ONE OR TWO STEP ACID MEDIATED CYCLOCONDENSATION PROCESS FOR THE PREPARATION OF 5-CARBETHOXY-2-THIOURACILS FROM DIETHYL ETHOXYMETHYLENEMALONATE AND THIOUREAS

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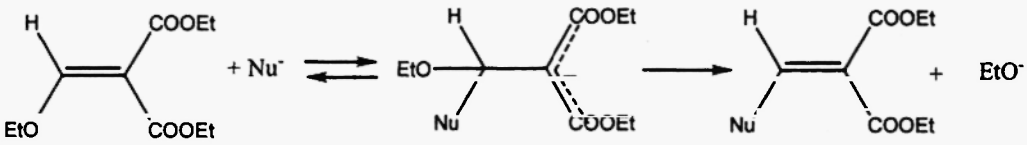
Abstract: An acid mediated synthesis of 5-carbethoxy-2-thiouracils via an one step cyclocondensation of diethyl ethoxymethylenemalonate and thioureas or the under milder reaction conditions, also obtained, thioureidomethylenemalonates, is described here.

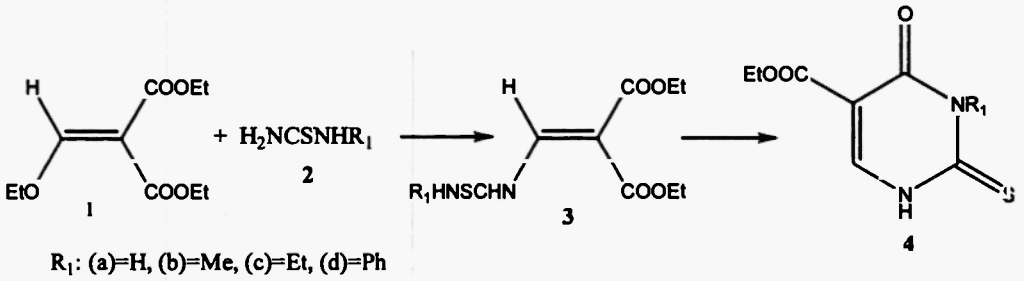
Pyrimidinone based derivatives have great biological significance because they exhibit a wide and growing range of antimicrobial, antiviral, and anticancer activities.[1] Especially 2-thiouracil derivatives have attracted much therapeutic interest as anti-HIV agents.[2] Specifically, some S-substitututed 2-thiouracils[3] displayed potent reverse transcriptase inhibiting activity and antiviral properties on cell lines infected with HIV-1 types. While, several 5,6-substituted 2-thiouracils have been evaluated for in vivo leishmanicidal activity on the general scope that the structural unit S-C(=N-)N displays leishmanicidal as well as immunostimulant properties[4,5]
Diethyl ethoxymethylenemalonate, (DEMM), has very often been exploited in preparations of different heterocycles but only a few reviews about this have been published.[6] Addition of amines to activated carbon-carbon double bonds is a variant of the Michael addition.[7a] In the case of primary amines by acidic catalysis, the monoaddition product affords,[7a] without catalysis, the bis(adduct).[7b]
Treatment of a nucleophile with an activated unsaturated system containing a leaving group, (nucleofuge), results in nucleophilic vinylic substitution, (S_NV), of the nucleofuge[8] and different reaction mechanisms for the S_NV route have been reviewed.[8,9] DEMM is a typical push-pull system containing two electron withdrawing groups. In such enol ethers or trifunctional electrocyclophiles[6b] the nucleophilic replacement of the ethoxy group is the predominant reaction.[10]
A two step mechanism that involves a tetrahedral intermediate has been proposed,[11] Scheme-1. A major conclusion that has emerged from these studies is that there is an



Scheme-1

unsually complex interplay of numerous factors that influence reactivity in these systems. These factors include inductive/field and resonance effects of the activating groups, π-donor effects of the leaving group, steric, anomeric, polarizability effects, and others. Even though some recognizable paterns are emerging, a comprehensive understanding of the relative importance of the various factors is not yet at hand.

