CONVENIENT ROUTE FOR STUDYING REACTIVITY OF ISOTHIOCYANATES TOWARDS BARBITURYL ISOTHIOCARBAMIDE

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The simple protocol for the synthesis of barbituryl isodithiobiurets without any catalyst has been developed. The reactivity of alkyl or aryl isothiocyanates towards barbituryl isothiocarbamide has been studied. The different reactivity, insolubility and high stability are output of our novel synthesized barbituryl isodithiobiurets. The mild reaction conditions, easy product workup and excellent yields, are the major advantages of present protocol.

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INTRODUCTION

A large class of barbiturate drugs which are used as hypnotics, sedatives, anticonvulsants, anesthetics, as central nervous system depressants and also have industrial applications.[1-6] In 1903 Fischer and Von Mering synthesized the first therapeutically active derivative of barbiturates by replacing the C-5 hydrogens of the barbituric acid ring with ethyl substituents, upon administration of this new barbiturate derivative, human subjects fell into a state of hypnosis or deep sleep, this new diethyl barbiturate, commonly called Veronal (Fig. 1a).[7,8]

The barbiturate moiety show a wide spectrum of medicinal activities including treat anxiety, insomnia, seizure disorders, migraine headaches and use in surgery as general anesthetics (Fig 1b).[9] All of the barbiturate derivatives which have been reported to have pronounced hypnotic activity are disubstituted in 5-position. While the 5,5'-dialkyl barbituric acids are the hypnotics most commonly encountered, certain 1,5,5'-trialkyl derivatives (Fig. 1c) are active, producing narcosis of short duration. Some 1,3,5,5'-tetraalkyl derivatives (Fig. 1d) produce a hypnotic action of very transient character. The study of a series of 1,3,5-trialkyl barbituric acids (Fig. 1e), which was undertaken to determine whether such compounds have hypnotic activity comparable to their 1,5,5'-isomers or are inactive like the 5-monoalkyl and 1,5-dialkyl barbituric acids.[10] The synthetic protocol of mono C-alkylation and mono C-benzylation of barbiturate intermediates has been developed.[11]

A variety organic isothiocyanates are good building block moiety used as precursor in many organic transformations.[12-14] Highly electrophilic centre carbon atom of NCS group reacts rapidly, and under mild conditions with oxygen, sulfur or nitrogen centered nucleophiles to give rise to carbamates, thiocarbamides or thiourea derivatives respectively. Organic isothiocyanates have shown excellent and tremendous diverse biological, medicinal, pharmaceutical and other valuable properties such as goitrogenic, anti-bacterial, anti-fungal, anti-protozoal, anti-carcinogenic[15] inhibitory effects upon soil nitrification[16] and bio-conjugate activities.[17-18]

Literature review uncovered that there is no direct C-S coupled barbituric acids. But the β-position of side chain of barbituric acid has been substituted with sulphur using 5-n-amyl-5-(β–bromoethyl)-barbituric acid with potassium ethyl xanthate. The resulting products on pharmacological screening tests indicated that, such compounds are not suitable for anesthetia or hypnosis. [19] The same reaction protocol of the C-S bond formation products at β–position has been extended to include the potassium thiocyanate and isothiouronium salts but did not give products with anticonvulsant action by the electrical method. [20]

Owing to the simplicity of the desired starting material, barbituryl isothiocarbamide (**2**) was prepared by simple reaction of monobromobarbituric acid [21] and thiourea by employing a well-known literature method. [22] In continuation we are reporting first time the synthesis of barbituryl isodithiobiurets by involving the barbituryl isothiocarbamide and alkyl/aryl isothiocyanates, these may prove important intermediate if investigated thoroughly (Scheme 1).

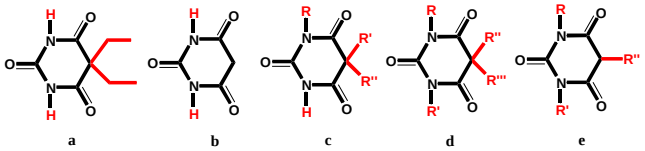
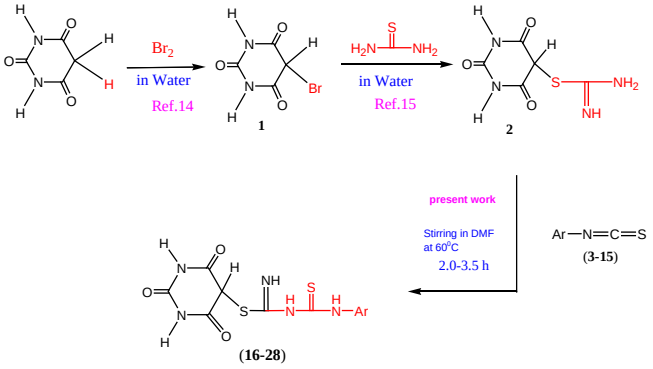


