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SYNTHESIS OF SOME NOVEL THIAZOLINES AND THIAZOLIDINONES DERIVATIVES

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ABSTRACT
A series of thiazolines**5a$_i$** and thiazolidinones**5b$_i$** have been synthesized from the phenylacetonitrile**1** as the starting material. All compounds were characterized on the basis of IR, NMR spectroscopy (^{1}H and ^{13}C) and by elemental analysis.

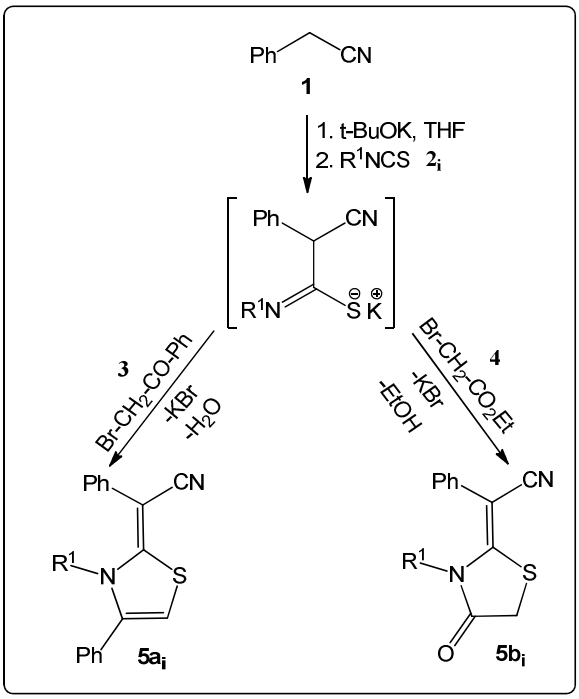
KEYWORDS
phenylacetonitrile; isothiocyanate; thiazoline;thiazolidinone.

INTRODUCTION

Heterocyclic compounds have attracted attention in recent time due to their increasing importance in the field of pharmaceuticals and industries[i,ii]. According to literature survey, thiazoles were reported to possess antimicrobial [iii], [iv], analgesic [v], anti-inflammatory[vi],anticonvulsant[vii], cardiotonic[viii], anticancer[ix], antitubercular[x]and anthelmintic[xi] activities. Antimicrobial activities of some substituted thiazoles are well established because it posses (S-C=N) toxophoric unit. Thiazoles have enhanced lipid solubility with hydrophilicity. Thiazoles are easily metabolized by routine bio-chemical reactions and are non-carcinogenic in nature[xii].In the present work, we develop a synthesis of novel series of thiazolines**5a$_i$** and thiazolidinones**5b$_i$** from benzylcyanid as a starting material.

RESULTS AND DISCUSSION

The condensation of arylacetonitriles**1** with isothiocyanates**2$_i$** performed in anhydrous THF, in the presence of potassium *tert*-butoxide, leads to a potassium thiolate intermediate [**A**]. This last one reacts *in situ* with brominated derivatives such the 2-bromoacetophenone **3** and the ethylebromoacetate**4**to give respectively the thiazolines**5a$_i$** and thethiazolidinones**5b$_i$** with high yields. (**Scheme 1, Table 1**)



Scheme 1: Synthetic pathway for the preparation of $5a_i$ and $5b_i$

Table 1: Yields of compounds synthesized **5a$_i$** and**5b$_i$**

Entry 5	R^1	Yield %
5a$_1$	*p*-Cl-Ph	69
5a$_2$	Ph	65
5a$_3$	*c*-C_6H_{11}	75
5b$_1$	Ph	78
5b$_2$	*c*-C_6H_{11}	66

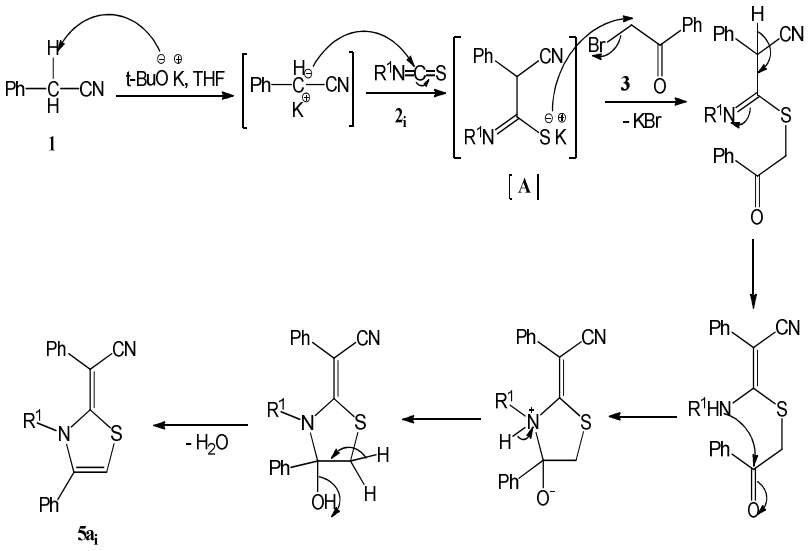
The structure of new compounds were established by spectroscopic methods (IR, NMR^{1}H and ^{13}C). The NMR spectra of the compounds were conformed with their structures. Furthermore, the IR spectra of compounds **5a$_i$**or **5b$_i$**displayed absorption at 2189 cm^{-1} corresponding to CN stretching vibrations and an amide function at 1742 cm^{-1}, while ^{1}H-NMR spectrum of **5a$_i$** revealed the absence of the methylene group of the brominated compound **3** and the appearance of a new signal corresponding to the C=C<u>H</u> protons of the thiazole ring at δ = 6.45 ppm. The formation of **5b$_i$** was confirmed by the disappearence of the ethanoate group of the brominated compound **4**.

