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Reaction of Thioamides with Zinc Enolate: Synthesis of Vinylogous Carbamates

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Abstract: Eschenmoser sulfur extrusion reaction is failed to produce vinylogous carbamate **II** from N-(*t*-Boc)pyrrolidine-2-thion **I** but, treatment of methyl bromozincacetate with N-(*t*-Boc)pyrrolidine-2-thion **I** afforded good yield of vinylogous carbamate **II**. This thio-Reformatsky reaction appeared to be sensitive to the structure of substrates i.e. ring size or N-protecting groups.

The Eschenmoser coupling reaction[1] represents a versatile and efficient method to prepare vinylogous carbamates by alkylation of thioamides with an appropriate electrophilic component followed by elimination of sulfur. In the course of our efforts to synthesis biologically active pyrrolidine alkaloids, we applied the Eschenmoser reaction to N-(*t*-Boc)pyrrolidine-2-thion **I** but we couldn't obtain corresponding vinylogous carbamate **II** at all probably because of reduced nucleophilicity of thioamide by inductive effect of N-(*t*-Boc). To overcome the situation we decided to investigate the reaction of some organometallic reagents such as organophosphorous ylide or organozinc reagent with N-(*t*-Boc)pyrrolidine-2-thion **I** expecting addition of organometallics to the thiocarbonyl and elimination of sulfur-metal complex affording desired vinylogous carbamate **II**. When we tried thio-Wittig reaction[2] to the N-(*t*-Boc)pyrrolidine-2-thion **I** with methyl (triphenylphosphoranylidene)acetate we could obtain desired vinylogous carbamate **II** with unsatisfactory yield (30%) after 4 days reflux in toluene (Scheme 1). From the literature survey, Ila and Junjappa et al. reported[3] that

Scheme 1

$BrCH_2CO_2Me/CH_3CN/RT/3d$, and $Ph_3P/Et_3N/CH_2Cl_2$, yield=0%
$Ph_3P{=}CHCO_2Me$/Toluene/reflux/4d, yield=30%
$BrCH_2CO_2Me/Zn$/THF/reflux/1h, yield=71%

ethyl bromozincacetate added to thiocarbonyl compounds such as thiocarbonates, dithioesters, and thioketones in carbophilic manner leading to C-C bond forming products followed by extrusion of either alkylthio group or sulfur. But attempted reaction of ethyl bromozincacetate with thioamides was reported unsuccessful. Recently Michael et al. reported[4a] zinc mediated condensation of diethyl bromomalonate with N-arylpyrrolidine-2-thions in the synthesis of tricyclic quinolone antibacterial agents. These reports encouraged us to try organozinc reagent to N-(*t*-Boc)pyrrolidine-2-thion **I** for obtaining corresponding vinylogous carbamate **II** of our interest. Actually treatment of methyl bromozincacetate generated from activated Zn[5] and methyl bromoacetate with N-(*t*-Boc)pyrrolidine-2-thion **I** cleanly produced desired vinylogous carbamate **II** within 1 hour under refluxing THF in 71% yield after chromatography purification (Scheme 1). To examine the scope of present successful reaction, we applied this thio-Reformatsky reaction to various typical substrates under the same condition and the results are summarized in the scheme 2 and 3. The reaction appeared to be sensitive to the structure of substrates i.e. ring size or N-protecting groups. Treatment of N-(*t*-Boc) or N-Cbzpyrrolidine-2-thions with methyl bromozincacetate gave good yields of corresponding vinylogous carbamates but, in case of thio-β-lactam and thio-ε-caprolactam, the yields of corresponding vinylogous carbamates were not so high and we

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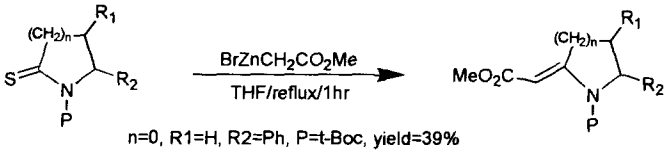
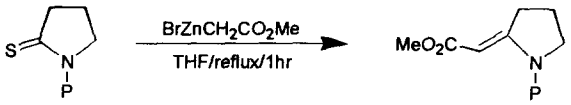
Scheme 2



n=0, R1=H, R2=Ph, P=t-Boc, yield=39%
n=1, R_1=H, R_2=H, P=t-Boc, yield=71%
n=1, R_1=OTBDMS, R_2=benzyl, P=t-Boc, yield=71%
n=1, R_1=OTBDMS, R_2=benzyl, P=Cbz, yield=73%
n=2, R_1=H, R_2=H, P=t-Boc, yield=0%
n=3, R_1=H, R_2=H, P=t-Boc, yield=33%

could not obtain vinylogous carbamates from N-(*t*-Boc)piperidine-2-thion under the same condition. The influence of the N-protecting groups of pyrrolidine-2-thion was also great. Electron withdrawing N-(*t*-Boc) or N-Cbzpyrrolidine-2-thions afforded good yields of corresponding vinylogous carbamates but, unprotected and N-methyl pyrrolidine-2-thion gave no corresponding vinylogous carbamates. In accordance with Michael's report,[4b] N-arylpyrrolidine-2-thions gave good yields of corresponding vinylogous carbamates except N-(4-nitrophenyl)pyrrolidine-2-thion which was inert under the same condition. Acyclic thioamide, N-phenacylmorphorine was also inert toward methyl bromozincacetate under the same condition.

Scheme 3



P=H, yield=0%
P=CH_3, yield=0%[6]
P=t-Boc, yield=71%[7]
P=Ph, yield=65%[6]
P=4-CH_3O-Ph, yield=80%
P=4-NO_2-Ph, yield=0%

In summary, it was found that a Eschenmoser sulfur extrusion reaction is failed to produce vinylogous carbamate **II** from N-(*t*-Boc)pyrrolidine-2-thion **I** but, treatment of methyl bromozincacetate with N-(*t*-Boc)pyrrolidine-2-thion **I** afforded good yield of corresponding vinylogous carbamate **II**. Therefore this thio-Reformatsky reaction could be a good complementary method to Eschenmoser sulfur extrusion reaction for electron deficient thioamides.

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References and Notes

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6. Similar results were reported in ref. 3 (P=CH_3) and ref. 4b (P=Ph).
7. We obtained only one isomer of vinylogous carbamate which was assigned as E isomer by judging from ^1H, ^{13}C NMR, and NOE experiments which showed no increment of intensity of C3 protons when irradiated to vinyl proton. The assignment of E-configuration was also supported by the chemical shifts of the methylene protons at C3 (~3.2 ppm) which fall into the deshielding zone of ester carbonyl group compared to those of Z-configuration (~2.7 ppm) as described in ref. 4b and 4c. ^1H NMR (300MHz, $CDCl_3$) δ 6.46 (t, 1H, *J*=1.73 Hz), 3.67 (t, 2H, *J*=7.22 Hz), 3.66 (s, 3H), 3.18 (td, 2H, *J*=1.76, 7.73 Hz), 1.88 (q, 2H, *J*=7.43 Hz), 1.52 (s, 9H). ^{13}C NMR (75.5MHz, $CDCl_3$) δ 20.83, 28.07, 31.85, 49.68, 50.55, 81.96, 95.45, 151.87, 157.64, 169.31