

Marty C. Wilkes

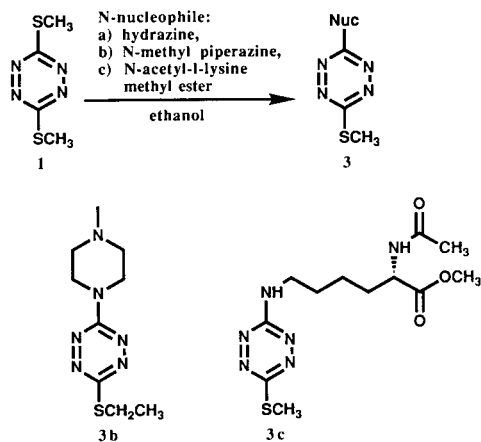
Monsanto Agricultural Co., A Unit of Monsanto Company,
St. Louis, Missouri 63198
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A new type of "azaphilic addition" reaction of methyl lithium to 3,6-bisalkylthio-1,2,4,5-tetrazines has been discovered. Methyl lithium adds at the tetrazine nitrogen of **1** affording **4** while nitrogen nucleophiles displace tetrazine alkylthio groups at carbon affording **3**. The structures of the *N*-alkyl products were determined by ¹H- and ¹³C-nmr and uv experiments. Reversing the order of methyl lithium addition caused the formation of a bicyclic tetrazine **6**. Grignard reagents add in the same fashion as methyl lithium.

J. Heterocyclic Chem., **28**, 1163 (1991).

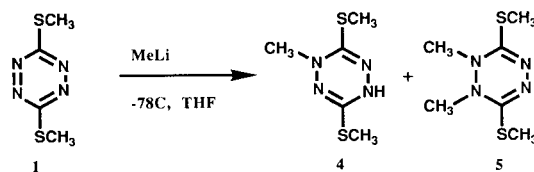
Nucleophilic substitution on carbon atoms has been studied extensively and nucleophilic reaction types are readily classified. In contrast nucleophilic additions of alkyl groups *via* organometallic reagents to heterocyclic nitrogen atoms are rarely observed [1] and poorly understood. This communication describes a remarkable dichotomy in location of addition of nitrogen nucleophiles in comparison with methyl lithium to 3,6-bisalkylthio-1,2,4,5-tetrazines [2]. Nitrogen nucleophiles displace tetrazine alkylthio groups at carbon whereas methyl lithium adds at nitrogen.

Initially, 3,6-bisalkylthio-1,2,4,5-tetrazines such as **1** [3,7,8] were treated with a series of nucleophiles to produce the corresponding monoalkylthiotetrazines substituted at the tetrazine carbon [9]. This reaction worked particularly well for amine nucleophiles such as hydrazine [10,11], *N*-methylpiperazine, and *N*-acetyl-L-lysine methyl ester which yielded the expected unsymmetrical derivatives **3**.



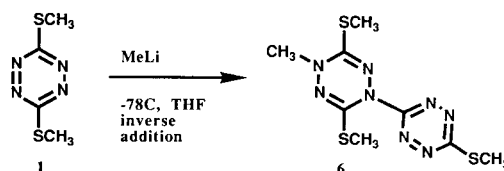
Changing to the harder nucleophile methyl lithium, displacement of the methylthio group at the tetrazine carbon was expected as before with the amine nucleophiles. Surprisingly, adding a THF solution of **1** to methyl lithium at -78° gave **4** and a small amount of **5** [12]. This "azaphilic addition" [13] reaction is novel for tetrazines; however re-

lated additions have been reported for 1,2,3-benzotriazines [1] and azodicarboxylates [14]. In contrast to the addition of methylmagnesium iodide to 4-methylthio-1,2,3-benzotriazine, no ring cleavage was observed in the tetrazine case.

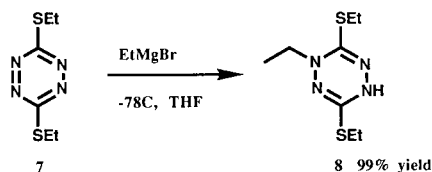


To determine the regiochemistry of the product **4** several experiments were conducted. When irradiating the *N*-H proton of **4** no NOE of the *N*-CH₃ or *S*-CH₃ peaks were observed. Uncoupled ¹³C-nmr spectra of **4** showed the *N*-CH₃ to be a sharp quartet while C(3) was a distorted heptet and C(6) was a quartet. The uv spectra in methanol for **4** displayed one major peak at 227 nm and a minor shoulder at 280 nm. Thus the *N*-CH₃ is located *para* to the NH in the nonconjugated dihydrotetrazine **4**. For **5**, the uv spectra in methanol exhibited two peaks at 239 nm and 294 nm indicating that the conjugated dihydrotetrazine structure with *ortho* *N*-CH₃ groups is formed in the above reaction.

Confirmation of the nucleophilic addition dichotomy was then observed by merely reversing the order of addition of **1** to methyl lithium. Adding methyl lithium slowly to **1** afforded **6** [15]. The formation of **6** demonstrates both nitrogen and carbon modes of addition to the tetrazine ring in stepwise fashion.



The "azaphilic addition" reaction of alkyl lithium reagents with tetrazines was extended to Grignard reagents [16] shown by the preparation of **8** as shown.



In summary, a new type of "azaphilic addition" reaction of 3,6-bisalkylthio-1,2,4,5-tetrazines with organometallic reagents has been discovered displaying a dichotomy of nucleophilic addition locations depending on the nucleophile and conditions employed. Further consideration of this interesting reaction and possible mechanistic explanations are in progress.

