Synthesis of 4H-thiazine

Aurelija Urbanaitė1*, Inga Čikotienė1

1 Faculty of Chemistry, Vilnius University, 24 Naugarduko St., Vilnius LT-03225, Lithuania; e-mail: aurelija.urbanaitė@chf.stud.vu.lt

Published in Khimiya Geterotsiklicheskikh Soedinenii, 2016, 52(1), 000–000

Submitted 28.10.2015
Accepted 17.11.2015

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 antibacterial4 agents. Moreover, thiazine derivatives can be used for gastrointestinal disorders5 or diabetes6 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 4H-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 H2SO4 and sodium carbamate could be used to convert N-(3-oxoalkyl)dithiocarbamates 1 into 2-(methylsulfanyl)-4H-1,3-thiazine 2 and its double bond isomer 3 in 65–80% yields. The position of the double bond depends on substituent R3.10 Very recently, an efficient way to obtain 4-(trifluoromethyl)-4H-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)-4H-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-ynylcarbamothioyl)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 alkenes.

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.\(^\text{13}\)

Thiazines 13 were prepared in moderate or good yields by El-Sayed’s research group from 2-imino-2H-chromene-3-carboxthioamide (11) and arylidenemalononitriles or arylideneacetoacetates 12 under basic catalysis.\(^\text{14}\)

**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.\(^\text{15}\)

**Cyclization with 3-mercaptoacrylamide**

A convenient method to synthesize 2,3-dihydro-1,3-thiazin-4(1H)-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.\(^\text{16}\) Similar protocol to synthesize bis(1,3-thiazin-4-ones)\(^\text{17}\) and spiro-1,3-thiazines\(^\text{18}\) was applied by Hamoda and coworkers. Moreover mercaptoacrylamides 16 react with 2-(dicyanomethylidene)-indane-1,3-dione (19) forming thiazine 20.\(^\text{19}\)

**Hetero-Diels–Alder reaction**

Hetero-Diels–Alder reaction was applied to obtain thiazines 23 from alkynes 21 and heterodienes 22,\(^\text{20}\) whereas Krayushkin et al. synthesized thiazines 23 applying boron trifluoride etherate.\(^\text{21}\)

**Biosynthesis**

The first example of a natural compound containing 5-hydroxy-4H-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).\(^\text{22}\)

**References**