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NOTE

One-Step Synthesis of 2-Thiazolidinone

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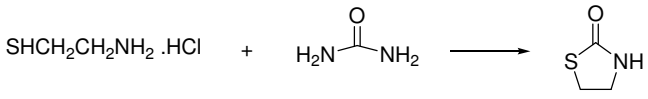
An efficient and direct access to thiazolidinone is developed. 2-Thiazolidinone is synthesized by urea and 2-aminoethylmercaptan hydrochloride and this one-step process proceeds with good yields, under mild conditions. The structure of the compound was confirmed by IR, ^{1}H NMR, MS and the product purity was 98 % by HPLC.

Keywords: Thiazolidinone, 2-Aminoethanethiol hydrochloride, Urea, Synthesis.

Thiazolidinone is considered as a biologically important active scaffold that possesses almost all types of biological activities. Thiazolidinone derivatives have been investigated for a range of pharmacologic indications such as antiinflammatory, antimicrobial, antiproliferative, antiviral, anticonvulsant, antifungal and antibacterial activities[1-4]. 2-Thiazolidinone is useful as intermediates for medicines and agricultural pesticides[5]. 2-Thiazolidinone is not only a useful intermediate, but also has good fungicidal activities toward various plant disease fungus. The research and developments for 2-thiazolidinone as key intermediate of Fosthiazate has the great significance for manufacture of Fosthiazate and the plant thelaziasis's prevention[6].

The conventional methods mentioned in the literature[7] have various drawbacks of their own. With these in mind, we recently choosed the 2-aminoethanethiol-urea method as industrial synthetic method. The synthetic route of the target compound is outlined in **Scheme-I**. 2-Aminoethylmercaptan hydrochloride was purchased from Aladdin Reagent Co. Ltd China, with an over 98 % purity.



Scheme-I: Synthesis of 2-thiazolidinone

Melting points (uncorrected) were determined on a XT4 MP apparatus (Taike Corp., Beijing, China). IR spectra were recorded by dispersing the compounds in KBr pellets on a Schimadzu FT-IR 157 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Avance II 400 MHz NMR spectrometer and all the chemical shift values were reported as δ (ppm). Mass spectra were recorded on a Agilent 6320 ion trap LC/MS instrument

2-Thiazolidinone: 2-Aminoethanethiol hydrochloride (11.4 g, 0.1 mol) and urea (9 g, 0.15 mol) were stirred and heated to 180 ºC and left undergoing reaction. In this while, since ammonia was emanated from the top of the condenser, the reaction was continued with the emanating ammonia kept absorbed in an aqueous hydrochloric acid solution. When the reaction was continued for 3 h following the rise of the temperature to 180 ºC, the emanation of ammonia ceased and the reaction was completed. The cooled reaction mixture was treated with water and the product was obtained by filtration. And extracted with toluene and distilled under a vacuum, white solid 8.8 g, yield 85 %, m.p. 49-51 ºC, IR (KBr, ν_{max}, cm^{-1}): 3300, 1680, 1550, 1100; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 3.35-3.41 (m, 2H), 3.57-3.61 (m, 2H), 6.95 (s, 1H, N-H); MS (ESI, m/z): 103.2 $[M]^+$.

TABLE-1
EFFECT OF REACTION TEMPERATURE ON THE YIELD OF THE PRODUCT

Reaction temp. (ºC)	140	160	180	200	210
Yield (%)	65	75	85	78	65
Reaction time (h)	5	4	3	2	1

2-Thiazolidinone is synthesized by urea and 2-aminoethylmercaptan hydrochloride and this one-step process proceeds

TABLE-2
EFFECT OF REACTION TIME ON THE YIELD OF THE PRODUCT

Reaction time (min)	120	150	180	210	240
Yield (%)	60	75	85	70	65
Reaction characteristics	Not complete	Not complete	Moderate	Byproducts	Byproducts

with high yields, under mild conditions. The structure of the target compound was confirmed by IR, ^{1}H NMR, MS and the purity was 98 % as determined by HPLC. The melting point of the product was 51 ºC, which was identical with reported value in the literature[8]. We also optimized the reaction conditions by testing several parameters, such as reaction time (Table-1), reaction temperature (Table-2) and different amounts of raw material (Table-3).

TABLE-3
EFFECT OF THE MOLAR RATIO OF UREA TO 2-AMINOETHANETHIOL HYDROCHLORIDE REACTION TEMPERATURE ON THE YIELD OF THE PRODUCT

Molar ratio (mol ratio)	1.0	1.2	1.5	2.0
Yield (%)	70	75	85	85
Purity (%)	81	85	98	98

With reaction temperature lower than 180 ºC, the reaction took place more slowly and a reaction time of 4-5 h, And when the reaction temperature higher than 180 ºC, the reaction took place more quickly and a reaction time of 1-2 h, but the yield was also reduced, so moderate reaction temperature was 180 ºC.

The reaction proceeded faster, it is found that raw materials were not completed and the yield decreased, on the other side byproducts were formed in long reaction time, so appropriate reaction time was 3 h.

As can be seen from the Table-3, the suitable molar ratio of urea to 2-aminoethanethiol hydrochloride is 1.5:1.0, the urea amount used reduced 20 compared to the literature[9].

By experiments utilizing an orthogonal design, optimum synthesis conditions were obtained as follows: the molar ratio of urea to 2-aminoethanethiol hydrochloride is 1.5:1.0, reaction temperature 180 ± 5 ºC, reaction time 3 h. Take the toluene as the extractive solvent, by 2-aminoethanethiol hydrochloride, yield may reach 85-90 %. Through the optimized response condition, the urea amount used reduced to 20 compared to the literature.

Conclusion

We have successfully reduced the number of steps and 2-thiazolidinone is now accessible in one steps with good yields. we optimized the reaction conditions by testing several parameters, such as extraction solvent, different amounts of raw material, reaction temperature and reaction time, *etc*. Short steps, high yield and ease of operation of the present approach would permit the *hitherto* most efficient access to 2-thiazolidinone.

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