Figure 1. Barbiturates



Scheme 1. Reactivity of alkyl/aryl isothiocyanates with barbituryl isothiocarbamide

EXPERIMENTAL

Synthesis of S-(2,4,6-trioxohexahydropyrimidin-5-yl)-1-(H)-5-aryl-2,4-isodithiobiurets (16-28)

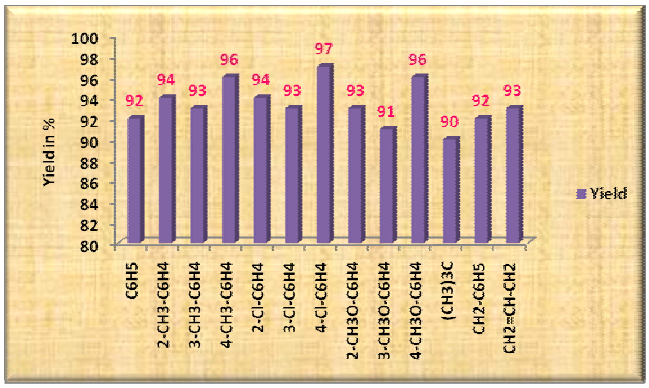
A mixture of 2-(2,4,6-trioxo-hexahydropyrimidin-5-yl) isothiourea (**2**, 2.5 mmol), alkyl/aryl isothiocyanate (**3-15**, 2.5 mmol), was stirred in DMF (20 mL) at 60 ^{0}C for 2.5 h till the consumption of starting material took place to afford a solid products (**16-28**). The progress of reaction was monitored by TLC. After completion of the reaction, crude products were filtered and further purified by recrystallization. The products were desulphurised by alkaline plumbite solution showing positive test of C=S grouping (Table 1 and Graph 1). The newly synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS studies.

Table 1. Synthesis of barbituryl isodithiobiurets via unlike reactivity of isothiocyanates

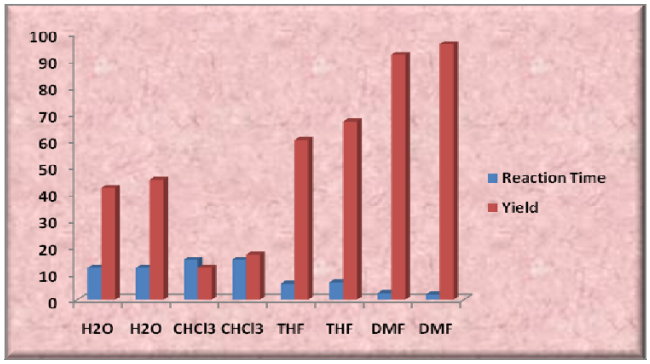
2, mmol	3-15, mmol	Ar	Time, h	16-28	Yield,[a] %
2.5	3 (2.5)	C_6H_5	2.5	16	92
3.9	4 (3.9)	2-CH_3-C_6H_4	2.0	17	94
3.9	5 (3.9)	3-CH_3-C_6H_4	3.0	18	93
3.9	6 (3.9)	4-CH_3-C_6H_4	2.0	19	96
3.9	7 (3.9)	2-Cl-C_6H_4	2.0	20	94
3.9	8 (3.9)	3-Cl-C_6H_4	3.5	21	93
3.9	9 (3.9)	4-Cl-C_6H_4	2.5	22	97
3.9	10 (3.9)	2-$CH_3OC_6H_4$	2.5	23	93
3.9	11 (3.9)	3-$CH_3OC_6H_4$	3.0	24	91
3.9	12 (3.9)	4-$CH_3OC_6H_4$	2.5	25	96
3.9	13 (3.9)	$(CH_3)_3C$	3.5	26	90
4.9	14 (4.9)	CH_2-C_6H_5	3.0	27	92
4.9	15 (4.9)	CH_2=$CHCH_2$	3.5	28	93

[a] isolated yield

We have synthesized thirteen title compounds and characterized them on the basis of spectral analysis like, IR, ^{1}H, ^{13}C NMR and HRMS.