DEMM has been used, for pyrimidine syntheses[12,13] by condensation with pseudothioureas, with urea and *N*-substituted ureas undergoes condensation by heating to give 5-carbethoxyuracils, while with higher *N*-alkylureas, alkylureidomethylenemalonates are obtained, which are converted to 3-alkyl-5-carbethoxyuracils in the presence of a basic catalyst. The condensation of DEMM was also carried out with urea and *N*-arylureas in the presence of a base,[14] on the same report the methylureiodomethylenemalonate resulting by thermal reaction of DEMM with methylurea, was converted with further heating to the corresponding uracil. The higher alkylurea homologs did not cyclized analogously, but their cyclization succeeded in the presence of a basic catalyst. The former research group later[15] allowed DEMM to react with thioureas to yield 5-carbethoxy-2-thiouracils under basic conditions,(sodium ethoxide/ethanol). The reaction route of formation of these hetererocycles, e.g. 2-thiouracils, includes a two step sequence, the initial step is a S_NV of the poor nucleofuge, (EtO^-), of DEMM **1**, with the binucleophile thioureas **2** to the thioureidomethylenemalonates **3** formation, which in the second step are cyclized to the desired 2-thiouracils **4**, Scheme-2.



R_1: (a)=H, (b)=Me, (c)=Et, (d)=Ph

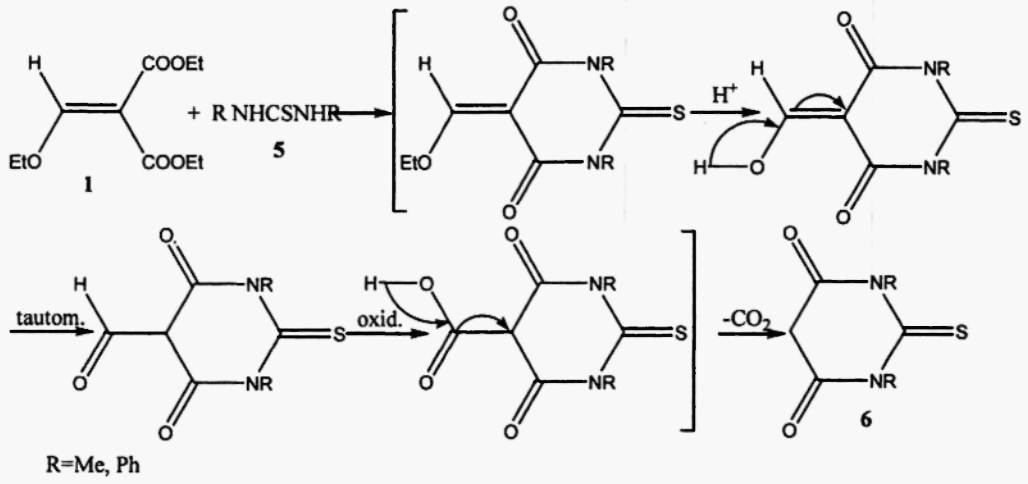
Scheme-2

The facility with which DEMM condenses with basic nitrogen compounds has been demonstrated in reactions with ammonia[13] and amines.[16]

Herein we are interested to study the reaction of DEMM with few thioureas under acid mediated conditions. Encouraging literature reports[17] on addition reaction of thiourea salts on acrylonitrile and acrylamides prompted us to attempt to add thiourea salts to DEMM, but these failed. The addition of thioureas on DEMM was succeeded in a solution of reactants in concentrated hydrochloric acid and ethanol, at room temperature, yielding quantitatively the thioureidomethylenemalonate derivatives **3**, which both, were obtained as pure products and characterized, or in situ transformed under stronger reaction conditions to **4**. This acidic catalysis of the reaction could be explained regarding the first step of substitution, accepting that the pure nucleofuge ethoxy anion becomes better leaving group by protonation. Regarding the cyclization to **4**, second step of the reaction, the acidic catalysis would be explained too, by an increase of the electrophilicity of the carboxylate carbonyl moiety, by protonation, making thus easier the second nucleophilic attack, by the amino group of thioureas.

It is worth noting that *N,N'*-dimethyl- and diphenylthioureas, **5**, did not react with DEMM at room temperature and on stronger reaction conditions gave the corresponding thiobarbituric acids **6**, through the reaction sequence indicated in Scheme-3. These results are in agreement with a two step mechanism, that involves the tetrahedral intermediate formation, (Scheme-1), prior the vinylic substitution, by addition of the nucleophile to the electron deficient double bond, explaining thus the former results from the reactions with the more sterically hindered on the nitrogen, *N,N'*-disubstituted thioureas.

