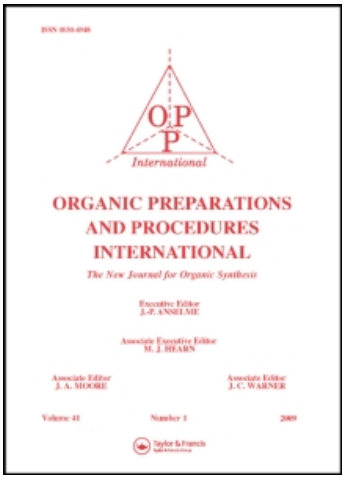

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AN EFFICIENT ONE-STEP METHOD FOR THE LARGE-SCALE SYNTHESIS OF 2,4-THIAZOLIDINEDIONE

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AN EFFICIENT ONE-STEP METHOD FOR THE LARGE-SCALE SYNTHESIS OF 2,4-THIAZOLIDINEDIONE

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(03/21/08)

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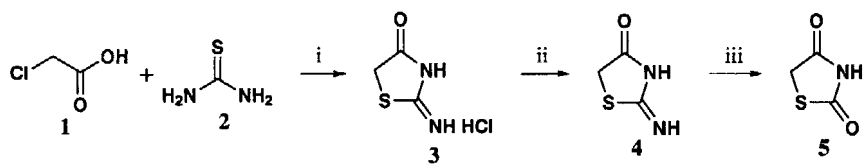
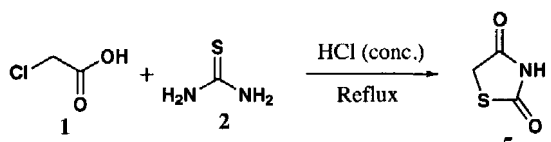
2,4-Thiazolidinedione (**5**) is a widely used industrial material for the synthesis of many biologically active agents, such as antimicrobial agents[1] and anti-diabetes drugs[2] including rosiglitazone,[3] picoglitazone,[4] ciglitazone,[5] troglitazone[6] and DRF-2189, *etc*. The high cost of these clinically used drugs limits their wide usage and is a direct consequence of the cost of this important industrial chemical. The conventional synthesis of **5** usually requires at least 2-3 steps from 2-chloroacetic acid (**1**) and thiourea (**2**) (*Scheme 1*)[7]. The use of sodium thiocyanate instead of **2** or ethyl chloroacetate instead of **1** does not afford a product of sufficiently high quality in good overall yields;[8] other alternative methods involve the use of toxic organic solvents and tedious work-up.[9]



i) H_2SO_4; ii) NaOH; iii) HCl

Scheme 1

Based on the procedures reported in literature,[7-9] and our research experience in synthesis of the thiazole heterocyles, we envisioned that these three steps could be carried out in one pot (*Scheme 2*). Herein, we report a novel efficient one-pot procedure from chloroacetic acid and thiourea for the preparation in high yield of pure **5**, after recrystallization from water.



Scheme 2

EXPERIMENTAL SECTION

Melting points were taken on a WRS-1 digital melting point apparatus and are uncorrected. Elemental analyses were performed on a Carlo-Elba 1106 elemental analyzer. IR spectra were recorded on a Nicolet FI-IR 360 Spectrophotometer. ^{1}H NMR spectra were on a Bruker AM-

300(400MHz) spectrometer with TMS as an internal standard. Chemical shifts were reported in δ. Mass Spectra were measured on a HP5988A instrument by direct inlet at 70ev. All materials were obtained from commercial suppliers and used as received.

2,4-Thiazolinedione (**5**).- To a 1 L three neck flask equipped with a thermometer, mechanical stirrer and a condenser, was added of 2-chloroacetic acid (**1**, 189 g, 2 mol), thiourea (**2**, 152 g, 2 mol), and 400 mL hydrochloride (30%). This mixture was stirred for 0.5 hour, and then heated to reflux at 110°C. The progress of the reaction was monitored by TLC (petroleum-ethyl acetate: 2:1) until the reaction was nearly completed after 3.5 hours. After 1 hour of reflux, 2-imino-4-thiazolidone (**4**) appeared as white solid and further refluxing converted **4** (without isolation) into **5**. The reaction mixture was gradually cooled to room temperature while being stirred whereupon a large amount of white crystal precipitated. The solid was collected, washed with a small amount of cold water(10 mL x 3) to give the crude product **5** (230 g, 98%) as white crystals which were recrystallized from 500 mL of water to give pure **5** (196 g, 84%), mp. 126-127°C, *lit.* [7]125-126°C; the use of activated carbon may be necessary to decolorize the product. The main impurity was identified by GC analysis to be **4**, pale yellow crystals with the mp. 256-258°C (dec.) *lit.*[10] 256-258°C. It should be eliminated during the recrystallization, otherwise, it will cause the color of product to become yellowish upon storage.
IR(KBr): 3398, 2800, 1731, 1677cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.75(s, 2H, -CH_2); 9.9(s, 1H, -NH); MS(*m/z*, %): 118 (M^{+1}). All these analytical data agreed with those reported in the literature.[7]

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AN IMPROVED APPROACH TO *N*-SUBSTITUTED MALEIMIDES AND PHTHALIMIDES BY MICROWAVE-PROMOTED MITSUNOBU REACTION

Submitted by (08/18/08)

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Maleimide derivatives are of high interest as substrates in biological applications. Due to its Michael-accepting ability the maleimido group is able to react with nucleophilic groups, *e. g.* thiol groups in biomolecules.[1] Therefore substrates containing terminal maleimido functionality can undergo covalent coupling to cysteine residues of enzymes or other proteins.[2] Bifunctional derivatives with a maleimido group attached to one end and a connectable functionality on the opposite end can be used for cross-linking proteins.[3,4] Maleimides are widely used as dienophiles with a variety of dienes in Diels-Alder-type cycloaddition reactions.[5,6]

In literature only few methods for the synthesis of *N*-substituted maleimides are described. A commonly used method is the reaction of an amine with maleic anhydride followed by dehydration.[7-9] However, this procedure is limited to amines which are stable to the dehydration conditions.[10] *N*-Substituted phthalimides, which can serve as a protecting group for the amino group, are conveniently prepared by reaction of potassium phthalimide with alkyl halides, in the first step of the Gabriel synthesis.[11] Alternatively, direct *N*-alkylation of maleimides and phthalimides can be accomplished by the Mitsunobu reaction, using alcohols as the alkyl group donors.[12] The activating agents in the Mitsunobu protocol are triphenylphosphine and azodicar-