Graph 1. Isolated yields of the prepared compounds



Graph 2. Yield of compound **16** and **19** as the function of reaction time in different solvents

Few of them were insoluble in most of the organic solvents. Title compounds **16**, **18**, **20**, **21** and **25** are soluble only in DMSO and rest of them including **17**, **19**, **22-24** and **26-28** are not soluble in suitable organic solvents, therefore we have provided the spectral data like IR, ^{1}H, ^{13}C NMR and HRMS of these title compounds but for rest of them only IR spectra have been given (Table 2).

RESULTS AND DISCUSION

The starting material barbituryl isothiocarbamide was prepared by the simple substitution reaction of monobromobarbituric acid with thiourea in water medium to produce C-S bond formation products. The nuclophilic addition reaction of barbituryl isothiocarbamide with aryl/alkyl isothiocyanates were carried out in DMF medium at 60 ^{0}C without any catalyst, not as much of required time for completion of reaction to accessible excellent yields.

During initial exploratory nucleophilic addition reaction of barbituryl isothiocarbamide (**2**) and aryl/alkyl isothiocyanates (**3-15**) were investigated to establish the feasibility of our strategy and to optimize the reaction conditions without any catalyst. It is further revealed that, when we have taken same proportion of reactant (**2**), and interacted with variable proportion of reactants (**3** and **6**) using four different solvents, but best result of C-N coupled products (**16** and **19**) were observed in DMF medium at 60 ^{0}C within very short period of time for completion of the reactions (Table 3 and Graph 2).

Table 2. Spectral data of synthesized compounds (**16-28**).

No.	Colour	Mp., °C[a]	IR, cm^{-1}	^{1}H NMR, DMSO-d_6, ppm	^{13}C NMR, DMSO-d_6 ppm	HRMS
16	White	297-300	3331.07, 3138.18, 3062.96 2837.19, 2357.57, 1714.72, 1651.07, 1633.71, 1556.55, 1253.73, 767.67, 694.71.	δ 9.749(s, 2H, NH), 7.483-7.095(s, 5H, Ar-H), 6.006(s, 1H, C-H), 2.020(s, 3H, NH).	δ 185.97, 171.07, 170.04, 152.47, 139.49, 128.45, 121.59, 118.06, 51.30.	Calcd. for $C_{12}H_{11}O_3N_5S_2$ 337.0337. Found: 337.0309.
17	Yellow	296	3332.09, 3074.53, 2951.09, 2357.01, 1712.79, 1693.50, 1681.93, 1556.55, 1263.37, 767.67, 717.52.	ISOS[b]	ISOS[b]	ISOS[b]
18	faint yellow	290	3323.91, 3074.53, 2970.38, 2337.72, 1712.79, 1693.50, 1666.50, 1556.55, 1253.73, 769.60, 731.02.	δ 9.537(s, 2H, NH), 7.340-6.900(s, 4H, Ar-H), 6.750(s, 1H, C-H), 2.075(s, 3H, CH_3), 2.041(s, 3H, NH).	δ 179.91, 173.29, 171.63, 167.36, 157.91, 137.80, 135.77, 136.85, 127.83, 125.70, 123.72, 53.44, 20.48.	Calcd. for $C_{13}H_{13}O_3N_5S_2$ 351.0460. Found: 351.0419.
19	yellow	310	3331.07, 3138.18, 3076.46, 2949.16, 2357.01, 1712.79, 1651.07, 1556.55, 1251.80, 812.03, 769.60.	ISOS[b]	ISOS[b]	ISOS[b]
20	faint yellow	265	3329.14, 3161.33, 3120.82, 3084.18, 2339.65, 1712.79, 1693.50, 1666.50, 1556.55, 1255.66, 765.74, 729.09.	δ 10.283(s, 2H, NH), 8.825-7.223(m, 4H, Ar-H), 6.605(s, 1H, C-H), 2.070(s, 3H, NH).	δ 181.12, 171.08, 170.18, 162.52, 152.78, 137.03, 136.16, 132.03, 128.18, 125.81, 122.15, 52.98.	Calcd. for $C_{12}H_{10}ClO_3N_5S_2$ 370.9914(Cl^{35}); 372.9884(Cl^{37}). Found: 370.9801(Cl^{35}); 372.9908(Cl^{37}).
21	cream	292	3331.07, 3159.40, 3045.60, 2339.65, 1714.72, 1693.50, 1681.93, 1556.55, 1253.73, 769.60, 729.09.	δ 10.282(s, 2H, NH), 8.247-7.252(m, 4H, Ar-H), 6.875(s, 1H, C-H), 1.225(s, 3H, NH).	δ 182.27, 170.74, 170.11, 166.27, 152.35, 140.89, 133.27, 130.08, 121.55, 117.74, 116.61, 51.11.	Calcd. for $C_{12}H_{10}ClO_3N_5S_2$ 370.9914(Cl^{35}); 372.9884(Cl^{37}). Found: 370.9901(Cl^{35}); 372.9808(Cl^{37}).
22	dirty cream	312	3323.35, 3147.83, 3047.53, 2339.65, 1714.72, 1693.50, 1681.93, 1556.55, 1255.66, 767.67.	ISOS[b]	ISOS[b]	ISOS[b]
23	dark yellow	275	3329.14, 3076.46, 2947.23, 2358.94, 1712.79, 1693.50, 1651.07, 1537.27, 1253.73, 767.50, 731.02.	ISOS[b]	ISOS[b]	ISOS[b]

