

N – Methyl thiomethylation and N-Hydroxymethylation of Phthalimide

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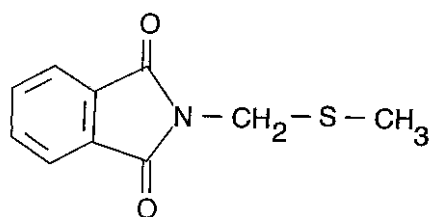
Abstract:

N- Methyl thiomethyl phthalimide (I) a new compound was obtained when phthalimide was refluxed with DMSO acetic anhydride reagent and DMSO alone at 180°C. A different route for the synthesis of N- Hydroxy methylphthalimide (II) with excellent yield has also been explored by this reaction.

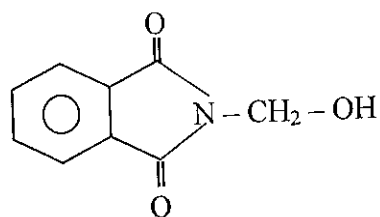
Key Words: DMSO, Acetic anhydride, Phthalimide, Methyl thiomethylation

Introduction:

Dimethylsulphoxide acetic anhydride reagent brings about oxidative cyclisation, dehydrogenation, dehydrocyclisation in different substrates. depending upon the nature of the substrate and reaction conditions ^{1,2}DMSO alone has been employed successfully to bring about methylene insertion and ylide formation in certain substrates at elevated temperatures³⁻⁶. N-substituted phthalimide derivatives have also been frequently synthesized⁷⁻⁸, however an exhaustive survey of literature revealed that phthalimide has never been exposed to DMSO-acetic anhydride reagent or DMSO alone. Since phthalimide contains an acidic hydrogen which can easily protonate the oxygen of DMSO, so it was exposed to DMSO-acetic anhydride reagent and DMSO alone at reflux temperature. Both the reactions afforded N-Methyl-thiomethyl phthalimide and N-Hydroxy methyl phthalimide derivatives (I) & (II).



(I)



(II)

Experimental:

Refluxed 5gms of phthalimide and 25 ml of DMSO for 6 hrs at 180°C. Tlc monitoring indicated formation of two products, cooling and dilution with excess of water afforded a white precipitate with characteristic smell which was filtered and dried, crystallization from methanol resulted a colourless single compound (I), m.p 115°C in high yields freely soluble in chloroform. Filtered and washed with cold water. Both sulphur and nitrogen were found to be present.

The mother-liquor after evaporation of solvent afforded solid residue and crystallization from benzene yielded hexagonal crystals of (II) m.p 140°C in minimal amounts .It is soluble in acetone & DMSO .Only nitrogen was found to be present.

In the second reaction a mixture of DMSO (15ml), acetic anhydride (7½ml) and phthalimide (5gms) was refluxed ($\sim 180^{\circ}\text{C}$) for 9hrs .Tlc monitoring indicated formation of two products .The reaction mixture was cooled, diluted with excess of water and extracted with ether. Washed ether layer several times with water and dried over anhydrous sodium sulphate Removal of solvent and crystallization from benzene afforded (II) m.p 140°C in high yields.

Mother-liquor, after evaporation of the solvent gave an oily residue, which upon crystallization from methanol at low temperature afforded an impure waxy solid. Column chromatography of which over silicagel using pet-ether as eluent resulted (I) m.p 115°C in small amounts.

Results and Discussion

DMSO acetic anhydride reagent being an excellent source of formaldehyde and thiomethanol, so phthalimide was exposed to this versatile reagent under varying conditions.

