Tetrahedron Letters, Vol. 33, No. 24, pp. 3449-3452, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Synthesis of Pyrimidines from 2-Trichloromethyl-4-dimethylamino-1,3-diaza-1,3-butadienes and Electron Deficient Acetylenes[1]

Angel Guzmán, Moisés Romero, and Francisco X. Talamás

Syntex, S.A. de C.V., División de Investigación
Apartado Postal 10-820, México 10, D.F., México

Joseph M. Muchowski*

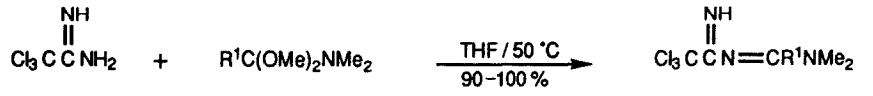
Syntex Research, Institute of Organic Chemistry
3401 Hillview Avenue, Palo Alto, CA 94304

Abstract: 2-Trichloromethyl-4-dimethylamino-1,3-diaza-1,3-butadienes(3), prepared from trichloroacetamidine(1) and amide acetals **2**, readily react with electron deficient acetylenes **4** to give 2-trichloromethylpyrimidines **5**.

The synthesis and reactions of 1,3-diaza-1,3-butadienes have been studied in considerable detail during the past two decades.[2] The overwhelming majority of these dienes are of little value with regard to the generation of pyrimidines by [4π + 2π] cycloaddition because the 1-substituent is such that aromatization of the cycloadduct is impossible. Sundaram, et al.[3] have recently reported that 1-methoxycarbonyl-2-methylthio-4-dimethylamino-1,3-diaza-1,3-butadiene readily reacts with dimethylacetylene dicarboxylate to produce dimethyl 2-methylthiopyrimidine-4,5-dicarboxylate via a dihydro intermediate which aromatizes by the formal loss of the elements of trimethyl carbamate. This prompts us to report our simplest and most useful solution to the above-mentioned aromatization problem.

1,3-Diaza-1,3-butadienes unsubstituted at position 1 have not been described, although they have been proposed as reaction intermediates in at least one instance.[4] We have found that compounds of this type can be efficiently prepared by heating a THF solution (50°C, 2-3 h) of trichloroactetamidine (**1**, Scheme 1) with a 10 mole % excess of the amide acetals **2a-c**.[5] These relatively stable diazadienes **3a-c**[6,7] undergo a facile reaction with the electron deficient acetylenes **4** to give pyrimidine derivatives **5** in fair to excellent yields (see Table). The trichloromethyl group in **5** is quite reactive, and these compounds are congeners of various other pyrimidines. Thus, catalytic hydrogenation (1 atm, excess Et_3N) of the dimethyl ester **5a** (Scheme 2) could be controlled to provide selectively the dichloro and monochloro compounds **6** and **7**, or to produce exclusively the completely dechlorinated product **8**. Reaction of **5a** with methanolic sodium methoxide (1 equiv, r.t.) took place to give the methoxy compound **9** by loss of trichloromethide. In contrast, **5a** reacted with sodium ethanethiolate or sodium thiophenolate (3 equiv) in the presence of an excess of the thiol (3 equiv, THF, r.t.) to produce the sulfides **10a** or **10b** exclusively in high yields. Raney nickel desulfurization of **10a** gave the methyl compound **8** identical to that obtained by complete reductive dehalogenation of **5a**. The formation of the sulfides **10a** and **10b** is efficient only in the presence

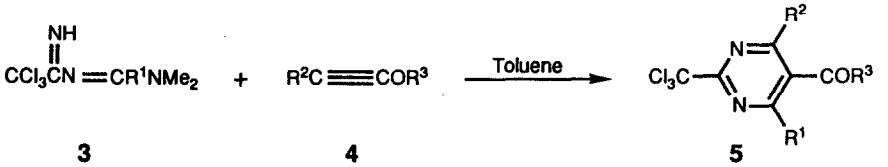
of the thiol and probably occurs, at least in part, by a process involving single electron transfer. Finally, it should be noted that **6**, **7**, **9**, **10a** and **10b** are obvious potential precursors of yet other pyrimidine derivatives and that the above reactions are characteristic of all the trichloro compounds **5** and are not restricted merely to **5a**.



