A New Method for the Preparation of 5-Alkyl- and 5,5-Dialkyl-1,3-thiazolidine-2,4-diones through Dianion Intermediates

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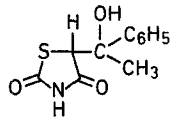
In connection with a continuing study of new heterocyclic multiple anions as synthetic intermediates[1,2], we have found that 1,3-thiazolidine-2,4-dione (**1**) and certain 5-alkyl-1,3-thiazolidine-2,4-diones (**3**) can be converted into preparatively useful dianions **2** and **4**, respectively, by means of alkali amides in liquid ammonia. Subsequent treatment of these dianions with alkyl halides results in selective alkylation at the highly nucleophilic carbanion site to afford 5-alkyl-1,3-thiazolidine-2,4-diones (**3**) from dianion **2**, and 5,5-dialkyl-1,3-thiazolidine-2,4-diones (**5**) from dianions of type **4**. These reactions represent the first examples of direct C-alkylation of the 1,3-thiazolidine-2,4-dione nucleus[3], and provide a facile new route to compounds of types **3** and **5**[4].

In order to minimize proton-metal exchange and the accompanying problem of polyalkylation[1], dianion **2** was prepared by means of two molecular equivalents of lithium amide in liquid ammonia and then treated with a twofold molar excess of the appropriate halide. This procedure resulted in clean monoalkylation to afford 5-alkyl derivatives **3a–f** in good yields (Table 1). Similar attempts to generate and alkylate dianions of type **4** with benzyl chloride were only moderately successful, presumably because of an unfavorable equilibrium involving incomplete formation of the dianions from the corresponding monoanions produced by initial ionization of the highly acidic NH proton. This difficulty was readily overcome by employing three molecular equivalents of potassium amide for dianion formation and then adding excess benzyl chloride to the reaction mixture. It may be seen from the results of these benzylations (Table 2) that the excess base and halide were not detrimental to the reaction, and that the substituents present in the dianions investigated offered little steric hindrance to further alkylation. It should be noted that the synthesis of 5,5-dialkyl derivatives containing both primary and secondary alkyl moieties is best accomplished by first introducing the secondary group through dianion **2**, and then attaching the primary substituent by means of potassium amide.

The synthetic potential of dianion **2** was further demonstrated by its reaction with acetophenone to afford carbinol **6** (45%) as a mixture of diastereomers.



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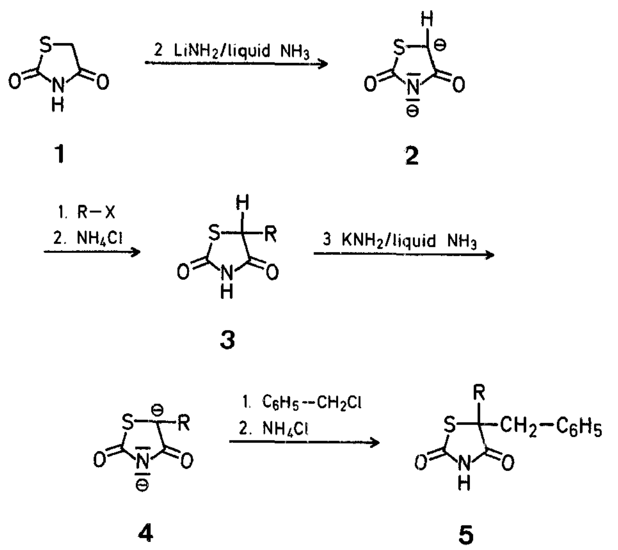
Previous attempts to effect condensation of this ketone with dione **1** have been unsuccessful, even under conditions designed to force the reaction to completion by dehydration of the initially formed carbonyl adduct[5].

The following procedures are representative of the preparation of compounds **2**–**5**.



5-Benzyl-1,3-thiazolidine-2,4-dione (3f):

To a solution of lithium amide[7] (0.147 mol), prepared from lithium metal (1.02 g, 0.147 g-atom) in commercial anhydrous liquid ammonia (500 ml) was added solid 1,3-thiazolidine-2,4-dione (**1**; 8.2 g, 0.07 mol). The resulting black suspension was allowed to stir for 20 min. At the end of this time, the reaction mixture was assumed to contain 0.07 mol of dianion **2** as its dilithio salt. A solution of benzyl chloride (18.61 g, 0.147 mol) in anhydrous ether (30 ml) was then added to the reaction mixture over a period of 2 min. The absence of the characteristic purple color associated with stilbene formation[8] verified that all the lithium amide had been consumed in the formation of dianion **2**. The reaction mixture was allowed to stir for 1 hr and was then neutralized by addition of solid ammonium chloride (10 g). The ammonia was removed (steam bath) as ether (300 ml) was added. The resulting ethereal suspension was treated with water (200 ml) and the layers were separated. The ethereal solution was dried ($MgSO_4$) and concentrated to give 9.26 g of recovered benzyl chloride. The basic aqueous solution was acidified by pouring it over a slurry of ice (200 g) and 12 *N* hydrochloric acid (100 ml). The resulting precipitate was extracted into ether, the ethereal extracts were washed with water, dried ($MgSO_4$), and concentrated to give 11.6 g of oil, which solidified upon trituration with petroleum ether. The crude solid was recrystallized from benzene/heptane and then from aqueous ethanol to give 8.21 g of benzyl derivative (**3f**; Table 1).

