THIADIAZOLOPYRIDINIUM SALTS: INTERMEDIATES FOR HETEROCYCLIC SYNTHESIS

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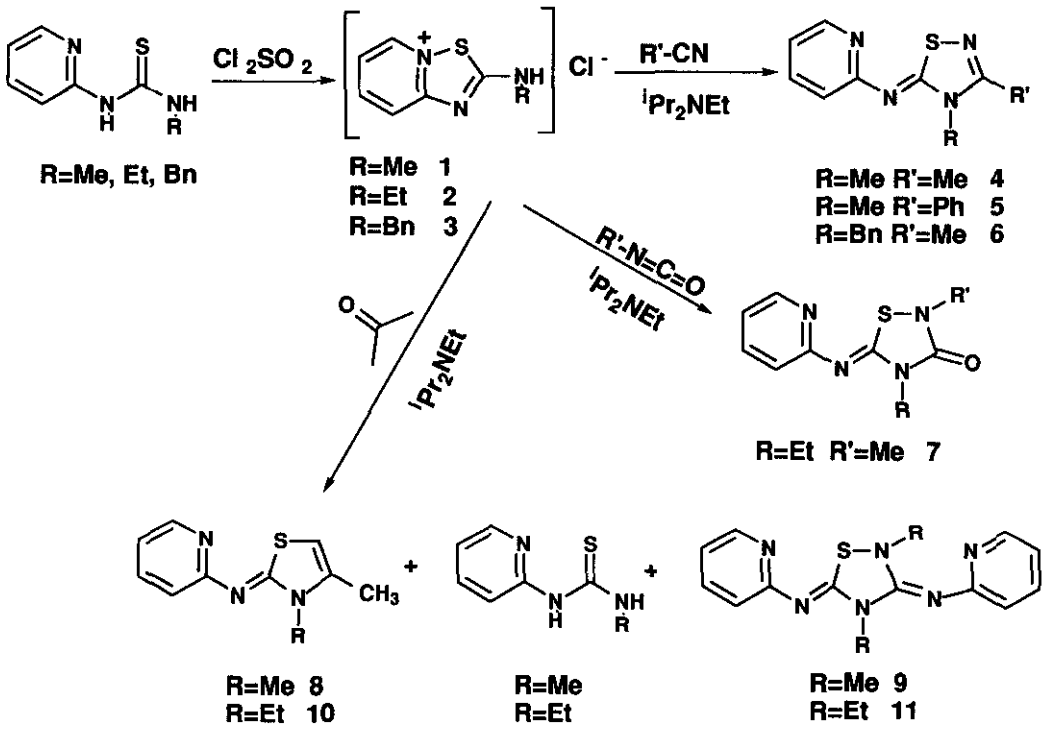
Abstract- The high reactivity of [1,2,4]thiadiazolo[2,3-*a*]pyridinium salts against electrophiles is described. This fact provides a new and efficient synthetic route to several heterocycles such as thiazolines, thiadiazolines and thiadiazolin-3-ones carrying pyridylimino substituents.

There are several reports dealing with the oxidation reaction of *N*-heteroarylthioureas.[1-4] However, studies concerning the chemical properties and the synthetic applications of the resulting thiadiazolo heteroarylium salts have not yet appeared. This preliminary communication describes the high reactivity of [1,2,4]thiadiazolo[2,3-*a*]pyridinium salts against electrophiles which opens an easy and efficient synthetic pathway to many heterocycles bearing pyridylimino susbtituents.

Following the procedure described by Harris,[1] treatment of *N*-alkyl- and *N*-benzyl-*N'*-(2-pyridyl)thioureas with sulphuryl chloride in toluene at room temperature gave the corresponding [1,2,4]thiadiazolo[2,3-*a*]pyridinium salts in good yields after short reaction time. These compounds showed chemical reactivity against electrophiles as depicted in Scheme 1. Thus, reaction in basic medium with alkyl and aryl nitriles provides a synthetic route to substituted 1,2,4-thiadiazolidines.[5] The nucleophilic addition is completed quantitatively in 2h reaction time at nitrile reflux temperature. Reaction with alkyl isocyanates yields 1,2,4-thiadiazolidin-3-ones in a new synthetic way.[6] The behaviour of thiadiazolopyridinium salts against carbonyl compounds has been also explored. In this case,[7] the crude reaction products showed a mixture of compounds in which we could isolate a product resulting from the addition of the reagent to the ketone, i.e., 2-imino-(2-pyridyl)-1,3-thiazoline, and two compounds whose structures imply a redox reaction. These were the *N*-methyl-*N'*-(2-pyridyl)thiourea and its oxidation derivative, the 3,5-diimino-1,2,4-thiadiazoline, generally known as Hector's base.



