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A High-yielding and Facile Preparation of *N*-substituted Thioureas by Substitution of Nitrosothioureas with Alkylamines

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Abstract:
High yields of *N*-mono- or di- alkyl substituted thioureas are readily achieved by the reaction of nitrosothioureas with alkylamines in acetonitrile at room temperature.

Keywords: N-nitroso compounds; thioureas; substitution

There is a rapidly growing interest in *N*-nitrosoamide chemistry because of the findings that certain *N*-nitroso compounds can act as potent anticarcinogens[1] and that nitric oxide (NO) has been demonstrated to play a variety of key roles in biological transformations.[2,3] Among all kinds of nitrosoamides, the chemistry and biochemistry of nitrosoureas has been most widely investigated.[4] In contrast, studies on the structurally similar nitrosothioureas, which also show potential antitumor properties and may even have less toxic side effects,[5-8] are far less advanced because of their instability, making preparation or property investigation difficult.[5,9-11] In our recent research on the NO transfer properties of nitrosothioureas[12] and of related compounds,[13,14] we found that nitrosothioureas reacted very easily with alkylamines resulting in high yields of substituted thioureas. There is no precedent for synthetic procedures of this kind in the literature. Because thioureas have been found to have many applications as insecticides, preservatives, rodenticides, and pharmaceuticals,[15] we believe that the new synthetic approach in the present work may be of value for providing a very facile and high-yielding preparation for this important category of compounds. Furthermore, since this preparation is nucleophile-mediated with *N*-nitrosothiourea as the electrophile, it may provide much-needed information regarding the

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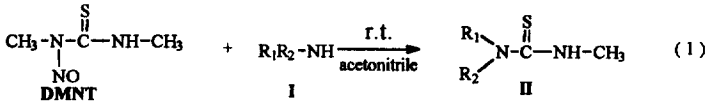
bio-transformations of the N-NO containing systems such as nitrosothioureas *in vivo*.

The reactions of two nitrosothioureas, *N*-nitroso-1,3-dimethylthiourea (DMNT) and *N*-nitroso-trimethylthiourea (TMNT), with a series of alkylamines are shown in eqs 1 and 2, respectively. The product information is listed in Tables 1 and 2, respectively.



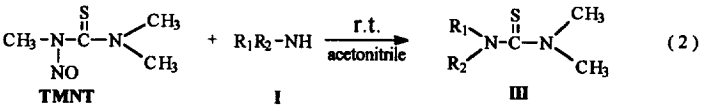
DMNT I II (1)

Ia: R_1 =Me, R_2 =H Ie: R_1 = cyclohexyl, R_2 =H IIi: R_1 = R_2 = *n*-Pr
Ib: R_1 =Et, R_2 =H If: R_1 = benzyl, R_2 =H IIj: R_1 = R_2 = *i*-Pr
Ic: R_1 = *n*-Pr, R_2 =H Ig: R_1 = *i*-Pr, R_2 =H IIk: R_1 = R_2 = *n*-Bu
Id: R_1 = R_2 =Me Ih: R_1 = R_2 =Et

Table 1 The isolated yields of II in the reactions of DMNT with amines[a].

Products	Reaction time (hrs.)	Yields (%)	m.p.(℃) obs.	m.p.(℃) lit.
IIa	4	96	62.5-63.5	62[16]
IIb	6	97	oil	oil[b]
IIc	8.5	96	77.5-78.5	77.5-78.5[16]
IId	4	95	87-87.5	87-88[16]
IIe	7	96	161.5-162.5	162-163[18]
IIf	10.5	93	70-71	70-71[19]
IIg	10	95	98.5-99.5	98-100[20]
IIh	5.5	97	27-28.5	25-28[21]
IIi	8	95	oil	oil[c]
IIj	12	93	74-75	—[d]
IIk	10	95	oil	oil[c]

[a] Reactions were carried out in MeCN at room temperature. [b]The IR of **IIb** was confirmed by ref. 17. [c]The IR and ^{1}HNMR of oils were confirmed by comparison with the samples which were prepared by standard methods.[22] The data are given in note 23. [d]The m.p. of **IIj** cannot be found in literature, but its IR was attained from Sadtler Standard Infrared Grating Spectra.



TMNT I III (2)

Ia: R_1=Me, R_2=H Ic: R_1= *n*-Pr, R_2=H
Ib: R_1=Et, R_2=H Id: R_1=R_2=Me

Table 2 The isolated yields of III in the reactions of TMNT with amines[a].

