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Synthesis of 2-(ethylsulfanyl)aniline derivatives through the unexpected ring opening of *N*-substituted-2(3*H*)-benzothiazolones

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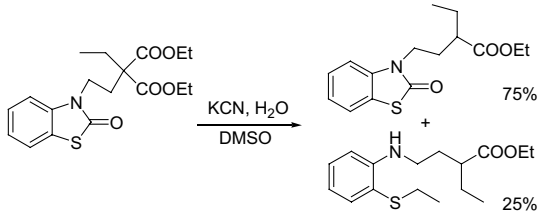
Abstract—The decarbalkoxylations of disubstituted geminal diesters by water–DMSO with added salts (KCN or NaCN) is a convenient preparative route leading to the corresponding monoesters. Herein, we described an efficient and very simple methodology for the preparation of 2-(ethylsulfanyl)aniline derivatives through the unexpected ring opening of the corresponding *N*-substituted-2(3*H*)-benzothiazolones in the presence of disubstituted geminal diester, KCN, and water–DMSO.

Ring opening of *N*-substituted-2(3*H*)-benzothiazolones to aminothiophenol derivatives is well known. Alkaline hydrolysis of *N*-substituted-2(3*H*)-benzothiazolone derivatives by aqueous sodium or potassium hydroxide in ethanol[1–3] led to the formation of the corresponding aminothiophenols. Addition of halogenated compounds in the same conditions allowed to obtain the thio-substituted derivatives.[4,5] Aminocarbothioates can also be synthesized by nucleophilic attack on the thiazolinone ring, with reagents such as secondary amines.[6]

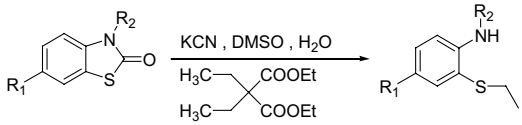
The Krapcho method which consisted on the decarbalkoxylations of disubstituted geminal diesters by water–DMSO with added salts (KCN or NaCN) is a convenient preparative route leading to the corresponding monoesters.[7–9] In an attempt to convert disubstituted geminal diester bearing a 2(3*H*)-benzothiazolone heterocycle to the corresponding ester, we used the procedure described above. Under these conditions, the decarbalkoxylation was not only effected but an unexpected ring opening of the thiazolinone occurred to produce the corresponding 2-alkylsulfanylaniline derivative with 25% yield (Scheme 1).



Scheme 1. Unexpected ring opening of *N*-substituted-2(3*H*)-benzothiazolone by Krapcho method.

The application of the salt-DMSO and disubstituted geminal diester reagents combination to effect ring opening of 2(3*H*)-benzothiazolone derivatives to the corresponding substituted 2-alkylsulfanylanilines was then studied (Scheme 2).

N-Methyl-2(3*H*)-benzothiazolone **1** was heated at reflux for 12 h with 1 equiv of diethyl 2,2-diethylmalonate, 2 equiv of water, and 1 equiv of KCN in DMSO to



Scheme 2. Ring opening of *N*-substituted-2(3*H*)-benzothiazolone derivatives.

Keywords: 2-(Ethylsulfanyl)aniline; Ring opening; *N*-Substituted-2-(3*H*)-benzothiazolones; Krapcho method.
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Table 1. Ring opening of *N*-methyl-2(3*H*)-benzothiazolone **1** with various salts

Salt	% Conversion[a,b]
NaCl	20
LiCl	33
NaBr	17
LiBr	23
NaCN	75
KCN	85

[a] Reagents: *N*-methyl-2(3*H*)-benzothiazolone (3 mmol), diethyl 2,2-diethylmalonate (3 mmol), KCN (3 mmol), H_2O (6 mmol), DMSO (15 mL) reflux for 12 h.
[b] HPLC analysis of a quenched aliquot.