Additionally, ^{13}C-NMR data also confirmed this result, showing the appearance of two signals at δ values of 106.35 and 171.92 ppm assigned to respective carbons of =CH of **5a$_i$**and the carboxamide group of **5b$_i$** of the thiazole ring. These values are in perfect

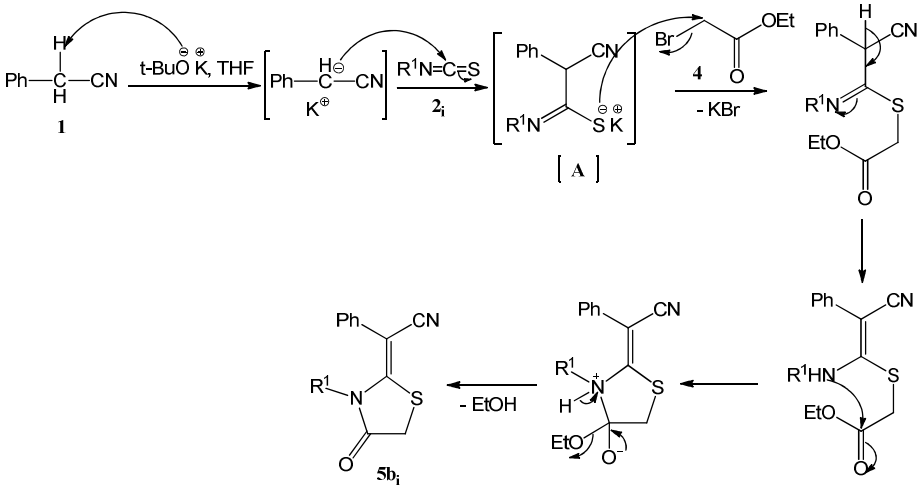
agreement with the literature data[xiii a-d]. The structure of all newly isolated compounds was fully confirmed by spectral and elemental analyses methods.

It is obvious that the formation of the thiazolinesis explained by a mechanism involving in the first step the action of isothiocyanates**2i** out of the phenylacetonitrile**1** used as starting material to afford the intermediate potassium sulphide salt [A]. After, this last reacts with a brominated derivate according to two possible reaction processes that after further intramolecularcyclocondensation leads to desired heterocycles**5a$_i$** and **5b$_i$**.

The possible mechanisms of **5a$_i$** and **5b$_i$** are shown in **Scheme 2** and **3** respectively.



Scheme 2. The possible mechanism to afford 5a$_i$



Scheme 3. The possible mechanism to afford 5b$_i$

CONCLUSION

We reported a simple and practical method for the preparation of novel thiazolines and thiazolidinones in a short reaction time and with good yields, under mild conditions. Our

findings are an important contribution to confirm the selectivity and the mechanism of this kind of reactions.

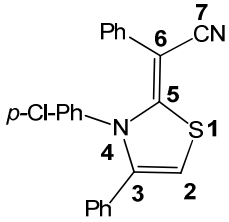
EXPERIMENTAL SECTION

The melting point was determined by Bûchi. Infrared spectra were recorded by using Shimadzu FTIR 8400S. ^{1}H, ^{13}C NMR spectra were recorded at 300, 75 MHz respectively on aBruker AC-300 with TMS as internal reference (for ^{1}H and ^{13}C). Materials: thin-layer chromatography (TLC): TLC plates (Merck, silica gel 60 F254 0.2 mm 200×200 nm); substances were detected using UV light at 254 nm. CHN elementary were performed at the INRAP (National Institute of Physico-Chemical Analysis (INRAP) Bio-technopoleSidiThabet, Tunisia) Perkin Elmer Model: Analyzer 2400 series II CHN.

General procedure for the preparation of thiazolines and thiazolidinones

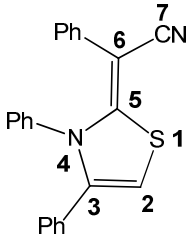
To a solution of THF (10 mL) and tBuOK (14 mmol) was added **1** (1 mmol) dropwise under nitrogen protection followed by stirring for 1 h. After that $\mathbf{2_i}$ (1 mmol) was added dropwise followed by stirring at room temperature. After 3 h, compound **3** or **4** (1 mmol) was introduced followed by stirring for one nignt. After the reaction was complete, the mixture was hydrolysed by adding a solution of water (9 mL) and hydrochloric acid (1 mL) followed by two extractions with chloroform (20 mL). The organic phase was dried on $MgSO_4$ anhydrous. Then the solution filtered and the residu was purified by column chromatography by Silica Gel (EtOAc). The residue obtained was recrystallized with ethanol.