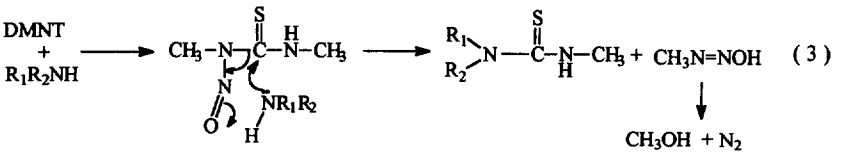
Products	Reaction time (hrs.)	Yields (%)	m.p.(℃) obs.	m.p.(℃) lit.
IIIa	7	96	87.5-88.5	87-88[16]
IIIb	20	94	oil	oil[b]
IIIc	20	91	oil	oil[b]
IIId	20	65	78-79	78-79[16]

[a] Reactions were carried out in MeCN at room temperature. [b]The IR and ^{1}HNMR of oils were confirmed by comparison with the samples which were prepared by standard methods.[22] The data are given in note 23.

The starting reagents DMNT and TMNT were prepared using Lown's method.[5] Then, DMNT(or TMNT, 0.3 mmol) and alkylamine (**I**, 1 mmol) were mixed in 20 ml of acetonitrile,

stirred at room temperature, and periodically monitored by TLC. When the reaction was complete, the mixture was evaporated and the residue was purified by chromatography (for oily products) or by recrystallization (for solid products) to afford the corresponding *N*-substituted thioureas (**II**, **III**).

Bolvin[24] reported a similar preparation of *N*-substituted ureas from nitrosomethylureas (i.e., the analogs of nitrosothioureas as in the present work), where the amines were believed to react with the decomposition products of nitrosoureas (i.e., isocyanates), rather than with nitrosoureas themselves. Nitrosoamides are known to be relatively unstable and so are the analogous nitrosothioureas which can also decompose to generate isothiocyanates,[9] whose reactions with alkylamines were found to give *N*-alkyl substituted thioureas as well. However, in our experiment, even after stirring at 30℃ for a prolonged period (24 hrs.), no detectable decomposition of DMNT could be detected by UV in acetonitrile. In addition, we found that the products from the reactions of TMNT with alkylamines were *N*-alkyl-*N'*,*N'*-dimethylthioureas, but not *N*-alkyl-*N'*-methylthioureas. Therefore, we propose that the reaction of nitrosothiourea with alkylamine may have proceeded *via* a direct nucleophilic substitution as shown in eq 3 rather than *via* an indirect reaction of isothiocyanate following decomposition of the starting nitrosothiourea in aqueous media.



(3)

The most striking feature one can see from the data in Tables 1and 2 is that the product yields for most reactions were nearly quantitative (>95%), indicating the high efficiency of this preparative method. It is realized, however, that compounds such as DMNT and TMNT in which the NO-bearing nitrogen is attached to a unsaturated double bond possess two electrophilic centers, i.e., the thiocarbonyl carbon and the NO-carrying nitrogen. If the N-NO bond is relatively strong, as in the present case[12] and in the nitrosourea case,[13] nucleophilic attack will occur mostly at the thiocarbonyl carbon, resulting in an intermediate which is believed to be responsible for their anti-cancer activities.[25,26] On the other hand, if the N-NO bond is relatively weak, as in the *N*-nitrososulfonamide cases, the reaction will choose the denitrosation pathway with the aid of nucleophilic attack at the NO-bearing nitrogen.[27-30] We propose here that, in addition to the high bond energies of the N-NO bonds in *N*-nitrosothiourea compounds, the matching of the softness of the thiocarbonyl carbon with the attacking amines may also help, resulting in the cleanness and high yields of the current preparation. Therefore, it is obvious that the method reported here is a

good substitute for preparation of substituted thioureas especially unsymmetrical species.

