Tetrahedron Letters No. 48, pp 4671 - 4674.
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0040-4039/79/1122-4671$02.00/0

Reaction of Some Amides and Thioamides with Diazomethane Catalyzed by Silica Gel

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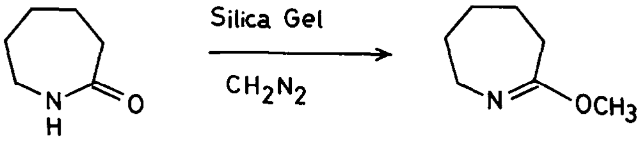
Certain amides and thioamides can easily be methylated with diazomethane in the presence of silica gel.

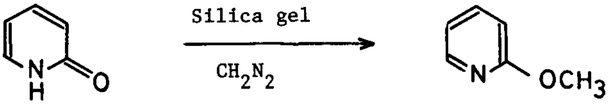
It has been previously shown that alcohols can easily be methylated with diazomethane in the presence of silica gel.$^{1)}$ In the silica gel catalyzed methylation with diazomethane, intermediate formation of methyl diazonium silicate on the surface of silica gel was posturated, while well known HBF_4 catalyzed methylation of amides occurs via intermediate formation of methyldiazonium tetrafluoroborate. $^{2)}$ From considerations of analogous features of these two catalysts was investigated the methylation of certain amides and thioamides with diazomethane catalyzed by silica gel. This note deals with preliminary results of the methylation of certain amides and thioamides with diazomethane in the presence of silica gel.

Caprolactam and valerolactam are known to be sluggishly methylated with diazomethane without catalyst.$^{2)}$ The rate of methylation is highly accelarated in the presence of silica gel. Typical experimental procedure is as follows. To a stirred suspension of caprolactam(91.9 mg), neutral silica gel (2.3g) and $NaHCO_3$ in ether(2.5 ml) was introduced gaseous diazomethane (generated from 5.24g of p-toluenesulfonyl-N-methylnitosoamide and aq. KOH). After 15 min., silica gel was removed by filtration, washed with 3ml of ethyl acetate containing 5% 2-propanol and 1% triethyl amine three times, and the combined solution was evoporated to give methyl caprolactim(87mg, 95%).



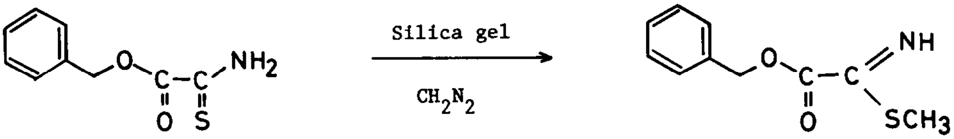
Butyrolactam,which failed to react with diazomethane without catalyst $^{2)}$, also afforded O-methyl butyrolactim in contrast to the selective N-alkylation catalyzed by HBF_4. J.W.Ralls reported that the ethylation of γ-butyrolactam with 2 moles equivalent of diazoethane affords N-ethyl butyrolactam and recovered γ-butyrolactam in 1:15 ratio.$^{2)}$ Selective N-ethylation of γ-butyrolactam has been explained in terms of the strain of five member lactam which decreases the conjugation between nitrogen and oxygen.$^{3)}$ R.Gompper related the site of substitution with the infrared stretching vibration frequency of the carbonyl bond.$^{4)}$ Further, the conversion of amides and thioamides to the corresponding imidates by reactive alkylating agents is also well precedented.[5)] Recently, P.Beak et.al. pointed out that alkylation of protomeric ambident nucleophile by methyl fluorosulfonate provides methylated products in which the methyl group is bonded to the heteroatom remote from the proton in the major tautomer, for cases in which initially formed salts are stable.[6)] From this point of view, N-ethyl butyrolactam described above might arise from subseqent ethylation of initially formed O-ethyl butyrolactim.

Methylation of α-pyridone with methyl fluorosulfonate provides N-methyl-α-pyridone in less than 50% yield.[6)] Reaction of α-pyridone with diazomethane in a mixture of ether and methanol is also known to afford a mixture of N-methyl-α-pyridone and 2-methoxypyridine in 53:39 ratio.[7)] In contrast to these well precedented cases, rather selective O-methylation of α-pyridone with diazomethane occured when silicic acid was used as catalyst.