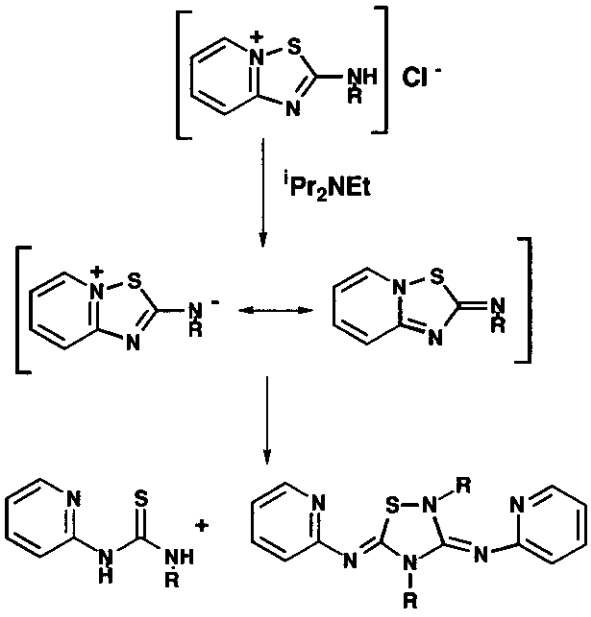
Scheme 1

The presence of tertiary amine as a weak base, in the reaction medium is necessary for the transformation to take place. Probably deprotonation at the exocyclic nitrogen giving an intermediate free base is involved in the mechanism of these reactions (Scheme 2). On a preparative scale, the free base was observed as a transient yellow colour which rapidly faded. Attempts to isolate this intermediate were unsuccessful.

The oxidative power of the free base is observed in the formation of thiourea and its corresponding Hector's base in the reaction medium when there is a competition between the nucleophilic attack and the redox reaction.

Further evidence of these oxidative properties was obtained when the thiadiazolopyridinium salts were treated with a weak base in an inert solvent. In this case, a facile transformation took place and the products isolated were the corresponding thiourea and its Hector's base (Scheme 2). It is worth mentioning that Hector's bases are known since 1890 and were obtained by oxidation of thioureas with peroxides. The mechanism of this reaction has been subject of many studies, being nowadays clearly established.[8]

All the synthesized compounds were characterized according to their analytical and spectroscopycal data, complemented with NOE, COSY and HETCOR experiments. Some general procedures and typical data are collected as notes.



Scheme 2

In conclusion, we have shown that the [1,2,4]thiadiazolo[2,3-*a*]pyridinium salts are intermediates in the synthesis of pyridylimino substituted heterocycles and provides new routes to the preparation of thiazolines, thiadiazolines and thiadiazolin-3-ones.