Compounds **3-8** are supported by satisfactory elemental analyses.

Acknowledgement.

I appreciate synthetic details provided by Dale Boger and I am also grateful for a sample of **1** provided by Eugene Le Goff.

REFERENCES AND NOTES

- [1] R. C. Storr, *J. Chem. Soc., Chem. Commun.*, 1344 (1983).
- [2] Theoretical and practical interest in tetrazine chemistry is increasing. For example, molecular orbital calculations have predicted the reactivity of tetrazines in inverse electron demand Diels-Alder reactions [3]. In the bioactivity arena certain tetrazine derivatives exhibit antimalarial [4], herbicidal [5], and acaricidal [6] activity. The title compounds may serve as bright color indicators for titrations of certain organometallic reagents.
- [3] R. Gleiter, V. Schehlmann and J. Spanget-Larsen, *J. Org. Chem.*, **53**, 5756 (1988).
- [4] L. M. Werbel, D. J. McNamara, N. Colbry, J. L. Johnson, M. J. Degnan and B. Whitney, *J. Heterocyclic Chem.*, **16**, 881 (1979).
- [5] K. G. Pilgrim and R. D. Skiles, US Patent 3,860,589 (1975).
- [6] J. H. Parsons, EP 005912 A1 (1979).
- [7] D. L. Boger and S. M. Sakya, *J. Org. Chem.*, **53**, 1415 (1988).
- [8] J. L. Johnson, B. Whitney and L. M. Werbel, *J. Heterocyclic Chem.*, **17**, 501 (1980).

[9] A. R. Katritzky, ed, *Advances in Heterocyclic Chemistry*, Vol **4**, 1965, pp 305-306.

[10] A. Mangia, F. Bortesi and U. Amendola, *J. Heterocyclic Chem.*, **14**, 587 (1977).

[11] During the reaction of **1** with hydrazine a previously unreported reduction of **1** to the corresponding dihydrotetrazine occurred as a side reaction.

[12] Preparation of **4** and **5**: To 25 ml of dry THF cooled to -78° was added (23 ml, 11.5 mmoles) 0.50 M methyl lithium in ether. A solution of (2.00 g, 11.5 mmoles) **1** in 50 ml of dry THF was then added dropwise over 30 minutes and stirred an additional 15 minutes turning the solution from red to yellow. The reaction was quenched by adding aqueous ammonium chloride solution and the products were extracted with ethyl acetate. The ethyl acetate layer was then extracted with 1 N hydrochloric acid. The acid extract was adjusted to pH-9 with 10% aqueous sodium hydroxide and then extracted with ethyl acetate and concentrated to afford 0.05 g of **5**, 2% yield; $^1\text{H-nmr}$ (deuteriochloroform): δ 2.78 (s, 6H, 2NCH₃), 2.39 (s, 6H, 2SCH₃); $^{13}\text{C-nmr}$ (deuteriochloroform): δ 158.2 (s, C3, C6), 38.4 (s, 2NCH₃), 13.5 (s, 2SCH₃). The above pH-9 aqueous layer was then adjusted to pH-10 and again extracted with ethyl acetate. After concentration of the ethyl acetate layer the product was recrystallized from chloroform/hexane to afford 0.27 g of **4**, 12% yield (mp 89-92°). Repeating the reaction with 2 equivalents of methyl lithium gave 1.84 g of **4**, 84% yield; $^1\text{H-nmr}$ (deuteriochloroform): δ 7.05 (brs, 1H), 3.06 (s, 3H, NCH₃), 2.38 (s, 3H, SCH₃), 2.34 (s, 3H, SCH₃); $^{13}\text{C-nmr}$ (deuteriochloroform): δ 154.3 (s, C3), 150.7 (s, C6), 39.3 (s, NCH₃), 14.6 (s, SCH₃), 14.4 (s, SCH₃).

[13] The term "azaphilicity" was previously coined to signify S_N2 reactions of nucleophiles on nitrogen. S. Oae and F. Yamamoto, *Tetrahedron Letters*, 5143 (1973).

[14] J. P. Demers and D. H. Klaubert, *Tetrahedron Letters*, **28**, 4933 (1987).

[15] Preparation of **6**: To a solution of (2.00 g, 11.5 mmoles) of **1** in 25 ml of dry THF cooled to -78° was added dropwise (23.0 ml, 11.5 mmoles) 0.5 M methyl lithium in ether turning the solution deep red. The mixture was allowed to warm up slowly to room temperature and stirred overnight. The crude product was applied to a pad of silica gel eluting with 5% ethyl acetate/hexanes to remove the starting material followed by 15% ethyl acetate/hexanes to elute the purple product which was recrystallized from dichloromethane/hexanes to afford 0.30 g of **6**, 16% yield (mp 137-138°); $^1\text{H-nmr}$ (deuteriochloroform): δ 3.27 (s, 3H, NCH₃), 2.71 (s, 3H, SCH₃), 2.61 (s, 3H, SCH₃), 2.51 (s, 3H, SCH₃); $^{13}\text{C-nmr}$ (deuteriochloroform): δ 170.3 (s), 161.5 (s), 157.1 (s), 143.8 (s), 39.3 (s, NCH₃), 16.0 (s, SCH₃), 14.9 (s, SCH₃), 13.6 (s, SCH₃).

[16] Quinone imines add Grignard reagents to the imine nitrogen; J. Brachi and A. Rieker, *Synthesis*, 708 (1977).