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References and Notes

[1] Loeppky R.N.; Michejda C.J. *Nitrosamines and Related N-Nitroso Compounds*. American Chemical Society: Washington, D. C., **1994**.
[2] Moncada S.; Palmer R.M.J.; Higgs E.A. *Pharmacol. Rev.* **1991**, *43*, 109-142.
[3] Itoh T.; Nagata K.; Matsuya Y.; Miyazaki M.; Ohsawa A. *Tetrahedron Lett.* **1997**, *38*, 5017-5020.
[4] Gnewuch C.T.; Sosnovsky G. *Chem. Rev.* **1997**, *97*, 829-1013 and references therein.
[5] Lown J.W.; Chauhan S.M.S. *J. Org. Chem.* **1983**, *48*, 507-512.
[6] Johnston T.P.; McCaleb G.S.; Montgomery J.A. *J. Med. Chem.* **1963**, *6*, 669-681.
[7] Lown J.W.; Chauhan S.M.S. *J. Chem. Soc., Chem. Comm.* **1981**, 675-676.
[8] Horakava K.; Drobnica L.; Nemeci P.; *Neoplama* **1971**, *18*, 355.
[9] Lown J.W.; Chauhan S.M.S. *J. Org. Chem.* **1983**, *48*,3901-3908.
[10] Isobe M. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 601-602.
[11] Isobe M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2844-2848.
[12] Xian M.; Cheng J.-P. Unpublished results of this laboratory.
[13] Cheng J.-P.; Xian M.; Wang K.; Zhu X.Q.; Ying Z.; Wang P.G. *J. Am. Chem. Soc.* **1998**, *120*, 10266-10267.
[14] Zhu X.; Xian M.; Wang K.; Lu Y.; Cheng J.-P. *J. Org. Chem.* Submitted.
[15] Schroeder D.C. *Chem. Rev.* **1955**, 181-228 and references therein.
[16] Schmidt E.; Striewsky W.; Hilzler F. *Ann.* **1948**, *560*, 222-231.
[17] Mido Y.; Mizuno H. *Spectrochim. Acta, Part A.* **1988**, *44A*, 445-447.
[18] Jeusen K.A.; Nielsen P.H. *Acta. Chem. Scand.* **1966**, *20*, 597-629.
[19] Okawata T.; Nakayama K.; Furukawa M. *Chem. Pharm. Bull.* **1983**, *31*, 507-512.
[20] Papesch V.; Schroeder E.F. *U.S. 2,615,020, Oct. 21*, **1952**.
[21] Kostir J.V.; Loukota L.; Vejdelek Z. *Chem. Listy.* **1946**, *40*, 281-282.
[22] Moore M.L.; Crossley P.S. *Organic Synthesis.* Coll. Vol. II. Edited by Hornig EC, John Wiley. New York. **1962**, 599, 617.
[23] Compound **IIi**: IR (KBr, cm^{-1}): 3320, 3000, 1550, 1370, 1275, 1135, 1075. ^1H NMR (90MHz, $CDCl_3$): δ0.9-1.1(t,J=7.1Hz,6H), δ1.4-1.6(m,4H), δ3.2(d,J=3.8Hz,3H), δ3.4-3.6(t,J=7.9Hz,4H), δ5.6(br,NH); **IIk**: IR (KBr, cm^{-1}): 3300, 2915, 1525, 1346, 1290, 1220, 1115, 1045. ^1H NMR (90MHz, $CDCl_3$): δ0.8-1.0(t,J=7.0Hz,6H), δ1.2-1.3(m,4H), δ1.5-1.7(m,4H), δ3.1(d,J=3.6Hz,3H), δ3.5-3.6(t,J=7.8Hz,4H), δ5.4(br,NH); **IIIb**: IR (KBr, cm^{-1}): 3420, 3030, 1535, 1360, 1330, 1285, 1170, 1105, 1065. ^1H NMR (90MHz,$CDCl_3$): δ1.1-1.3(t,J=7.2Hz,3H), δ3.2(s,6H), δ3.6-3.8(m,2H), δ5.8(br,NH); **IIIc**: IR(KBr,cm^{-1}): 3400, 3040, 1550, 1380, 1270, 1187, 1136, 1085. ^1H NMR (90MHz, $CDCl_3$): δ0.9-1.1(t,J=7.2Hz,3H), δ1.6-1.8(m,2H), δ3.3(s,6H), δ3.5-3.7(m,2H), δ5.4(br,NH).
[24] Bolvin J.L.; Bolvin P.A. *Can. J. Chem.* **1951**, 478-481.
[25] Pratt W.B.; Ruddon R.W.; Ensminger W.D.; Maybaum J. *The Anticancer Drugs*, Oxford University Press, New York, **1994**.
[26] Prestayko A.W.; Crook S.T.; Baker L.H.; Carter S.K.; Schein P.S. *Nitrosoureas: Current status and new developments*, Academic Press, New York, **1981**.
[27] Leis J.R.; Rios A. *J. Chem. Soc., Perkin Trans. 2* **1996**, 857-863.
[28] Leis J.R.; Pena M.E.; Rios A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 587-593.
[29] Garcia-Rio L.; Lglesias E.; Leis J.R.; Pena, M.E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 29-37.
[30] Shirlene M.N.; Williams, D.L.H. *J. Chem. Soc. Perkin Trans 2* **1989**, 755-758.