1 **2** **3a**, R^1 = H; **3b**, R^1 = Me; **3c**, R^1 = Ph

Scheme 1

Table. Reaction of 1,3-Diaza-1,3-dienes with Electron Deficient Acetylenes[a,b]



3 **4** **5**

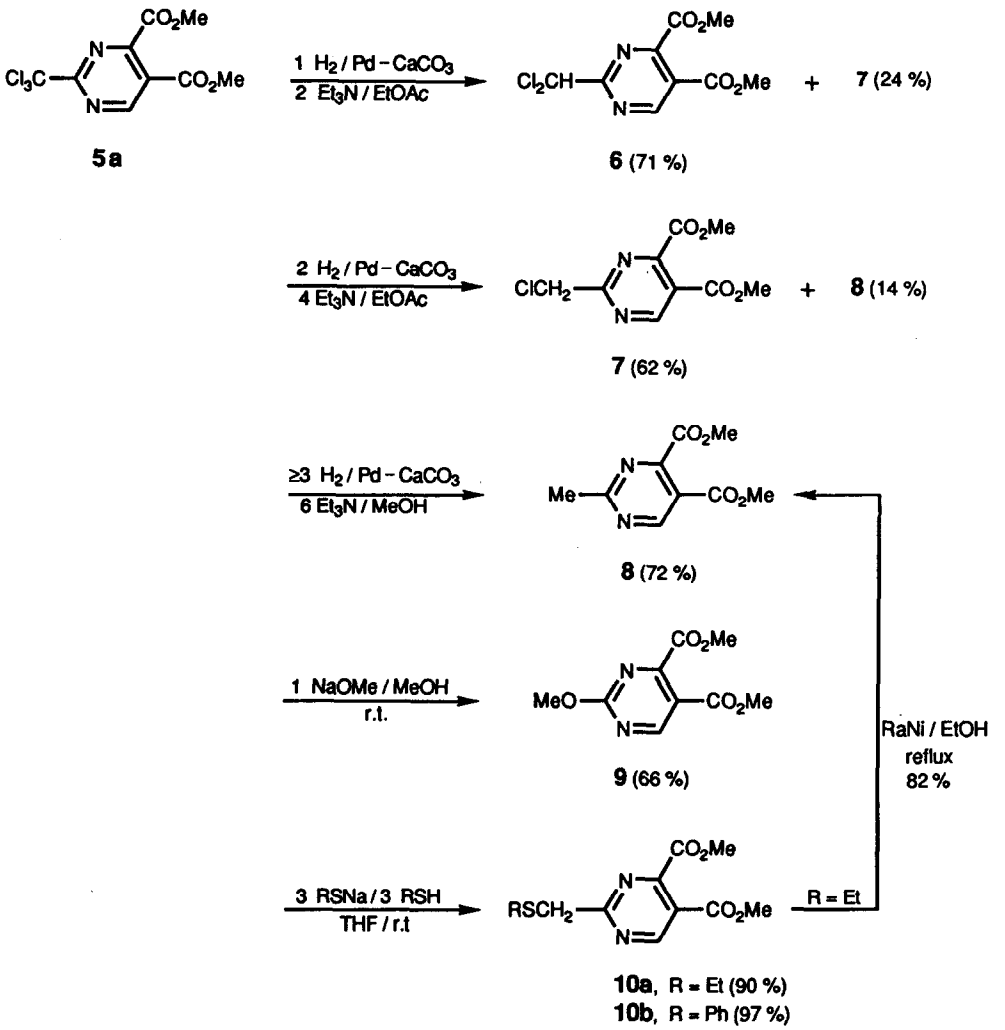
R^1	R^2	R^3	temp (°C)	time (h)	% yield	mp (°C)
H	CO_2Me	OMe	r.t.	0.25	98	65-66
H	H	OEt	70	2	75	67-68
H	Ph	OMe[c]	101[d]	30	51	68-69
H	H	H[c]	r.t.	0.5	66	75-76
Me	CO_2Me	OMe	r.t.	0.25	76	67-69
Me	H	OEt	80	1	65	oil
Ph	CO_2Me	OMe	r.t.	0.5	73	111-112
Ph	H	OEt	101[d]	3	56	oil
Ph	Ph	OMe	101[d]	24	38	165-166
Ph	H	H	r.t.	0.5	43	99-100

[a] 4 Moles acetylene/mole **3** unless indicated otherwise.

[b] The dimethylamine-acetylene adduct is also formed in all cases.

[c] 2 Moles acetylene/mole **3**.

