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A NOVEL ONE-POT SYNTHESIS OF SUBSTITUTED 4-t-BUTYLDIMETHYLSILYLOXY-THIAZOLES

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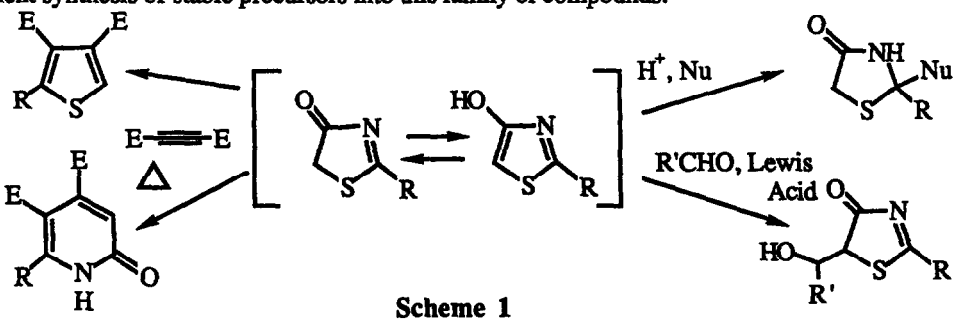
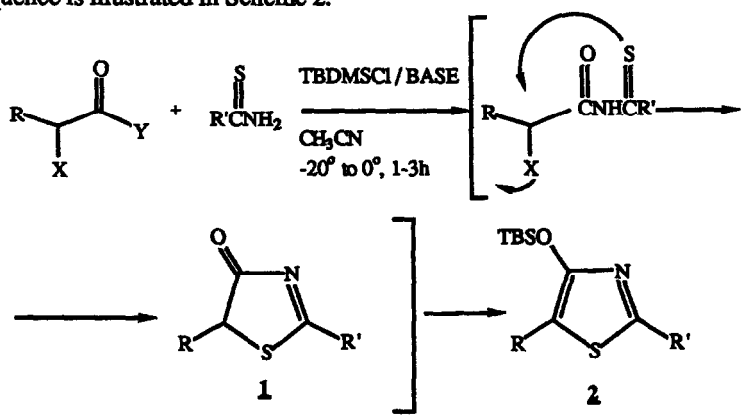
Summary: The reaction of 2-halo-acylimidazolides or halides with primary thioamides in base give 2-halo-N-acylthioamides, which cyclize to the substituted 4-thiazolones and are trapped as the novel 4-t-butyldimethylsilyloxythiazoles in fair to good yield. The 2-aryl-4-t-butyldimethylsilyloxythiazoles undergo a [4+2] cycloaddition reaction with dimethoxyacetylene dicarboxylate [DMAD] to give substituted 2-pyridones in fair yield.

Substituted 4-(5H)-thiazolones[1-4] are a poorly studied class of compounds which offer potentially interesting applications in aldol condensations, as N-acylimine precursors, and as substrates in cycloaddition reactions. [Scheme 1]. Due to the ease with which 4-thiazolones self condense,[3,5] there is a need for a reliable and efficient synthesis of stable precursors into this family of compounds.

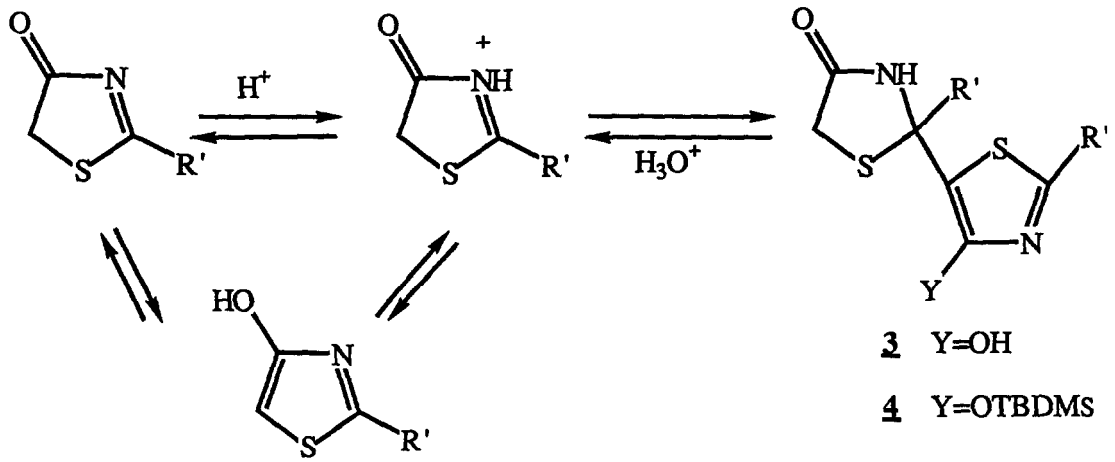


Scheme 1

Herein we describe a simple method for the in situ synthesis of 4-t-butyldimethylsilyloxy (TBDMS) thiazoles. The reaction sequence is illustrated in Scheme 2.