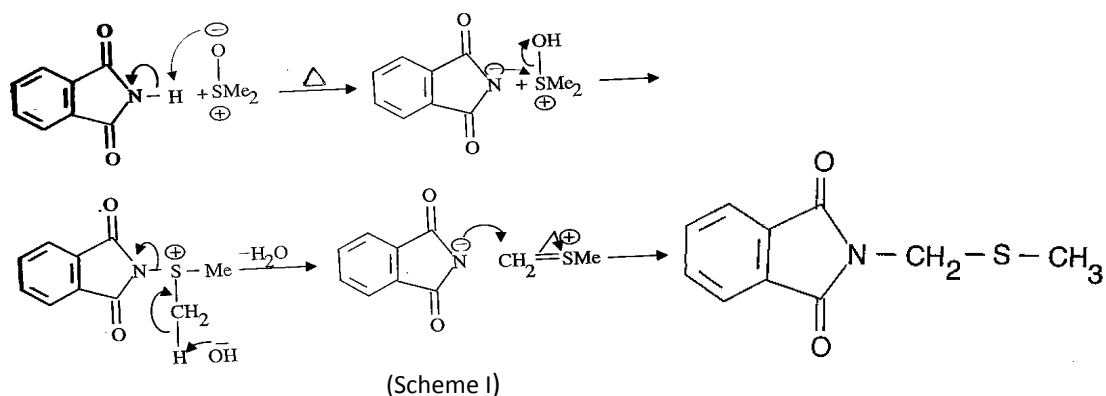
At room temperature it was found to be practically insoluble in DMSO and soluble at water bath temperature. when allowed to stand at 100°C for a pretty long time but no transformation was observed. However, the reaction between phthalimide and DMSO reached completion at reflux temperature in 6 hours and work up of this mixture through addition of water gave a white precipitate which upon crystallization from methanol afforded a pure product in good yield (70%) labeled as (I). The motherliquor crystallized from benzene yielded the second compound in small amounts labeled as (II).

The compound (I) responded positively when tested for the presence of sulphur and nitrogen. On the basis of the mass spectrum showing mol. Ion at m/z 207 and elemental analysis, its molecular formula was found to be $\text{C}_{10}\text{H}_9\text{NO}_2\text{S}$.

The nmr spectrum of this compound shows AA $\overline{\text{BB}}$ pattern for four aromatic protons of a symmetrically orthodisubstituted benzene⁹ in the region of δ 7.72 – 7.89. Apart from these there are two singlets, one at δ 4.75 equivalent to two methylene protons attached to sulphur and nitrogen and other at δ 2.27 equivalent to three protons assigned to S–methyl group.

The ir spectrum of the compound shows a strong and broad band spread over the region of $1620 - 1690 \text{ cm}^{-1}$ which can be attributed to the aromatic carbon – carbon stretching and the carbonyl vibrational bands, the latter usually observed in the region of $1650-1695 \text{ cm}^{-1}$ for amides .Absence of N-H stretching vibrational band in the region of $3400-3520 \text{ cm}^{-1}$ is in favour of the structure.

Formation of (I) as major product in this reaction is understandable as oxygen of DMSO gets protonated at reflux temp., which suffers loss of water and ultimately forms the methyl thiomethyl product. The mechanism proposed for the formation of (I) is given as (Scheme I).



The second compound (II) was found to have nitrogen and devoid of sulphur and carboxylic group on the basis of usual tests.

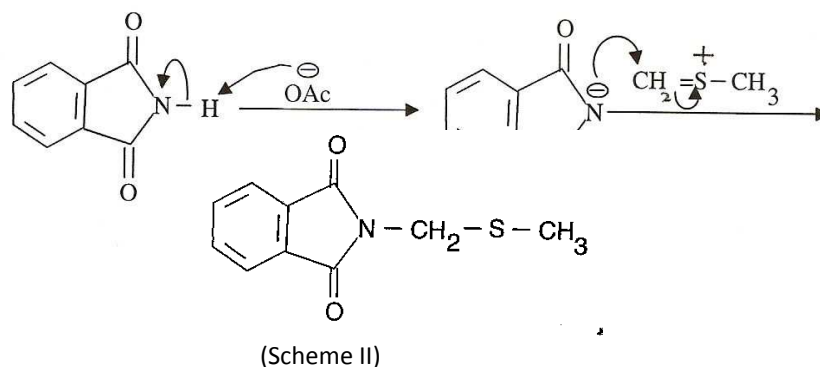
The ir spectrum of this compound shows a hydroxyl band at 3450cm^{-1} and a broad amide carbonyl band centered at 1660cm^{-1} .

