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HETERO CYCLE IN FOCUS

Synthesis of 4*H*-thiazine

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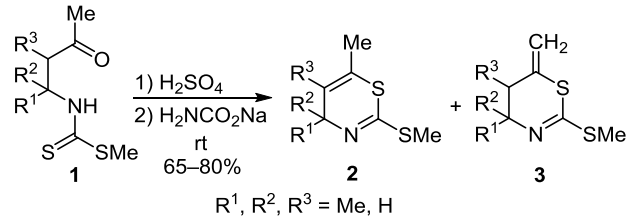
Introduction

Thiazines represent an important class of heterocyclic compounds due to their valuable biological properties. For example, some derivatives of thiazine are cannabinoid receptor agonists,[1] also they can act as an antihypotensive,[2] antitubercular,[3] and antibacterial[4] agents. Moreover, thiazine derivatives can be used for gastrointestinal disorders[5] or diabetes[6] prevention. Condensed heterocyclic systems possessing thiazine ring have been reported as antioxidants,[7] analgesic, anti-inflammatory agents,[8] or calcium channel modulators.[9] Also it should be noted that thiazines are useful intermediates in synthetic organic chemistry.

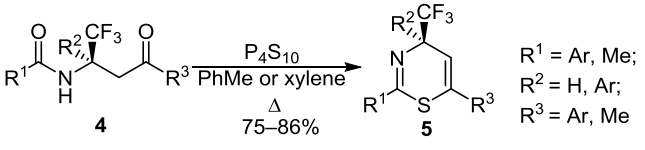
The synthetic ways for the preparation of 4*H*-thiazine ring can be classified into several groups: intramolecular cyclizations; reactions between thioureas or thioamides and Michael acceptors; reactions between thioureas and malonic acid derivatives; reactions between 3-mercaptoacrylamides and carbonyl compounds or Michael acceptors, and hetero-Diels–Alder reactions. There are also some reports about biosynthetic pathways to thiazine rings.

Intramolecular cyclization

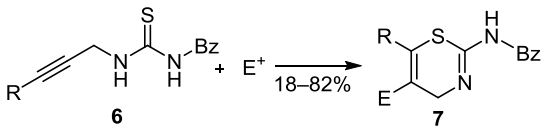
Concentrated H_2SO_4 and sodium carbamate could be used to convert *N*-(3-oxoalkyl)dithiocarbamates **1** into 2-(methylsulfanyl)-4*H*-1,3-thiazine **2** and its double bond isomer **3** in 65–80% yields. The position of the double bond depends on substituent R^3.[10]



Very recently, an efficient way to obtain 4-(trifluoromethyl)-4*H*-1,3-thiazines **5** was demonstrated. It was shown that enantiomerically enriched trifluoromethylamides **4** react with phosphorus pentasulfide *via* thionation of carbonyl groups followed by intramolecular cyclization and loss of hydrogen sulfide to give chiral 4-(trifluoromethyl)-4*H*-1,3-thiazines **5**. The absolute configuration of the desired products was retained and almost no racemization was observed.[11]



In 2015, we have demonstrated a new method of the formation of functionalized thiazines **7** *via* electrophile-promoted 6-*endo*-dig cyclization of *N*-(3-arylprop-2-ynyl-carbamothioyl)benzamides **6**.[12]

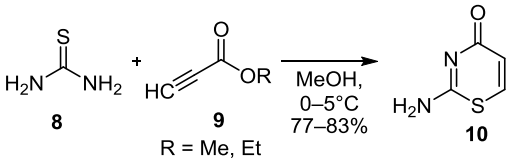


Aurelija Urbanaitė was born in Panevėžys, Lithuania in 1989. She graduated from Vilnius University, obtaining her Master of Science degree in 2014. Currently she is a Ph.D. student in group of Prof. I. Čikotienė. Her research interests include heterocyclic chemistry, new synthetic methods of organic molecules, as well as reactivity of functionally substituted alkynes.

Inga Čikotienė was born in Vilnius, Lithuania in 1979. She graduated with honors from Vilnius University in 2003 and obtained her Ph.D. in chemistry at Vilnius University in 2006. At present, she is professor and research group leader at Vilnius University. Her scientific interests include organic synthesis, investigations of reaction mechanisms and medicinal chemistry.

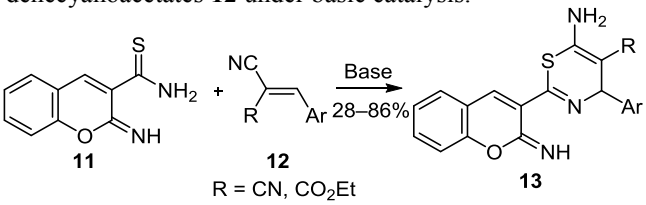
Reactions between thiourea or thioamides and Michael acceptors

Recently a selective synthesis of 1,3-thiazinone **10** in good yields was illustrated by Peddinti et al. by means of reaction of thiourea (**8**) with acetylene monocarboxylates **9** in methanol.[13]