In the alkylations of dianion **2** with the other halides listed in Table 1, replacement of the ammonia by ether was followed by adding the resulting ethereal suspension to 250 g of ice and 100 ml of 12 *N* hydrochloric acid. The ethereal layer was separated and the aqueous acid solution extracted with ether. The combined ethereal extracts were washed with water, dried ($MgSO_4$), and concentrated. In this manner, butyl derivative **3e** was isolated as a solid. Alkyl derivatives **3a–d** were obtained as oils, which were distilled to afford the solid products listed in Table 1.

5-Benzyl-5-methyl-1,3-thiazolidine-2,4-dione (5a):

To a solution of potassium amide[9] (0.060 mol), prepared from potassium metal (2.35 g, 0.060 g-atom) in liquid ammonia (300 ml) was added a solution of 5-methyl-1,3-thiazolidine-2,4-dione (**3a**; 2.62 g, 0.20 mol) in anhydrous tetrahydrofuran (30 ml). The resulting gray suspension was allowed to stir for 25 min. to form dianion **4a**. A solution of benzyl chloride (7.60 g, 0.060 mol) in anhydrous tetrahydrofuran (30 ml) was then added rapidly and the reaction mixture was allowed to stir for 1 hr before being neutralized with solid ammonium chloride (4.3 g). The ammonia was removed (steam bath) as hexane (200 ml) was added. The resulting suspension was poured into water (150 ml) and stirred until dissolution was complete. The aqueous phase (pH 9) was adjusted to pH 12 with conc. ammonium hydroxide and the

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Table 1. Alkylations of Dianion **2** to form 5-Alkyl-1,3-thiazolidine-2,4-diones (**3**)[a]

Alkyl halide	Product			
	R (Compound)	Yield %	m.p. (b.p.)	Lit. m.p.
CH_3J	CH_3 (**3a**)	58	43–46° (147–159°/1.35 mm)	41°[b]
C_2H_5Br	C_2H_5 (**3b**)	64	60.5–62° (159–160°/1.85 mm)	63°[b]
n-C_3H_7J	n-C_3H_7 (**3c**)	59	37–40.5° (141–143°/0.5 mm)	40°[b]
i-C_3H_7Br	i-C_3H_7 (**3d**)	65	47–53.5° (145–148°/0.7 mm)	58°[b]
n-C_4H_9Br	n-C_4H_9 (**3e**)	76[c]	81–82°	81°[b]
C_6H_5—CH_2Cl	C_6H_5—CH_2— (**3f**)	57[c]	103–104.5°	–[d]

[a] The I.R. ($CHCl_3$) and N.M.R. ($CDCl_3$) spectra of all derivatives of type **3** were consistent with their assigned structures.
[b] A. F. Minka, Farmatsevt. Zh. (Kiev) **18**, 24 (1963); C. A. **61**, 1848 (1964).
[c] Recrystallized from ethanol/water.
[d] A satisfactory elemental analysis (± 0.3% in C, H, and N) was obtained for this new compound.

Table 2. Benzylation of Dianions **4** to form 5,5-Dialkyl-1,3-thiazolidine-2,4-diones (**5**)[a,b]

Dianion	Product			
	R (Compound)	Yield %	m.p.	Recryst. solvent
4a	CH_3 (**5a**)	76	99–100°	ethanol/water
4b	C_2H_5 (**5b**)	52	80–81.5°	hexane
4c	n-C_3H_7 (**5c**)	65	133.5–136°	heptane
4d	i-C_3H_7 (**5d**)	40	133–136°	acetone/heptane
4e	n-C_4H_9 (**5e**)	63	96.5–98°	heptane
4f	C_6H_5—CH_2— (**5f**)	76	150.5–152°	benzene

[a] The I.R. ($CHCl_3$) and N.M.R. ($CDCl_3$) spectra of all compounds of type **5** were consistent with their proposed structures.
[b] Satisfactory analytical values (±0.3% in C, H, and N) were obtained for compounds **5a–f**.

layers were separated. The aqueous phase was extracted twice more with hexane and then poured into a slurry of ice (150 g) and 12*N* hydrochloric acid (75 ml). The oil that separated was extracted into tetrahydrofuran/ether (1:5, 150 ml). The tetrahydrofuran/ether extracts were dried ($MgSO_4$) and concentrated to give 4.43 g of crude semisolid product, which was recrystallized initially from acetone/heptane and then from aqueous ethanol; yield: 3.34 g (Table 2).

5-(1-Hydroxy-1-phenylethyl)-1,3-thiazolidine-2,4-dione (6):

To a suspension of dianion **2** (0.07 mol) in liquid ammonia (400 ml) was added a solution of acetophenone (10.09 g, 0.084 mol) in anhydrous ether (30 ml). The reaction mixture was allowed to stir for 20 min. and was then neutralized by pouring it into a solution of ammonium chloride (10 g) in liquid ammonia (150 ml). The ammonia was replaced by ether (350 ml) and the resulting suspension was added to water (300 ml). The ethereal layer was separated and the basic aqueous layer was extracted once more with ether. The remaining aqueous solution was acidified with 12*N* hydrochloric acid and the resulting precipitate was extracted into ether. The ethereal extracts were washed with water, dried ($MgSO_4$), and concentrated; yield: 7.43 g (45%). An analytical sample was obtained by recrystallization from benzene and then ethanol/heptane; m.p. 122–136.5°.

$C_{11}H_{11}NO_3S$	calc.	C 55.68	H 4.67	N 5.90
	found	55.76	4.85	5.85

N.M.R. (DMSO-d_6): $\delta = 12.64$ (s, 1, NH), 7.96 (m, 5, phenyl), 6.46 (s, 1, OH), 5.28 (s, 1, CH), 1.94 (s, 3, CH_3).

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