As it was expected the corresponding reactions of *N,N*-dimethyl- and diphenylthioureas gave the *N,N*-disubstituted thioureidomethylenemalonate derivatives **3e**, and **3f**, respectively.



Scheme-3

In conclusion, we have releazed a convenient synthetic approach towards the preparation of some 5-carbethoxy-2-thiouracils, through an one-pot acid mediated cyclocondensation of available diethyl ethoxymethylenemalonate and thioureas, or a two step reaction via the intermediates thioureidomethlenemalonates. The method offers another route to the synthesis of 5-carbethoxy-2-thiouracils, using acid mediated conditions, allowing the separation of the intermediates thioureidomethylenemalonates.

Experimental

General. NMR spectra were recorded at ambient temperature using a Varian Gemini 2000 300 MHz spectrometer. The data are reported as follows: chemical shift are quoted in ppm on the δ scale, multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants are given in (Hz). Micro analyses were performed by microanalytical laboratory of CNRS (France). Melting points are reported uncorrected. IR spectra were obtained at a Nicolet Magna 560 spectrometer, as potassium bromide pellets, and were calibrated against the polystyrene 1600 cm^{-1} band, and given in reciprocal centimeters..

General procedure for the preparation of thioureidomethylenemalonates **3**. In a solution of the proper thiourea **1** 39 mmol in concentrated hydrochloric acid 5 ml, ethanol 15 ml was added. To this solution diethyl ethoxymethylenemalonate 8.43 g, 39 mmol, was added and the new solution was allowed under stirring, at room temperature, for one day for **3b-d**, and four days for **3a**. The resulting solid was collected by filtration, and washed with cold ethanol to give an almost pure sample, ^1H NMR, of the product **3**. After recrystallization from the proper solvent an analytically pure sample of **3** was obtained, in yields 65-93%.

Malonic acid-(thioureidomethylene)-diethyl ester, 3a: yield 67%, mp 163-164 ^{0}C. Anal. Calcd for $C_9H_{14}N_2O_4S$: C, 43.89; H, 5.73; N, 11.38; S, 12.99. Found: C, 43.61; H, 5.50; N, 11.53; S, 13.11. IR: 3510, 3485, 1734, 1635, 1627, 1562. ^{1}H NMR (DMSO-d_6): 1.19-1.26 (m, 6H, two CH_3), 4.12-4.24 (m, 4H, two CH_2), 8.97 (d, J=13.5 Hz, 1H, =CH), 9.07 and 9.19 (two br s, 2H, NH_2), 10.98 (d, J=13.5 Hz, 1H, NH). ^{13}C NMR (DMSO- d_6): 14.06, 14.16, 60.24, 60.54, 99.49, 150.44, 164.38, 166.21, 181.81.

Malonic acid-(methylthioureidomethylene)-diethyl ester, 3b: yield 93%, mp 156-158 ^{0}C. Anal. Calcd for $C_{10}H_{16}N_2O_4S$: C, 46.14; H, 6.20; N, 10.77; S, 12.29. Found: C, 46.23; H, 6.27; N, 10.60; S, 12.08. IR: 3495, 1732, 1631, 1625, 1560 ^{1}H NMR (DMSO- d_6): 1.20-1.27 (m, 6H, two CH_3), 3.02 (d, J=3.5 Hz, 3H, >N-CH_3), 4.11-4.25 (m, 4H, two CH_2), 9.08 (d, J=13.5 Hz, 1H, =CH), 9.93 (br s, 1H, -NHMe), 11.07 (d, J= 13.5 Hz, 1H, NH). ^{13}C NMR (DMSO- d_6): 14.02, 14.12, 31.80, 60.04, 60.34, 98.38, 150.18, 164.35, 166.28, 180.64.

Malonic acid-(ethylthioureidomethylene)-diethyl ester, 3c: yield 69%, mp 122-124 ^{0}C. Anal. Calcd for $C_{11}H_{18}N_2O_4S$: C, 48.16; H, 6.62; N, 10.22; S, 11.66. Found: C, 48.10; H, 6.48; N, 10.45; S, 11.71. IR: 3490, 1734, 1627, 1562 ^{1}H NMR (DMSO- d_6): 1.13-1.27 (m, 9H, three CH_3), 3.50-3.53 (m, 2H, NCH_2Me), 4.10-4.25 (m, 4H, two OCH_2), 9.09 (d, J=13.5 Hz, 1H, =CH), 9.93 (t, J=3.5 Hz, 1H, NHEt), 11.05 (d, J=13.5 Hz, 1H, NH). ^{13}C NMR (DMSO- d_6): 13.10, 14.01, 14.11, 60.02, 60.33, 98.38, 150.25, 164.36, 166.35, 179.46.