Scheme 2



Scheme 3

A representative procedure for example 2b is described below. To a 100 mL round bottomed flask containing 10 mL of anhydrous acetonitrile was added thiobenzamide (2.74 g, 20 mmol) and triethylamine (3 9 g, 60 mmol). The mixture was cooled to -20 ° and a preformed solution of 2-bromobutyryl imidazole [prepared by adding carbonyldiimidazole (3.40 g, 40 mmole) to 2-bromobutyric acid (6.60 g, 40 mmole) in 10 mL of anhydrous acetonitrile and stirring for 10 minutes at 0 °] was added dropwise to the reaction mixture over several minutes. The reaction mixture was stirred at -20 ° for 30 minutes then t-butyldimethylsilyl chloride (3 65 g, 24 mmole) in 5 ml of acetonitrile was added all at once and the mixture was stirred at 0 ° for 3 hours. The reaction mixture was poured into cold water (100 mL), extracted with with ether (3 x 50 mL). The ether fractions were pooled and backwashed with saturated brine (50 mL). The ether layer was dried over anhydrous potassium carbonate, filtered and the solvent removed under reduced pressure. Bulb to bulb distillation (bp=88-90 °, 0.1mm Hg) gave 4.0g (63% yield) of 2b.

Preliminary experiments show that 2a and 2c undergo cycloaddition reactions with excess dimethylacetylene dicarboxylate (DMAD) at elevated temperatures to give regioselectively substituted 2-pyridones in fair yields.[10] No thiophene derivatives were isolated from the reaction mixture. The 2-alkyl-4-TBDMS-oxythiazoles failed to give any identifiable products. Jacobi[11] reported the first example of a Diels-Alder reaction involving a thiazole ring with an acetylenic dienophile. He found that variants of this reaction are possible by imposing proper geometric constraints on the activated dienophile sidechain. Our experiments show that the 4-TBDMS-oxy substituent attenuates the aromaticity and nucleophilicity of the thiazolone relative to simple thiazoles, consistent with Jacobi's observations [Scheme 4]. In summary, we have described a simple synthesis of the previously unreported class of substituted 4-TBDMS-oxythiazoles. These compounds should find applications in the study of 4-(5H)thiazolones and their derivatives.

Table I lists the isolated yields of the 4-TBDMS-oxythiazoles (2a-2g) and indicates variations in the basic experimental conditions.

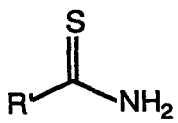
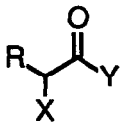
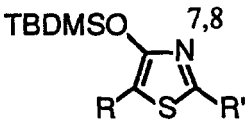
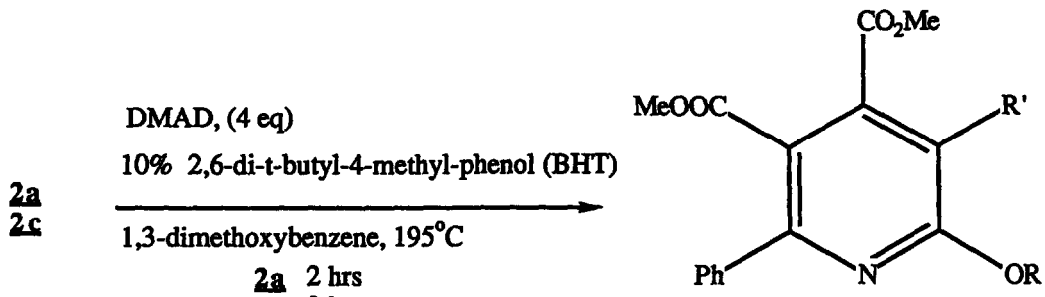
THIOAMIDE 	ACYLATING AGENT (2 eq) 	REACTION CONDITIONS A, B or C [12]	PRODUCT (% YIELD) 
R'=C_6H_5	R=H, X=Cl, Y=Cl	C	2a 43%
R'=C_6H_5	R=H, X=Cl, Y=Cl	B	2a 50%
R'=C_6H_6	R= Et, X=Br, Y=OH	A	2b 63%
R'=C_6H_5	R=C_6H_5, X=Cl, Y=Cl	C	2c 45%
R'=CH_2Ph	R=H, X=Cl, Y=Cl	A	2d 73%
R'=CH_2Ph	R=C_2H_5, X=Br, Y=OH	A	2e 78%
R'=CH_3	R=C_2H_5, X=Br, Y=OH	A	2f 67%
R'=CH_2Ph	R=C_2H_5, X=Cl, Y=OH	A	2g 59%

Table 1

The nature of the acylating agent, whether an acyl halide or acylimidazole, has little effect on the product yield. Excess acylating agent (1.5 to 2 equivalents) is necessary for optimum product yield, presumably due to decomposition of the initial acylating agent prior to reaction. The isolated product yields obtained in this study correspond closely to that obtained by Walter[6] for the synthesis of the respective N-acylthioamides under similar conditions (45-75% yields). This strongly implies that the in situ acylation is the limiting step in improved product yield.