Cont. of Table 2.

24	faint yellow	305	3329.14, 3076.46, 2947.23, 2358.94, 1712.79, 1693.50, 1651.07, 1556.55, 1253.73, 767.50, 731.02.	ISOS[b]	ISOS[b]	ISOS[b]
25	light cream	311	3331.07, 3138.18, 3074.53, 2949.16, 2337.72, 1712.79, 1693.50, 1666.50, 1556.55, 1251.80, 827.46, 769.60	δ 9.4094(s, 2H, NH), 7.2128-7.1945(d, 2H, J= 7.3Hz, Ar-H), 6.8265-6.8090(d, 2H, J= 7.0Hz, Ar-H), 6.5743(s, 1H, C-H), 3.7119(s, 3H, $ArOCH_3$), 2.080(s, 3H, NH).	δ 182.22, 170.92, 170.20, 166.28, 154.27, 149.74, 132.85, 127.35, 119.82, 113.78, 55.04, 49.49.	Calcd. for $C_{13}H_{13}O_4N_5S_2$ 367.0409. Found: 367.0397
26	pink	307	3331.07, 3074.53, 2951.09, 2358.94, 1714.72, 1693.50, 1651.07, 1556.55, 1255.66, 769.50.	ISOS[b]	ISOS[b]	ISOS[b]
27	dark yellow	269	3331.07, 3074.53, 2951.09, 2843.07, 2339.65, 1714.72, 1693.50, 1651.07, 1556.55, 1255.66, 767.67, 729.09.	ISOS[b]	ISOS[b]	ISOS[b]
28	dirty cream	302	3329.14, 3138.18, 2949.16, 2841.15, 2339.65, 1712.79, 1554.68, 1253.73, 910.60, 769.60.	ISOS[b]	ISOS[b]	ISOS[b]

[a]Compounds decomposed at particular temperature; [b] ^1H, ^{13}C NMR and HRMs data not given due to insolubility of compounds in organic solvents. (ISOS- Insolubility in Organic Solvents)

Table 3. Optimization of reaction conditions.

Entry	2 mmol	3 or 6 mmol	Products	Solvent	Reaction Time, h	Yield, %
1	39	3 (39)	16	H_2O	12	42[a]
2	39	6 (58)	19	H_2O	12	45[a]
3	39	3 (39)	16	$CHCl_3$	15	12[a]
4	39	6 (78)	19	$CHCl_3$	15	17[a]
5	39	3 (39)	16	THF	6	60[a]
6	39	6 (48)	19	THF	6.5	67[a]
7	39	3 (39)	16	DMF	2.5	92[b]
8	39	6 (39)	19	DMF	2.0	96[b]

[a] Reaction under reflux; [b]Reaction under stirring at 60 ^0C

For optimization, we have taken same fraction of reactant (2), and interacted with inconsistent quantity of reactants (**3** and **6**) using various solvents like chloroform, tetrahydrofuran and DMF to yield products respectively in 42-45 %, 12-17 %, 60-67 % and 92-96 % amounts. It was further clear that, the polarity of solvents was playing majorrole in reaction but polarity of solvent is not directly proportional to reactivity of reactants because though water

is more polar than THF, yields and requisite time for completion of reactions were unlike. Therefore it has been further cleared that, the polarity of solvent has no role to play for completion of reactions.

CONCLUSION

The synthesis of barbituryl isodithiobiurets presents real challenge for C-N bond formation due to the simple nucleophilic addition of alkyl/ aryl isothiocyanates, stirring in DMF at 60 ^{0}C. Therefore, we believe that present protocol for the synthesis of selective and structurally diverse C-N bond formation in DMF medium without any catalyst as a very efficient, simple, high yielding methodology to yield products with high melting points and high stability.

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