Malonic acid-(phenylthioureidomethylene)-diethyl ester, 3d: yield 65%, mp 251-253 ^{0}C. Anal. Calcd for $C_{15}H_{18}N_2O_4S$: C, 55.88; H, 5.63; N, 8.69; S, 9.93. Found: C, 55.61; H, 5.70; N, 8.73; S, 10.12. IR: 3500, 1730, 1631, 1560. ^{1}H NMR (DMSO- d_6): 1.14-1.28 (m, 6H, two CH_3), 4.13-4.28 (m, 4H, two CH_2), 7.20-7.47 (m, 5H, arom.), 9.14 (d, J=13.5 Hz, 1H, =CH), 11.32 (d, J=13.5 Hz, 1H, NH), 11.70 (br s, 1H, NHPh). ^{13}C NMR (DMSO- d_6): 14.05, 14.10, 60.20, 60.54, 123.67, 128.46, 128.77, 129.10, 149.57, 164.16, 166.23, 178.11.

Malonic acid-(*N,N*-dimethylthioureidomethylene)-diethyl ester, 3e: yield 75%, mp 147-148 ^{0}C Anal. Calcd for $C_{11}H_{18}N_2O_4S$: C, 48.16; H, 6.62; N, 10.22; S, 11.66. Found: C, 48.24; H, 6.51; N, 10.31; S, 11.47. IR: 3496, 1737, 1631, 1560 ^{1}H NMR (DMSO- d_6): 1.18-1.27 (m, 6H, two CH_3), 3.14 (s, 6H, -N<Me_2), 4.21-4.30 (m, 4H, two CH_2), 9.12 (d, J=13.5 Hz, 1H, =CH), 10.90 (d, J= 13.5 Hz, 1H, NH). ^{13}C NMR (DMSO- d_6): 14.08, 14.19, 41.04, 60.11, 60.38, 98.35, 150.21, 164.40, 166.31, 181.13.

Malonic acid-(*N,N*-diphenylthioureidomethylene)-diethyl ester, 3f: yield 70%, mp 177-179 ^{0}C Anal. Calcd for $C_{21}H_{22}N_2O_4S$: C, 63.30; H, 5.56; N, 7.03; S, 8.05. Found: C, 63.08; H, 5.31; N, 7.23; S, 8.20. IR: 3485, 1733, 1627, 1558 ^{1}H NMR (DMSO-d_6): 1.15-1.31 (m, 6H, two CH_3), 4.14-4.26 (m, 4H, two CH_2), 7.15-7.51 (m, 10H, arom.), 9.33 (d, J=13.5 Hz, 1H, =CH), 10.65 (d, J=13.5 Hz, 1H, NH). ^{13}C NMR (DMSO- d_6): 14.11, 14.20, 60.27, 60.46, 123.80, 128.46, 128.77, 129.10, 149.10, 164.21, 166.40, 181.58.

Cyclocondensation of thioureidomethylenemalonates **3** to the corresponding 2-thiouracils 4. Method (a): A mixture of thioureidomethylenemalonate **3**, 20 mmol in ethanol 15 ml and concentrated hydrochloric acid 2.5 ml, was refluxed for 1.5-4 h. The resulting solid was filtered off, washed with cold ethanol and dried. After recrystallization from ethanol the analytically pure 2-thouracils **4** were obtained in yields 57-81%.