4-*p*-Chlorophenyl-3-phenyl-5-phenylacetonitrilthiazol-2-ylidene ($5a_1$)



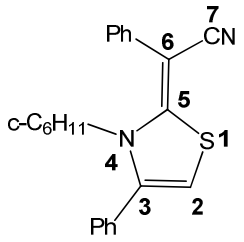
Brown solid; mp= 130°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm}: 6,41 (s, 1H, H-C_2); 7,00-7,45(m, ,H_{arom}). ^{13}C NMR ($CDCl_3$, 75 MHz)δ_{ppm}:107,47 (C_2); 143,51 (C_3); 157,32 (C_5); 93,66 (C_6); 119,44 (C_7); 125,62-134,47 (C_{arom}). Anal. Calc. for $C_{23}H_{15}ClN_2S$ (386.90g.mol^{-1}): C, 71.40; H, 3.91; N, 7.24; found C, 71.42; H, 3.25; N, 7.21 %

3,4-Diphenyl-5-phenylacetonitrilthiazol-2-ylidene ($5a_2$)



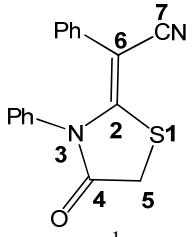
Beige solid; mp =186°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm}: 6,10 (s, H-C_2); 7,00-7,32 (m, ,H_{arom}). ^{13}C NMR ($CDCl_3$, 75 MHz)δ_{ppm}:105,77 (C_2); 140,51 (C_3); 155,32 (C_5); 96,66 (C_6); 117,04 (C_7); 125,96-138,77 (C_{arom}). Anal. Calc. for $C_{23}H_{16}N_2S$ (352.45g.mol^{-1}): C, 78.30; H, 4.53; N, 7.94; found C, 78.28; H, 4.33; N, 7.94 %

4-Cyclohexyl-3-phenyl-5-phenylacétonitrilthiazol-2-ylidene ($5a_3$)



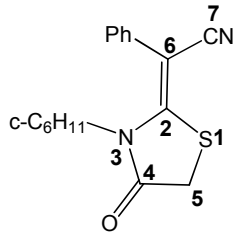
Yellow solid; mp = 163°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} : 5,89 (s, H-C_2); 1,15-3,56 (m, H $_{c\text{-}hex}$); 6,91-7,32 (m, H_{arom}). ^{13}C NMR ($CDCl_3$, 75 MHz)δ_{ppm} :100,76 (C_2); 141,82 (C_3); 156,64 (C_5); 88,65 (C_{18}); 119,65 (C_{25}); 29,46-57,27 (m, C $_{c\text{-}hex}$); 126,19-130,84 (m, C_{arom}). Anal. Calc. for $C_{23}H_{22}N_2S$ (358.50g.mol^{-1}): C, 76.98; H, 6.13; N, 7.81; found C, 76.40; H, 6.24; N, 7.76 %

3-Phenyl-2-phenylacetonitrilthiazolidin-4-one ($5b_1$)



Yellow solid;mp = 138°C. IR ($CHCl_3$, ν cm^{-1}): CN=2230; -CO =1736.^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} : 3,71-3,78 (H_5); 7,05-7,43 (m, H_{arom}). ^{13}C NMR ($CDCl_3$, 75 MHz)δ_{ppm} : 175,96 (C_2); 171,76 (C_4); 33,15 (C_5); 96,45 (C_6); 115,73 (C_7); 118,18-142,64 (m, C_{arom}). Anal. Calc. for $C_{17}H_{12}N_2OS$ (292.35g.mol^{-1}): C, 69.77; H, 4.10; N, 9.50; found C, 79.70; H, 4.01; N, 9.48 %

3-Cyclohexyl- -2-phenylacetonitrilthiazolidin-4-one ($5b_2$)



Yellow solid; mp = 156°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_{ppm} : 3,63-3,68 (H-C_5); 1,16-2,95 (m, $H_{c\text{-}hex}$); 7,20-7,98 (m, H_{arom}). ^{13}C NMR ($CDCl_3$, 75 MHz)δ_{ppm} :194,42 (C_2); 171,49 (C_4); 33,45 (C_5); 100,33 (C_6); 117,96 (C_{19}); 23,18-55,40 (m, $C_{c\text{-}hex}$); 127,41-133,67 (m, C_{arom}). Anal. Calc. for $C_{17}H_{18}N_2OS$ (298.40g.mol^{-1}): C, 68.36; H, 6.03; N, 9.38; found C, 66.97; H, 6.10; N, 9.34 %

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