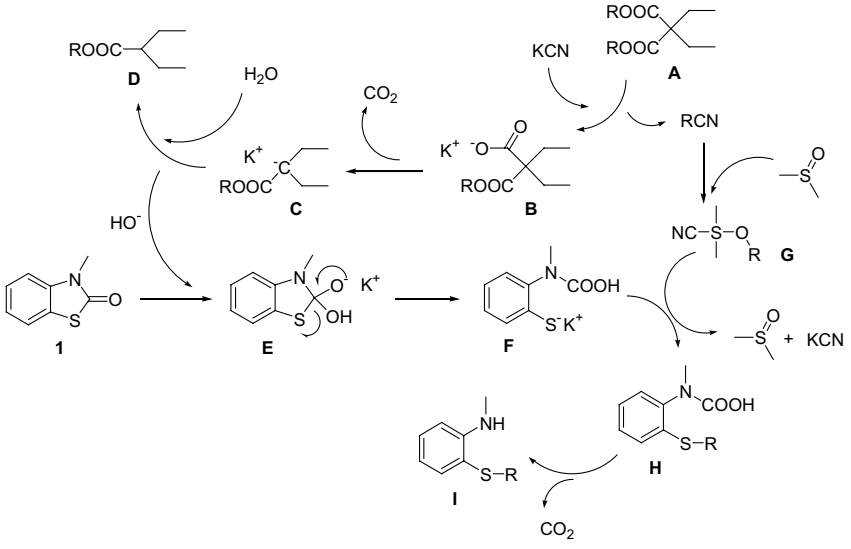
provide the corresponding 2-ethylsulfanyl-*N*-methylaniline **12** with 80% yield (Table 2). We noticed that the alkyl chain borne by the sulfur atom agreed with the alkyl chain of the malonic derivative.

To confirm this observation, we realized ring opening reaction of **1** using dimethyl 2,2-diethylmalonate and obtained a methylsulfanyl derivative. To more fully probe the salt effect, a variety of salts were studied for the ring opening of *N*-methyl-2(3*H*)-benzothiazolone. It can be seen from the data in Table 1 that the addition of a cyanide salt dramatically increased the rate of the ring opening with regard to chloride or bromide salts. The best rate of conversion was obtained using KCN with 85% 2-ethylsulfanyl-*N*-methylaniline conversion and 80% yield of isolated product.

Decarboxylation of malonic esters in DMSO by water with added salts, as KCN, led to the formation of the corresponding monoesters and CO_2 but also to the formation of 1 equiv of KOH, which reacted with CO_2 to form HCO_3^-, and 1 equiv of alkylcyanide.[9] In order to determine the effect of the solvent, DMF was used instead of DMSO in the same conditions than in Scheme 2, but no ring opening occurred. DMSO seemed to form a sulfonium complex with alkyl cyanide allowing stabilization and activation of it.[14] Diethyl malonate and diethyl ethylmalonate were used instead of the diethyl disubstituted malonate but the reaction mixture led to recovery of initial heterocycle. This indicated that the presence of a labile proton was not favorable for the ring opening.

From these results, the following mechanism was envisaged as outlined in Scheme 3. Nucleophilic attack of CN^- on the diethyl disubstituted malonic ester **A** led to the formation of alkyl cyanide RCN and monocarboxylic ester **B**, which underwent a concerted decarbalkoxylation to directly yield carbanion **C**. Hydrolysis of the carbanion provided the decarboxylated monoester **D** and hydroxide anion, which can react by nucleophilic attack on the carbonyl group of **1**. Electronic rearrangement led to the carbamic acid thiophenate **F**. Alkyl cyanide seemed to react with DMSO to give transient oxosulfonium ion **G**, which reacted with thiophenate to furnish the alkylsulfanyl derivative **H** and regenerate DMSO. Final decarboxylation of carbamic acid allowed obtention of the corresponding amine **I**.