5-Carbethoxy-2-thiouracil, 4a: yield 57%, mp 252-254 ^{0}C, lit.[18] mp 245 ^{0}C. IR: 3520, 1745, 1670. ^{1}H NMR (DMSO-d_6): 1.26 (t, J=7.8 Hz, 3H, CH_3), 4.17 (q, J=7.8 Hz, 2H, CH_2), 7.96 (s, 1H, C6). ^{13}C NMR (DMSO- d_6):
5-Carbethoxy-3-methyl-2-thiouracil, 4b: yield 64%, mp 204-206 ^{0}C (dec.), lit.[15] mp 205 ^{0}C (dec.). IR: 3485, 1747, 1667. ^{1}H NMR (DMSO-d_6): 1.24 (t, J=7.6 Hz, 3H, CH_3-C), 3.50 (s, 3H, CH_3-N), 4.18 (q, J=7.6 Hz, 2H, CH_2), 7.97 (s, 1H, C6). ^{13}C NMR (DMSO- d_6): 14.01, 33.32, 60.40, 105.66, 145.40, 156.65, 162.24, 176.80.
5-Carbethoxy-3-ethyl-2-thiouracil, 4c: yield 59%, mp 255-257 ^{0}C, lit.[15] mp 257 ^{0}C. IR: 3490, 1745, 1671. ^{1}H NMR (DMSO-d_6): 1.16 and 1.24 (two t, J=7 Hz, 6H, two CH_3), 4.18 and 4.29 (two q, J=7 Hz, s, 4H, two CH_2), 7.94 (s, 1H, C6). ^{13}C NMR (DMSO- d_6): 11.13, 14.10, 41.15, 60.41, 106.03, 145.52, 156.15, 162.24, 176.32.
5-Carbethoxy-3-phenyl-2-thiouracil, 4d: yield 81%, mp 274-276 ^{0}C (dec.), lit.[15] mp 276 ^{0}C (dec.). IR: 3510, 1745, 1665. ^{1}H NMR (DMSO-d_6): 1.24 (t, J=7 Hz, 3H, CH_3), 4.19 (q, J=7 Hz, 2H, CH_2), 7.20-7.51 (m, 5H, arom.), 8.08 (s, 1H, C6). ^{13}C NMR (DMSO- d_6): 14.10, 60.44, 106.72, 128.26, 128.46, 129.13, 139.26, 146.26, 157.00, 162.33, 177.90.
Method (b): To a solution of the appropriate thiourea 39 mmol, in concentrated hydrochloric acid 5 ml, ethanol 15 ml and then DEMM 8.43 g, 39 mmol were added, and the mixture was refluxed for 1.5-4 h. After cooling the formed solid was collected, and washed with ethanol. After recrystallization from ethanol the above referred 2-thiouracils 4 were obtained as analytically pure compounds.
1,3-Disubstituted-2-thiobarbituric acids: Following the method (b), using *N,N'*-dimethyl- or diphenylthiourea and DEMM, under reflux conditions for 4 h, we separated 1,3-dimethyl-2-thiobarbituric acid and 1,3-diphenvl-2-thiobarbituric acid respectively. 1,3-Dimethyl-2-thiobarbituric acid: mp 183-185 ^{0}C, lit.[19] mp 183 ^{0}C. ^{1}H NMR (DMSO-d_6)[20]: 3.59 and 3.76 (two s, 6H, two CH_3), 8.79 (s, 1H, =CH-), 12.80 (br s, 1H, OH enolic). 1,3-Diphenyl-2-thiobarbituric acid: mp 258-259 ^{0}C, lit.[21] mp 258-259 ^{0}C. ^{1}H NMR (DMSO-d_6)[20]: 7.11-7.37 (m, 10H, arom.), 8.84 (s, 1H, =CH-), 13.45 (br s, 1H, OH enolic).

References

1. (a) H. Tanaka, M. Ubasawa, K. Sekiya, I. Nitta, M. Baba, S. Shigeta, R. T. Walker, E. De Clercq, T. Miyasaka, *J. Med. Chem.*, **35**, 337-345 (1992). (b) M. Artico, *Drugs Fut.*, **27**, 159-175 (2002). (c) A. Mai, M. Artico, R. Rango, G. Sbardella, S. Massa, C. Musiu, M. Mura, F. Marturana, A. Cadeddu, G. *Maga*, P. La Colla, *Bioorg. Med. Chem.*, **13**, 2065-2077 (2005). (d) N. G. Kundu, P. Das, J. Bazarini, E. De Clercq, *Bioorg. Med. Chem.*, **5**, 2011-2018 (1997) (e) K. Felczak, A. Drabikowska, J. A. Vilpo, T. Kulikowski, D. Shugar, *J. Med. Chem.*, **39**, 1720-1728 (1996).
2. (a) A. Mai, M. Artico, G. Sbardella, S. Massa, A.-G. Loi, E. Tramontano, P. Scano, P. La Colla, *J. Med. Chem.*, **38**, 3258-3263 (1995). (b) A. Mai, M. Artico, G. Sbardella, S. Quartarone, S. Massa, A.-G. Loi, A. De Montis, F. Scintu, M. Putsolu, P. La Colla, *J. Med. Chem.*, **40**, 1447-1454 (1997). (c) A. Mai, M. Artico, G. Sbardella, S. Massa, E. Novellino, G. Greco, A.-G. Loi, E. Tramontano, M.-E. Marongiu, P. La Colla, *J. Med. Chem.*, **42**, 619-6, 7427 (1999). (d) A. Mai, G. Sbardella, M. Artico, R. Ragno, S. Massa, E. Novellino, G. Greco, A. Lavecchia, C. Musiu, M. La Colla, C. Murgioni, P. La Colla, R. Loddo, *J. Med. Chem.*, 44, 2544-2554 (2001).