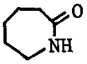
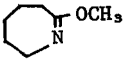
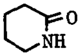
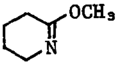
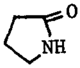
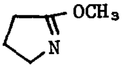
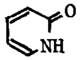
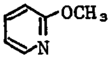
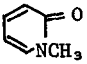
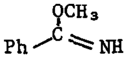
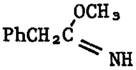
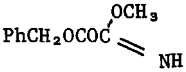
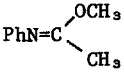
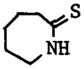
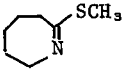
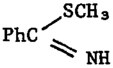
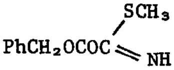
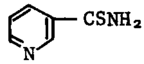
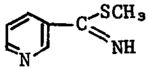
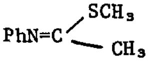
Some acyclic amides such as benzamide, acetanilide, and phenylacetamide can also be methylated with diazomethane in the presence of silica gel, but the rate of methylation of acyclic amides is much slower than that of cyclic amides. The results are summarized in Table 1. The following amides failed to react with diazomethane in the presence of silica gel; $CH_3CONH(CH_2)_5COOCH_3$, $PhCONHCH_2COOCH_3$, $CH_3CONHCH_2COOCH_3$, $PhNHCO(CH_2)_5NHCOCH_3$, $PhCONHCH_3$, $PhCH_2CH(NHCOCH_3)COOCH_3$. Structural features on the reactivity of amides remain to be undetermined.

Besides amides, some thioamides can be more easily methylated with diazomethane in the presence of silica gel than acyclic amides.[8)] Thus, thiocaprolactam and benzyl thiooxamidate were quite easily methylated to afford methyl thiocaprolactim and S-methyl benzyl thiooxamimidate in a high yield respectively. Similarly, thiobenzamide, thioacetanilide and thionicotinamide gave corresponding methyl thioimidates in high yields.



To date various reagents for the alkylation of amides and thioamides have been exploited, but neutral and mild reaction condition of silica gel catalyzed methylation described above will add to a new methodology to the methylation of amides and thioamides, especially having acid or base sensitive moiety in the molecule. Further, selective O-methylation of γ-butyrolactam and α-pyridone would give an additional proof on the reactivity of protomeric ambident nucleophiles.

Table 1 Methylation of Amides and Thioamides with Diazomethane Catalyzed by Silica Gel[a]

Example	Starting Material	Amount of Silica Gel (wt.eq.)	Diazomethane (mol.eq.)	Conversion (%)	Products(yield,%)
1		25	30	100	 (95)[b]
2		20	20	100	 (85)[b]
3		20	20	100	 (89)[b]
4		20	25	100	  (90)[3:2][c]
5	″	20[d]	25	100	″ ″ (90)[95:5][c]
6	$\mathrm{Ph{-}CONH_2}$	30	40	54	 $\mathrm{Ph{-}C(OCH_3){=}NH}$ (83)[b]
7	$\mathrm{PhCH_2CONH_2}$	34	40	33	 $\mathrm{PhCH_2C(OCH_3){=}NH}$ (100)[b]
8	$\mathrm{PhCH_2OCOCONH_2}$	20	45	100	 $\mathrm{PhCH_2OCOC(OCH_3){=}NH}$ (87)[b]
9	$\mathrm{PhNHCOCH_3}$	50	60	34	 $\mathrm{PhN{=}C(OCH_3)CH_3}$ (100)[b]
10		30	20	100	 (94)[b]
11	$\mathrm{PhCSNH_2}$	20	20	100	 $\mathrm{PhC(SCH_3){=}NH}$ (78)[b]
12	$\mathrm{PhCH_2OCOCSNH_2}$	20	52	100	 $\mathrm{PhCH_2OCOC(SCH_3){=}NH}$ (93)[b]
13		20	20	86	 (71)[b]
14	$\mathrm{PhNHCSCH_3}$	20	20	100	 $\mathrm{PhN{=}C(SCH_3)CH_3}$ (98)[b]

a) To the mixture of starting material and silica gel in ether was introduced the diazomethane, generated from N-methyl-N-nitroso-p-toluene-sulfonamide, in the temperature range of 0-10°C. b) Isolated yield. c) Isolated yield of the mixture of O- and N-methylated product. The ratio was calculated from the NMR spectrum.

d) Silicic acid was used in place of neutral silica gel.

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(Received in Japan 23 August 1979)