Several 6-substituted *N*-methyl-2(3*H*)-benzothiazolones **2**–**5** and *N*-substituted-2(3*H*)-benzothiazolones **6**–**11** were screened[15] and results are summarized in Table 2. *N*-Methyl-2(3*H*)-benzothiazolones derivatives **2**–**5** were prepared by bromination,[10] nitration,[10,11] or acylation[12] of 2(3*H*)-benzothiazolone followed by *N*-methylation. The 6-methoxy derivative[13] was synthesized from its 2-aminobenzothiazole analogue using $NaNO_2$ in acid conditions. *N*-Alkylation of 2(3*H*)-benzothiazolone with NaH and various halogenated derivatives in DMF led to the formation of **6**–**11**. Very good yields of the desired opened products were obtained with *N*-methyl-2(3*H*)-benzothiazolone substituted with bromine (compound **2**) or electron withdrawing groups, as nitro (compound **4**) and benzoyl (compound **5**). With electron donating group as methoxy (compound **3**), the reaction of ring



Scheme 3. Mechanism proposed for ring opening of *N*-methyl-2(3*H*)-benzothiazolone.

Table 2. Ring opening of substituted 2-(3*H*)-benzothiazolone derivatives produced via Scheme 2

Substrate	R_1	R_2	Product (yield[a] %)
1	H	CH_3	**12** (80)
2	Br	CH_3	**13** (89)
3	OCH_3	CH_3	**14** (67)
4	NO_2	CH_3	**15** (83)
5	C_6H_5CO	CH_3	**16** (81)
6	H	CH_2CH_3	**17** (78)
7	H	$CH_2CH_2CH_3$	**18** (76)
8	H	$CH_2C_6H_5$	**19** (55)
9	H	CH_2CH_2Br	**20** (0)
10	H	CH_2CH_2OH	**21** (0)
11	H	$CH_2COOCH_2CH_3$	**22** (65)

[a] Isolated yield.

opening seemed to be less favorable. Reactions with *N*-ethyl, *N*-propyl, and *N*-benzyl derivatives **6**–**8** were accomplished equally well along with somewhat reduced yields. We next explored the scope of the present method by treating *N*-(functionally labeled)-2(3*H*)-benzothiazolones **9**–**11** at present reaction conditions. Only degradation occurred for the *N*-bromo- and *N*-hydroxyethyl **9** and **10** while the reaction with **11** was successful to give *N*-acetate opened derivative **22** with 65% yield. It is important to notice that very weak yields (<5%) on ring opening are obtained using NH-2(3*H*)-benzothiazolones. The presence of acidic proton on the thiocarbamate moiety seemed to neutralize, as for non and 2-monosubstituted malonates, hydroxide anion what prevented the ring opening.

In summary, the present procedure provided an efficient and very simple methodology for the preparation of 2-(alkylsulfanyl)aniline derivatives from ring opening of the corresponding *N*-substituted-2(*3H*)-benzothiazolones in the presence of disubstituted geminal diester, KCN, and water–DMSO.

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15. A typical procedure: *N*-methyl-2(3*H*)-benzothiazolone (3 mmol), diethyl 2,2-diethylmalonate (3 mmol), KCN (3 mmol), and H_2O (6 mmol) were stirred under reflux for 12 h in DMSO (15 mL). After cooling, the reaction mixture was hydrolyzed with aqueous NH_4Cl and extracted twice with ethyl acetate. The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The black residue was purified by chromatography (SiO_2, petroleum ether/ethyl acetate 7/3) to afford 2-(ethylsulfanyl)-*N*-methylaniline, as colorless oil, in 80% yield. IR ν_{max} (KBr) 3220, 2940, 1585, 1495 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, J = 7.10 Hz), 2.74 (q, 2H, J = 7.10 Hz), 2.91 (s, 3H), 5.11 (m, 1H), 6.65 (m, 2H), 7.27 (dd, J = 1.45, 6.70 Hz, 1H), 7.43 (dd, J = 1.50, 6.75 Hz, 1H).