3. C. Mugnaini, F. Manetti, J. A. Esté, I. Clotet-Codina, G. Maga, R. Cancio, M. Botta, F. Corelli, *Bioorg. Med. Chem. Lett.*, **16**, 3541-3544 (2006).
4. K. Das, A. D. Clark, P. J. Lewi, J. Heeres, M. R. De Jonge, L. M. H. Koymans, H. M. Vinkers, F. Daeyaert, D. W. Ludovici, M. J. Kukla, B. De Corte, R. W. Kavash, C. Y. Ho, H. Ye, M. A. Lichtenstein, K. Andries, R. Pauwels, M.-P. De Bethume, P. L. Boyer, P. Clark, S. H. Hughes, P. A. J. Janssen, E. J. Arnold, *J. Med. Chem.*, **47**, 2550-2560 (2004).
5. K. Das, P. J. Lewi, S. H. Hughes, E. Arnold, *Prog. Biophys. Mol. Biol.*, **88**, 209-231 (2005).
6. (a) V. Milata, *Aldrichim. Acta*, **34**, 20-27 (2001). (b) K. S. Sardesai, *Bombay Technol.*, **8**, 36-40 (1957/58). *Chem. Abstr.*, **54**, 4378a (1960).
7. (a) S. M. McElvain, K. Rorig, *J. Amer. Chem. Soc.*, **70**, 1820-1826 (1948). (b) M. Freifelder, *J. Amer. Chem. Soc.*, **82**, 2386-2389 (1960).
8. Z. Rappoport, *Adv. Phys. Org. Chem.*, 7, 1-49 (1969).
9. Z. Rappoport, *Recl. Trav. Chim. Pays-Bas*, **104**, 309-349 (1985).
10. J. Kuthan, D. Ilavský, J. Krechl, P. Trška, Collect. *Czech. Chem. Commun.*, 44, 1423-1433 (1979).
11. For reviews, see: (a) Z. Rappoport, *Acc. Chem. Res.*, **14**, 7-15 (1981). (b) G. Modena, *Acc. Chem. Res.*, 4, 73-80 (1971). (c) B. A. Shainyan, *Usp. Khim.*, **55**, 942-973 (1986).
12. (a) H. L. Wheeler, T. B. Johnson, C. O. Johns, *Amer. Chem. J.*, **37**, 392-405 (1907). (b) H. L. Wheeler, C. O. Johns, *Amer. Chem. J.*, **38**, 594-602 (1908).
13. L. Claisen, E. Hasse, *Ann.*, **297**, 75-98 (1897).
14. C. W. Whitehead, *J. Amer. Chem. Soc.*, 74, 4267-4271 (1952).
15. C. W. Whitehead, J. J. Travesco, *J. Amer. Chem. Soc.*, **78**, 5294-5299 (1956).
16. C. C. Price, R. M. Roberts, *J. Amer. Chem. Soc.*, **68**, 1204-1208 (1946).
17. L. Bauer, T. L. Welsh, *J. Org. Chem.*, **141**, 1343-1345 (1961).
18. R. E. Cline, R. M. Fink, K. Fink, *J. Amer. Chem. Soc.*, **81**, 2521-2527 (1959).
19. R. G. Shepherd, *J. Chem. Soc.*, 4410-4419 (1964).
20. These ^{1}H NMR spectra corresponds to the enol forms of thiobarbituric acids.
21. H. Schulte, *Chem. Ber.*, **87**, 820-824 (1954).

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