The nmr spectrum of the compound showing a doublet ($J=5.5\text{Hz}$) equivalent to two methylene protons centered at $\delta 5.13$, a triplet equivalent to one hydroxyl proton at $\delta 6.18$ and AA BB pattern between $\delta 7.73-7.86$ for four aromatic protons. The mass spectrum of this compound showing mol. Ion at $m/z 177$ was also in full agreement with the structure assigned (I).

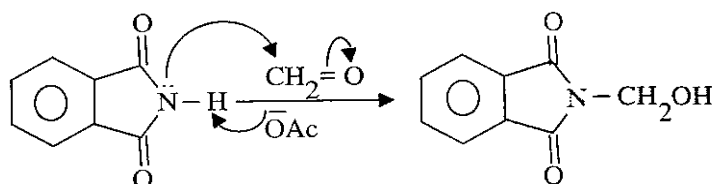
Formation of N-Hydroxy methyl phthalimide (II) in this reaction, that too in small amounts can be rationalized on the basis that some of the $\text{CH}_2=\text{S}-\text{CH}_3$ and water molecules generated during this reaction, react with each other to ultimately yield thiomethanol and formaldehyde. The latter then interacts with phthalimide to give this compound.

The reaction between phthalimide and DMSO-acetic anhydride reagent reached completion in 9hrs at reflux temperature. Workup of the reaction mixture ultimately afforded again the same products but the (I) was in small amount and (II) with a good yield (75%), earlier synthesized from formaldehyde with much less yield¹⁰

Formation of N-methyl thiomethyl phthalimide (I) that too in small amounts can be attributed to the fact that phthalimide must have interacted with some unreacted $\text{CH}_2=\text{S}-\text{CH}_3/\text{OAc}$ as given below Scheme II.



Formation of (II) in this reaction indicates the incorporation of formaldehyde which is one of the products of prolonged interaction between DMSO and acetic anhydride.



Spectral Data

FTIR

ν_{\max} (KBr),
1620 – 1690 (Broad multiplets), 1500 (very weak)
1400, 1350, 1220 – 1260, 950 and 85cm^{-1}

$^1\text{H NMR}$

CDCl_3 300MHZ
7.72 – 7.89 (4H,m,Ar-H), 4.75 (2H,s,N-CH₂-S-protons)
2.27(3H,s, S-CH₃ protons)

Mass. M/z 207 (M^+), 192, 160 (base peak)
104, 76 and 61.

Elemental Analysis.

Found (= 58.29%, H=3.41% and
% N = 6.98%.

Cal. For C =57.97%, H = 4.34%
% N=6.76%

II. ν_{\max} (KBr)

3450 (broadish), 1600-1720 (broad centered at 1660),
1440,1380, 1300cm^{-1}

$^1\text{HNMR}(\delta)$ 7.73-7.86 (4H,m, Ar-H),5.13 (2H,d,(J=5.5Hz), N-CH₂)
 CDCl_3 300 MHz

6.18 (1H,t,CH₂-OH)
Mass m/z 177(M^+), 160, 147 (base peak), 130, 104 & 76

Elemental analysis

Found C=61.63%, H 3.95% and N= 8.01%
Calculated for C= 61.01%, H=3.95% and N=7.90% %

Conclusion

In general it is concluded that DMSO-acetic anhydride or DMSO alone act as good reagents for N-H containing 1,3- diketo compounds . Better results than expected were obtained for both the compounds. Silica gel acts as a convenient adsorbent. Ir bands, ¹H NMR signals and mass peaks were quite significant leading to the final structure determination of the compounds.

Acknowledgement

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