The rate of product formation depends on both starting materials and on the enolizing base. Imidazole works about as well as triethylamine when R or R' is phenyl, presumably due to increased stability of the intermediate enolate. With mono or 2,5-dialkyl substitution, a stronger base like triethylamine is required to appreciably accelerate the reaction rate. Excess base (3 eq) increases the reaction rate and improves product yield while heating the reaction lowers the overall yield. When thiobenzamide and chloroacetyl chloride are reacted together for 18 hours at 25 ^{o} in acetonitrile with three equivalents of triethylamine , a crystalline solid 3 (mp=162-164 ^{o} dec) is obtained which does not correspond to 1a (R=H, R'=Ph) (mp=106-108 ^{o})[3]. This product is readily silylated with TBDMSCl/TEA in methylene chloride to give 4 (mp=197-198 ^{o}). Proton and ^{13}C NMR determined that 3 is the dimeric addition product (60 % yield)[9]. The 4-(5H)-thiazolone 1a adds to the N-acylimine carbon-nitrogen double bond in a polar solvent unless trapped as the enol. Surprisingly, one can take either 3 or 4 (R=H, R'=Ph) in benzene, heat it with a catalytic amount of HCl for 30 minutes and isolate a 60 to 70% yield of 2-phenyl-4(5H)-thiazolone 1a. This is to our knowledge the first reported example of a reversible intermolecular condensation reaction mediated through a stable N-acyliminium ion intermediate [Scheme 3].



Scheme 4

5a R'=H, R=OTBDMS, 73%
5b R'=H, R=OH, 95%
6a R'=Et, R=OTBDMS, 48%
6b R'=Et, R=OH, 95%

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7. All new compounds gave satisfactory elemental analyses and spectral characterizations.
8. ^{1}H-NMR, (δ, TMS standard, $CDCl_3$) (2a) 1H (s), 6.1; 3H (m), 7.4; 2H (m), 7.9: (2b) 3H (t),1.1; 2H (q), 2.0; 3H (m), 7.4; 2H (m) 7.9: (2c) 6H (m), 7.2-7.4; 4H (m), 7.7-7.9: (2d) 2H (s), 4.1; 1H (s), 5.8; 5H (s) 7.25 : (2e) 3H (t), 1.1; 2H (q), 2.55; 1H (s), 4.1; 5H (s), 7.3: (2f) 3H (t), 1.1; 1H (s), 2.45; 2H (q), 2.55: (2g) 3H (t), 1.1; 2H (q), 2.6; 2H (s), 4.1. The TBDMS proton signals are deleted in the table.
9. ^{1}H-^{13}C 2D-NMR correlation studies (HECTOR and COLOC) established the structure of these compounds unequivocally . We wish to thank Mr. Robert Reamer for his assistance in obtaining these spectra
10. ^{1}NMR, (δ, TMS standard, $CDCl_3$) (5a) 6H (s), 0.3; 9H (s), 0.95; 3H (s), 3.7, 3H (s), 3 9; 1H (s), 7.1; 3H(m), 7.35; 2H(m), 7.55: (5b) 3H (s), 4.65; 3H (s), 3.95; 1H (bs), 6.9; 1H (s), 7.3; 5H (m), 7.5. Anal. Cal. for $C_{15}H_{13}NO_5$ C=62.73, H=4.56, N=4.87; Found C=62.58, H=4.48, N=4.70. (6a) 6H (s), 0.3; 9H (s), 0.95; 3H (t), 1.15; 2H (q), 2.6; 3H (s), 3.55; 3H (s), 3.9; 3H (m), 7.35; 2H (m), 7.45: (6b) 3H (t), 1.1; 2H (q), 2.45; 3H (s), 3.5; 3H (s), 3.9; 5H (m), 7.4. Anal. Cal. for $C_{17}H_{17}NO_5$ C=64.77, H=5.43, N=4.44, Found C=64.40 , H 5.47, N=4.41.
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12. A: 3 eq triethylamine, 1.2 eq TBDMSCl, -20° 1 h, then 0° 3h, B: 3 eq imidazole, 1.2 eq TBDMSCl, -20° 1h, then 0° 8h; C: 4 eq imidazole, 1.2 eq TBDMSCl, -20° 1h, then 0° 1h.

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