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Synthesis of a Cumyl Analogue in Nitrothiazole Series and $S_{RN}1$ Reaction at Tertiary Carbon

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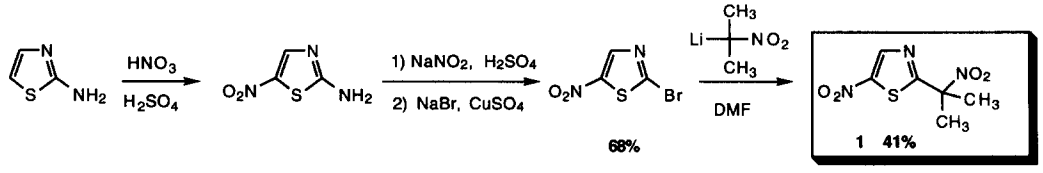
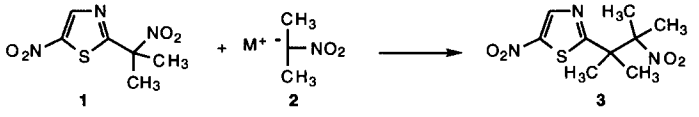
Abstract: A new alkylating agent, 2-(1-methyl-1-nitroethyl)-5-nitrothiazole, bearing a tertiary nitro nucleofuge, reacts with 2-nitropropane anion by $S_{RN}1$ mechanism leading to the C-alkylation product.

Since the initial proposal by Kornblum[1] and Russell[2] of the radical chain mechanism put forward to explain the *C*-alkylation of nitronate anions by *p*-nitrobenzyl chloride and its designation as $S_{RN}1$ by Bunnett,[3] the extensions of that reaction at sp^3 carbons attached to heterocyclic systems have been studied extensively.[4] However, if that reaction at tertiary carbon is well documented in the *p*-nitrocumyl system,[5] there is only one example with a heterocyclic analogue in nitrothiophene series where Norris[6] has reported respectively 41 and 11 % of *C* and *O*-alkylation products. The proportion of *C*-alkylate was lower than that obtained in the *p*-nitrocumyl system described by Kornblum[5b] (85%) reflecting some change in reactivity of the intermediate radical in heterocyclic series. As part of our continuing studies on the $S_{RN}1$ reactions, the pharmacological interest of thiazole ring led us to describe the first $S_{RN}1$ reactions in 5-nitrothiazoles.[7] In connection with mechanistic studies including structure-reactivity-activity, we have synthesized the new alkylating agent 2-(1-methyl-1-nitroethyl)-5-nitrothiazole and explored its reactivity with 2-nitropropane salts **2**.

The nitro compound **1**[8] has been prepared in three steps from the inexpensive and commercially available 2-aminothiazole by nitration, diazotation and Sandmeyer reaction[9] and S_NAr reaction with **2**[6,10] in an appropriate solvent (DMF and not CH_3OH which gives 20% of 2-methoxy-5-nitrothiazole and resins).



The tertiary nitro compound **1** reacts with 2-nitropropane anion **2**$^-$ to give the C-alkylate derivative **3**[8] as indicated in the following scheme. The results of the study of this reaction under different experimental conditions are reported in the Table.



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Influence of experimental conditions in the reaction of **1** and **2**[a].

Entry	M	Solvent	Scavenger	**3** % Yield
1	Li	MeOH	-	54
2	Li	DMF	-	71
3	Li	DMSO	-	62
4	NBu_4	CH_2Cl_2-H_2O[b]	-	47
5	NBu_4	CH_2Cl_2-H_2O[c]	-	31
6	NBu_4	$C_6H_5CH_3$-H_2O[b]	-	38
7	NBu_4	$C_6H_5CH_3$-H_2O[c]	-	29
8	Li	DMF	*p*-$NO_2C_6H_4NO_2$ (1 eq)	9
9	Li	DMF	TEMPO (1 eq)	16
10	Li	DMF	O_2 (bubbling)	36
11	Li	DMF	dark, O_2 (bubbling)	31

[a]All reactions were performed with **1** (100 mg; 0.46 mmol) by using a 2/1 ratio of **2**, under nitrogen and irradiation with two 60 W tungsten lamps during 12 h. [b]Phase-transfer catalysis with NBu_4Br (0.1 eq.). [c]Phase-transfer conditions with NBu_4OH 40% in water.

The best *C*-alkylation product yield is obtained in aprotic solvents (DMF, DMSO) while in methanol or under phase-transfer conditions, the *C*-alkylation product yield decreases. Confirmation of the $S_{RN}1$ nature of the reaction is given by the study in the presence of classical inhibitors.[11] Addition of *p*-dinitrobenzene, TEMPO or bubbling dioxygen through the solution in the dark strongly decrease the yield of **3**. In these reactions, it has not been possible to isolate the tertiary alcohol resulting from the competitive *O*-alkylation process.

In conclusion, this result shows that the $S_{RN}1$ reaction with a new alkylating agent in nitrothiazole series bearing a tertiary nitro nucleofuge gives higher yield in *C*-alkylation comparatively to the thiophenic analogue.

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8. New derivatives were purified by column chromatography and gave convenient elemental analyses. **1**, yellow solid, mp 74-75 °C (cyclohexane), ^1H NMR ($CDCl_3$) δ 2.13 (s, 6H); 8.51 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 26.88 (CH_3, C5, C5'); 88.78 (C, C4); 142.52 (CH, C2); 144.69 (C, C3); 172.17 (C, C1). **3**, yellow solid, mp 91-92 °C (cyclohexane), ^1H NMR ($CDCl_3$) δ 1.63 (s, 6H); 2.12 (s, 6H); 8.37 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 29.63 (CH_3, C7, C7'); 31.93 (CH_3, C5, C5'); 53.48 (C, C4); 74.05 (C, C6); 143.49 (CH, C2); 144.94 (C, C3); 187.11 (C, C1).
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