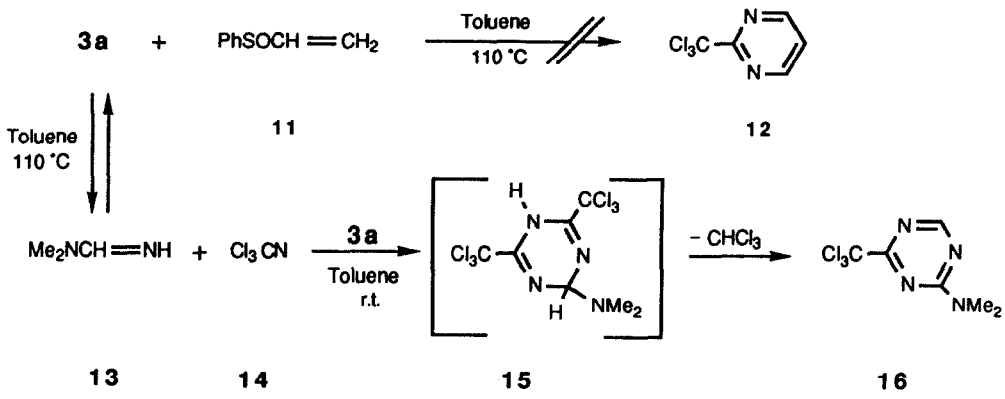
[d] Reflux temperature in Mexico City.



Scheme 2

An attempt to effect the cycloaddition of **3a** with phenyl vinyl sulfoxide (**11**[5]; toluene, 101°C; Scheme 3) illustrates one of the properties characteristic of all of the 1-unsubstituted-1,3-diaza-1,3-dienes that we have studied. None of the expected pyrimidine **12** was formed; the only product isolated (20% yield) was the triazine **16**. This compound arises by fragmentation of **3a** to N,N-dimethylformamidine (**13**) and trichloroacetonitrile (**14**, slow), rapid cycloaddition of the latter with **3a**, and subsequent 1,5-hydrogen shift and loss of the elements of chloroform from the cycloadduct **15**. Both the fragmentation and the cycloaddition processes have literature precendent.[4] As expected, **3a** undergoes cycloaddition with trichloroacetonitrile at room temperature, giving the triazine **16** in over 80% yield.

The full details of this study will be described elsewhere in due course.



Scheme 3

Acknowledgement

We thank Professor L. E. Overman, U.C. Irvine, for helpful discussions of several aspects of this study.

References and Notes

1. Contribution no. 849 from the Syntex Institute of Organic Chemistry.
2. Boger, D.C.; Weinreb, S.M. *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press: San Diego, **1987**; pp. 272-274. For other leading references, see also: Sain, B.; Singh, S.A.; Sandhu, J.S. Tetrahedron Lett., **1991**, *32*, 5151; Mazumdar, S.M.; Mahajan, M.P. Tetrahedron Lett., **1991**, *47*, 1473; Barluenga, J.; Tomás, M.; Ballesteros, A.; López, L.A. Tetrahedron Lett., **1989**, *30*, 4573; Luthardt, P.; Würthwein, E-U. Tetrahedron Lett., **1988**, *29*, 921; Cook, S.; Sykes, P. J.C.S. Perkin Trans. 1, **1977**, 1791.
3. Ibnasud, I.; Malar, E.J.P.; Sundaram, N. Tetrahedron Lett., **1990**, *31*, 7357.
4. Burger, K.; Penninger, S. Synthesis, **1978**, 524.
5. **2a** and **2b** are commercially available. For the synthesis of **2c**, see: Hanessian, S.; Moralioglu, E. Can. J. Chem., **1972**, ***50***, 233.
6. All new compounds were characterized by the usual spectroscopic techniques and had satisfactory elemental analyses.
7. Compound **3a**: oil; IR($CHCl_3$) 3438(m), 3316(s), 3003(s), 1634(s), 1587(s), 833(m) cm^{-1}; ^1H NMR($CDCl_3$) δ 3.06 (s, 3H), 3.08 (s, 3H), 8.21 (bs, 1H), 8.30 (s, 1H); ^{13}C NMR($CDCl_3$) δ 35.43, 41.36, 97.62, 157.93, 168.74.
8. Paquette, L.A., Carr, R.V.C. Org. Syn., **1985**, *64*, 157.

(Received in USA 4 March 1992)