ACKNOWLEDGMENT

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5. *General Procedure*: To a suspension of the [1,2,4]thiadiazolo[2,3-*a*]pyridinium salt (2.3 mmol) in the corresponding nitrile (15 ml), an equimolar quantity of *N,N'*-diisopropylethylamine was added. The reaction mixture was refluxed for 2h. The solvent was evaporated *in vacuo* and the residue was recrystallized from the adequate solvent.
   Typical analytical and spectroscopycal data of compound. **4**: mp (H_2O) 144-145°C.
   ^{1}H Nmr ($CDCl_3$) d : 2.41 (s, 3H, C-C$\underline{H}_3$); 3.65 (s, 3H, N-C$\underline{H}_3$); 6.86 (m, 1H, $J_{H5,H3}$= 2 Hz, $J_{H5,H4}$= 8 Hz, $J_{H5,H6}$= 5 Hz, $\underline{H}$-5); 7.21 (d, 1H, $J_{H3,H4}$= 9 Hz, $\underline{H}$-3); 7.62 (m, 1H, $J_{H4,H3}$= 9 Hz, $J_{H4,H5}$= 8 Hz, $J_{H4,H6}$= 2 Hz, $\underline{H}$-4); 8.40 (m, 1H, $J_{H6,H5}$= 5 Hz, $J_{H6,H4}$= 2 Hz, $\underline{H}$-6).
   ^{13}C Nmr ($CDCl_3$) d: 16.50 (C-$\underline{C}H_3$); 32.83 (N-$\underline{C}H_3$); 155.96, 167.56 (C-3 and C-5 thiadiazoline moiety), 116.98, 118.45, 137.57, 144.80 153.06 (C-3, C-5, C-4, C-6 and C-2 pyridine moiety).
6. *General Procedure:* A solution of the [1,2,4]thiadiazolo[2,3-*a*]pyridinium salt (2.3 mmol), the isocyanate (4.6 mmol) and *N,N'*-diisopropylethylamine (2.3 mmol) in THF (20 ml) was refluxed for 2 h. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel column using appropriate AcOEt:Hexane mixtures.
   Typical analytical and spectroscopycal data of comp. **7**: AcOEt:Hexane 3:1, mp 124-125°C
   ^{1}H Nmr ($CDCl_3$) d: 1.32 (t, 3H, J_{CH2CH3}= 7 Hz, $CH_2C\underline{H}_3$); 3.05 (s, 3H, N-C$\underline{H}_3$); 4.06 (q, 2H, J_{CH2CH3}= 7 Hz, C$\underline{H}_2CH_3$); 6.88 (m, 1H, $J_{H5,H3}$= 1 Hz, $J_{H5,H4}$= 8 Hz, $J_{H5,H6}$= 4 Hz, H-5); 7.26 (d, 1H, $J_{H3,H4}$= 9 Hz, H-3); 7.64 (m, 1H, $J_{H4,H3}$= 9 Hz, $J_{H4,H5}$= 8 Hz, $J_{H4,H6}$= 2 Hz, H-4); 8.27 (d, 1H, $J_{H6,H5}$= 4 Hz, H-6).
   ^{13}C Nmr ($CDCl_3$) d: 12.94 (C-$\underline{C}$H3); 28.59 (N-CH3); 38.86 (N-CH2); 115,60, 119.35, 137.82, 140.03, 153.21 (C-3, C-5, C-4, C-6, C-2 pyridine moiety); 157.17, 158.40 (C=N, C=O thiadiazolidin-3-one moiety)
7. *General Procedure:* To a suspension of the [1,2,4]thiadiazolo[2,3-*a*]pyridinium salt (2.3 mmol) in acetone (50 ml), *N,N'*-diisopropylethylamine (2.3 mmol) was added. The reaction mixture was refluxed for 6 h. The solvent was eliminated *in vacuo* and the residue was chromatographed on silica gel column using appropriate CH_2Cl_2:MeOH mixtures.
   Typical analytical and spectroscopycal data of comp. **8**: CH_2Cl_2:MeOH 100:1, mp 90-92°C.
   ^{1}H Nmr ($CDCl_3$) d: 2.22 (d, 3H, $J_{CH,CH3}$= 2 Hz, C-C$\underline{H}_3$); 3.53 (s, 3H, N-C$\underline{H}_3$); 6.23 (m, 1H, $J_{CH,CH3}$= 2 Hz, C$\underline{H}$=C); 6.80 (m, 1H, $J_{H5,H4}$= 7 Hz, $J_{H5,H6}$= 4 Hz, $J_{H5,H3}$= 1 Hz, H-5); 6.90 (m, 1H, $J_{H3,H4}$= 8 Hz, $J_{H3,H5}$= 1 Hz, $J_{H3,H6}$= 1 Hz, H-3); 7.60 (m, 1H, $J_{H4,H5}$= 7 Hz, $J_{H4,H3}$= 8 Hz, $J_{H4,H6}$= 2 Hz, H-4); 8.30 (m, 1H, $J_{H6,H5}$= 4 Hz, $J_{H6,H4}$= 2 Hz, $J_{H6,H3}$= 1 Hz, H-6)
   ^{13}C Nmr ($CDCl_3$) d: 14.54 (C-$\underline{C}$H3); 31.69 (N-$\underline{C}$H3); 99.51, 133.33, 160.48 (C-5, C-4 and C-2 thiazoline moiety), 115.59, 119.14, 136.77, 145.81, 158.94 (C-3, C-5, C-4, C-6 and C-2 pyridine moiety).
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