8 **9** **10**

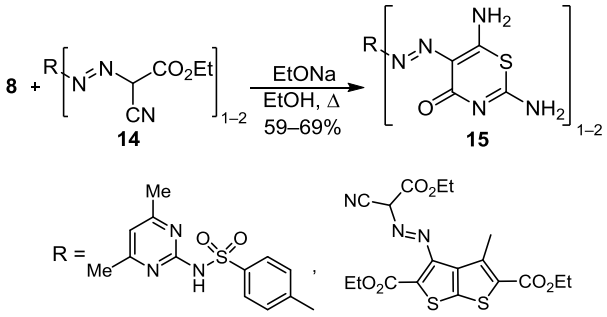
Thiazines **13** were prepared in moderate or good yields by El-Sayed's research group from 2-imino-2*H*-chromene-3-carbothioamide (**11**) and arylidenemalononitriles or arylidenecyanoacetates **12** under basic catalysis.[14]



11 **12** **13**

Reaction between thiourea and malonic acids

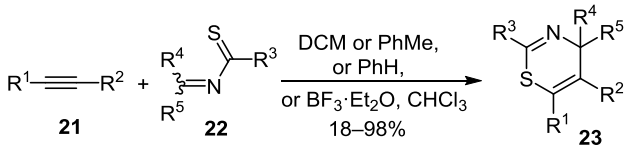
Treatment of thiourea (**8**) with ethyl 2-cyano-2-diazenylacetate **14** in boiling ethanol in the presence of sodium ethoxide yielded the thiazines **15** which were formed after thiol group addition to the cyano group and subsequent cyclization.[15]



14 **15**

Hetero-Diels–Alder reaction

Hetero-Diels–Alder reaction was applied to obtain thiazines **23** from alkynes **21** and heterodienes **22**,[20] whereas Krayushkin et al. synthesized thiazines **23** applying boron trifluoride etherate.[21]

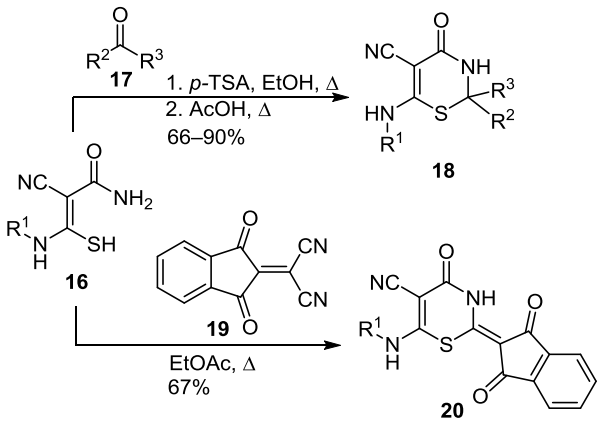


21 **22** **23**

R^1 = CO_2Me, CO_2Et, thienyl;
R^2 = CO_2Me, thienyl, H;
R^3 = aryl, OEt, 3'-thymidinyl;
R^4 = H, Me, CO_2Et, thienyl, furyl;
R^5 = NMe_2, *t*-Bu, Me, thienyl, furyl

Cyclization with 3-mercaptoacrylamide

A convenient method to synthesize 2,3-dihydro-1,3-thiazin-4(1*H*)-ones **18** was demonstrated by Pinchuk et al. Thiazinone derivatives were synthesized by cyclocondensation of 3-alkyl(aryl)amino-2-cyano-3-mercaptoacrylamides **16** with aldehydes or ketones **17** in boiling ethanol using *p*-TSA or in glacial acetic acid.[16] Similar protocol to synthesize bis(1,3-thiazin-4-ones)[17] and spiro-1,3-thiazines[18] was applied by Hamoda and coworkers. Moreover mercaptoacrylamides **16** react with 2-(dicyanomethylidene)-indane-1,3-dione (**19**) forming thiazine **20**.[19]

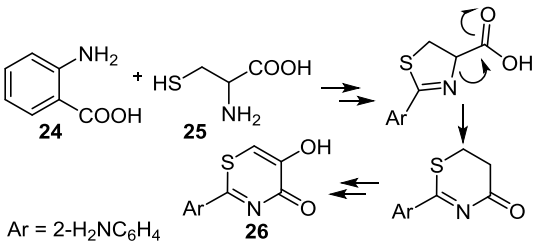


17 **18** **16** **19** **20**

R^1 = Me, Et, Bn, Ph; R^2 = Me, H; R^3= Me, *i*-Pr, Ph, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, (*R*)-2,3-dihydro-1,4-benzodioxin-6-yl, 6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl; R^2+R^3 = cycloalkylidene

Biosynthesis

The first example of a natural compound containing 5-hydroxy-4*H*-1,3-thiazin-4-one **26** core is thiasporine A showing cytotoxicity against the lung cancer cells. Thiasporine A is formed *via* biosynthetic pathway from anthranilic acid (**24**) and cysteine (**25**).[22]



24 **25** **26**

Ar = 2-$H_2NC_6H_4$

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