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NITROKETENE-S,N-ACETALS AS PRECURSORS FOR NITROACETAMIDES AND THE ELUSIVE NITROTHIOACETAMIDES#.

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Abstract: *1-Amino-1-methylthio-2-nitroethenes (2) can be converted in high yields to the Nitroacetamides (3) by Hg^{2+} catalysed hydrolysis and to the Nitrothioacetamides (4) by Na_2S in ethanol-acetic acid.*

We wish to report a facile general method for the synthesis of amides of nitroacetic acid and nitrothioacetic acid. The reaction proceeds at ambient temperature and because of the mildness of the conditions, lends itself to the synthesis of N-nitroacetyl or nitrothioactyl derivatives of aminoacids and peptides without the risk of racemisation or other destructive side reactions.

The conversion of nitroacetic ester to the corresponding amides by reaction with amines needs harsh conditions and leads to only moderate yields.[1,2] The reason for this is the high acidity of nitroacetic ester (pK_a 5.62) leading to salt formation with the amine. Another approach which has been described is the nitration (LDA, -25^{o}, C_3H_7-O-NO_2) of a pre-formed amide;[3] this is hardly a general approach, especially if the amine moiety has racemization-prone chiral centres.

Nitrothioacetamides are even more difficult of access. Conceptually, nitrothioacetamides (4) in which R_1 is H and R_2 is alkyl or aryl could be made by addition of nitromethane to isothiocyanates. Although salts of such compounds are known,[4,5] corresponding nitrothioacetamides themselves do not seem to have been reported. For the nitrothioamides (4) in which R_1, R_2 are not H, the only method reported is the trapping of nitrothioketene by the

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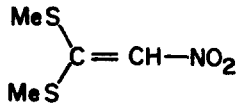
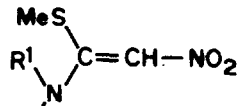


(1)



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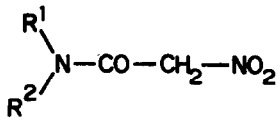
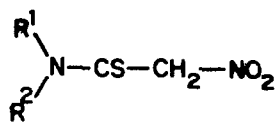


(3)

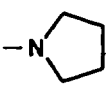


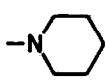
(4)

$-NR_1R_2$

a : $-NHMe$

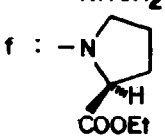
b : $-NMe_2$

c : 

d : 

$-NR_1R_2$

e : $-NHCH_2Ph$

f : 

g : $-NH-CH(CH_3)-Ph$ S(-)

Table

Physical data for the nitroacetamides (3) and nitrothioacetamides (4).

Compounds	M.p	Compound	M.p
3a	75-76	4c	78
3b	79-80	4d	Oil
3c	105-106	4e	88
3d	74-75	4f	oil
3e	87-89		
3f	liquid		
3g	149		

secondary amine.[6] A very recent report records the inaccessibility of nitrothioacetamides by thionation of nitroacetamides - all such attempts have led to destruction of the nitro group, possibly by a redox reaction.[7]

Reaction of 1,1-bismethylthio-2-nitroethene (1)[5] with pyrrolidine (CH_3CN, 30°, one equivalent of the amine) gave 1-methylthio-1-pyrrolidino-2-nitroethene (2c). Hg^{2+}catalysed hydrolysis of this (CH_3CN:H_2O, 3:1, 30°) gave the nitroacetamide (3c), m.p.105-106°; IR(nujol): 2700, 1650, 1570, 1460, 1380cm^{-1}; ^1H NMR ($CDCl_3$): 1.875(m,4H), 3.42(m,4H), 5.125(s,2H). ^{13}C NMR($CDCl_3$): 22.96, 24.71, 45.02, 45.22, 77.00, 158.46.

Treatment of (2c) in ethanol (deoxygenated by flushing with N_2) containing acetic acid (2 equivalents) with dry Na_2S (1.5 equivalent) for 3h at RT under N_2 led to the formation of the nitrothioacetamide (4c) in 68% yield, m.p: 78° IR(nujol): 1560,1500,1460,1260,1200,760 cm^{-1}. ^1H NMR($CDCl_3$): 2.08(m,4H), 3.75(m,4H), 5.48 (s,2H). ^{13}C NMR($CDCl_3$): 23.68, 25.9, 51.13, 54.10, 83.27, 182.3. MS: 174(M^+).

The nitroacetamides (3a-g) and nitrothioacetamides (4b-4f) were obtained similarly in greater than 70% yield.[8] Especially interesting is the reaction of (1) with (L-) ethyl prolinate to give (2f) (70% yield), $[\alpha]_D^{EtOH}$= -58.59°, which on Hg^{2+} catalysed hydrolysis gave the amide (3f) (74% yield) as an oil, $[\alpha]_D^{EtOH}$= -90.97°. ^1H NMR ($CDCl_3$): (<u>trans</u> conformer), 1.27(t, 3H), 1.8 to 2.4(m, 4H), 3.4 to 3.75(m, 2H), 4.19(q, 2H), 4.42 to 4.6 (m, 1H) 5.29(dd, 2H); (<u>cis</u> conformer), 1.31(t, 3H), 1.8 to 2.4(m, 4H), 3.4 to 3.75(m, 2H), 4.12(q, 2H), 4.4 to 4.6(m, 1H), 5.2(dd, 2H). ^{13}C NMR: (<u>trans</u> conformer), 13.73, 24. 29, 28.77, 46.68, 59.20, 61.10, 77.16, 159.55, 170.94. (<u>cis</u> conformer), 20.24, 22.08, 30.64, 46.91, 59.24, 62.02, 77.16, 159.96, 170.64. The compound (2f) on treatment with Na_2S gave the thioamide(4f). $[\alpha]_D^{EtOH}$: -120.20. ^1H NMR ($CDCl_3$): (<u>trans</u> conformer), 1.25(t, 3H), 1.8 to 2.6(m, 4H), 3.65 to 3.9(m, 2H), 4.18(q, 2H), 4.7 to 5.1(m, 1H), 5.53(dd, 2H), (<u>cis</u> conformer), 1.29(t, 3H), 1.8 to 2.6(m, 4H), 3.65 to 3.9(m, 2H), 4.21(q, 2H), 4.7 to 5.1(m, 1H), 5.38(dd, 2H). ^{13}C NMR: (<u>trans</u> conformer), 13.67, 24.63, 28.92, 51.57, 61.19, 65.78, 83.19, 169.12, 184.64, (<u>cis</u> conformer), 20.59, 22.14, 30.92, 54.45, 62.31, 63.30, 83.19, 169.04, 184.85.[9] It is interesting that neither (3) nor (4) exhibits any trace of the enol or ene-thiol tautomer in NMR($CDCl_3$).

The syntheses reported here open up the possibility of utilising the nitroacetyl group as a potential peptide synthon; this would be consequent on the diastereoselective alkylation of the methylene group in substrates such

as (3f), and reduction of nitro to an amino group. It is also conceivable that N-nitrothioacetyl derivatives of suitable aminoacid derivatives can function as precursors for regiospecifically thionated peptides. A future report will focus on these aspects.

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