aldehydes and active methylene compounds provides access to a library of thiazolo[3,2-*a*]pyridines. The reactions of malononitrile, as a representative active methylene compound, were investigated first. The reaction of 2-nitromethylenethiazoline with malononitrile and a broad range of aldehydes was carried out in dry acetonitrile with triethylamine at room temperature. Typically 0.5 equiv of triethylamine was used, although smaller quantities can be used with little reduction in yield. After 3 h, reactions were complete (TLC analysis) in all cases, with excellent yields being obtained with aldehydes possessing electron-withdrawing and electron-donating substituents, as well as those with *ortho* substituents (Table 1).

The identity of these compounds is fully supported by the spectroscopic data obtained. Compound **4g**, with two *ortho* substituents, showed hindered rotation of the aryl ring, with all 14 carbon atoms giving distinct resonances in the ^{13}C NMR spectrum, as well as distinct ^{1}H peaks for the 3 hydrogen atoms on the aromatic ring. As an additional complication, these compounds are only fully soluble in DMSO. Running the ^{1}H NMR spectra in DMSO-d_6 gave good results, although the peak due to adventitious water in the DMSO invariably obscured the CH_2S resonance. In the ^{13}C NMR spectrum, the methine resonance (C-7) in some instances overlapped with the deuterated solvent peak, although careful examination of the DEPT spectra allowed unambiguous assignment. The same products were formed, albeit in much lower yield and purity, with aliphatic aldehydes.

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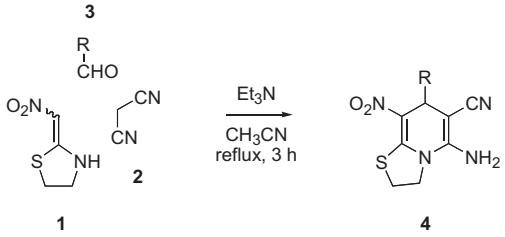
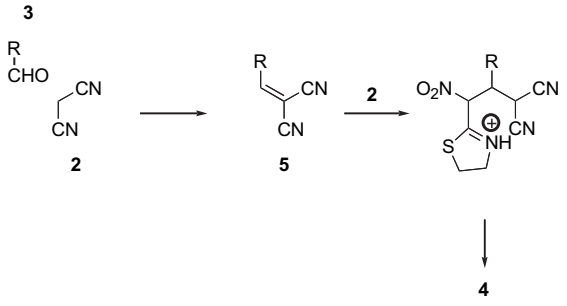
Table 1
Reactions of 2-nitromethylenethiazoline with malononitrile and aldehydes



Compound	R	Yield/%
4a	C_6H_5	95
4b	4-FC_6H_4	90
4c	4-ClC_6H_4	94
4d	4-BrC_6H_4	79
4e	2-FC_6H_4	93
4f	2,4-$Cl_2C_6H_3$	99
4g	2,6-$Cl_2C_6H_3$	97
4h	2-BrC_6H_4	97
4i	2-HO−5-BrC_6H_3	82
4j	4-$O_2NC_6H_4$	99
4k	4-$Me_2NC_6H_4$	90

This reaction presumably proceeds by an initial Knoevenagel condensation of the aldehyde and active methylene compound followed by conjugate addition of the enamine and cyclisation (Scheme 1).



Scheme 1. Likely sequence of steps for the formation of compounds **4**.

The reaction also works with ethyl 2-cyanoacetate, with three representative examples being shown in Table 2. In this case, the intermediate could cyclise onto either the nitrile or the ester; only the products (**7**) of cyclisation onto the nitrile were observed. Although these reactions were carried out for a shorter time compared to the experiments in Table 1, the reactions with malononitrile were not closely monitored, and it is likely that they were also complete within 1 h. The reactions can also be carried out under solvent-free conditions by simply grinding the reagents together for 10 min in a mortar, making this a particularly attractive protocol.

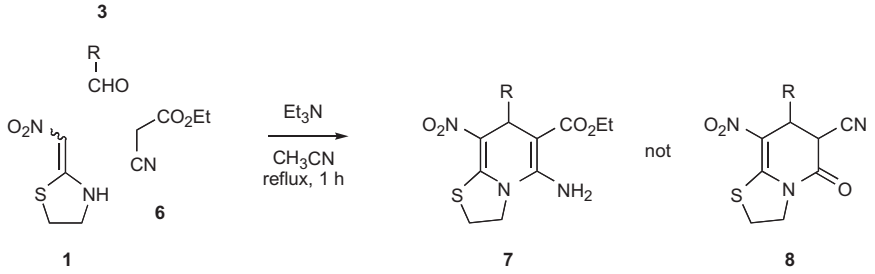
Reactions with 2-phenylsulfonylacetonitrile also gave a similar outcome, although in this case the spectra were complicated by the presence of enamine and imine tautomers **10** and **11**. As shown in Table 3, the relative proportions of the tautomers are close to 1:1 with the exception of **10e**/**11e**. The ratios observed vary only slightly when the spectra are re-run on a different sample from the same batch of compound, so we are confident that compound **10e**/**11e** is a genuine anomaly.

It is tempting to attribute the dramatically different ratio of compounds **10e**/**11e** to steric hindrance, although one might have then expected that the imine tautomer would permit the phenylsulfonyl group to position itself further from the 2,6-dichlorophenyl ring. It would appear that the imine tautomer is present in each case as a single diastereoisomer. In order to understand this process, calculations were carried out on compounds **10a**, **11a**, **10e** and **11e**. The minimum energy conformations of these four compounds were located using Spartan 10[12] at the AM1 semi-empirical level. These conformations were then minimised at the Hartree−Fock level using the 3-21G basis set. The first observation is that the H−C−C−H dihedral angle defining the imine stereochemistry is 74.3° and 85.6° in compounds **11a** and **11e**, respectively. This is suggestive of trans stereochemistry based on the apparent lack of coupling between these hydrogen atoms.

In both cases the enamine tautomer **10** is calculated to be more stable. In the case of **10a**/**11a** the difference is 22.5 kJ mol^{-1}, while in the case of **10e**/**11e** the difference is 30.6 kJ mol^{-1}. Therefore, while the calculations are unable to reproduce the similar levels of stability for the tautomers **10a** and **11a**, they do show that the preference for the enamine tautomer in **10e**/**11e** should be more pronounced compared to **10a**/**11a**, as observed. It is clear from the structures (Fig. 1) that the 2,6-dichlorophenyl ring in compounds **10e** and **11e** must be perpendicular to the dihydropyridine ring as a result of the bulk of the chlorine atoms. This results in destabilisation of the imine tautomer, since the methine hydrogen at position 7 is pushed closer to the sulfone (H7···O=2.360 Å in compound **11a**; 2.254 Å in compound **11e**).

As with the previous case, compound **10e** showed hindered rotation of the 2,6-dichlorophenyl ring, with the ^{13}C resonances for the methine carbon atoms in this ring being broadened and the quaternary carbons not readily distinguished.

Table 2
Reactions of 2-nitromethylenethiazoline with ethyl 2-cyanoacetate and aldehydes



Compound	R	Yield/%[a]
7a	4-ClC_6H_4	78 (88)
7b	4-BrC_6H_4	73
7c	4-$NO_2C_6H_4$	70 (79)

[a] Yields in parentheses refer to reactions carried out under solvent-free conditions grinding with a pestle in a mortar.