2nd International Electronic Conference on Synthetic Organic Chemistry (ECSOC-2), http://www.mdpi.org/ecsoc/, September 1-30, 1998

[a0009]

A General Approach to the Synthesis of 4,7-Disubstituted Cephams

Anatoly D. Shutalev

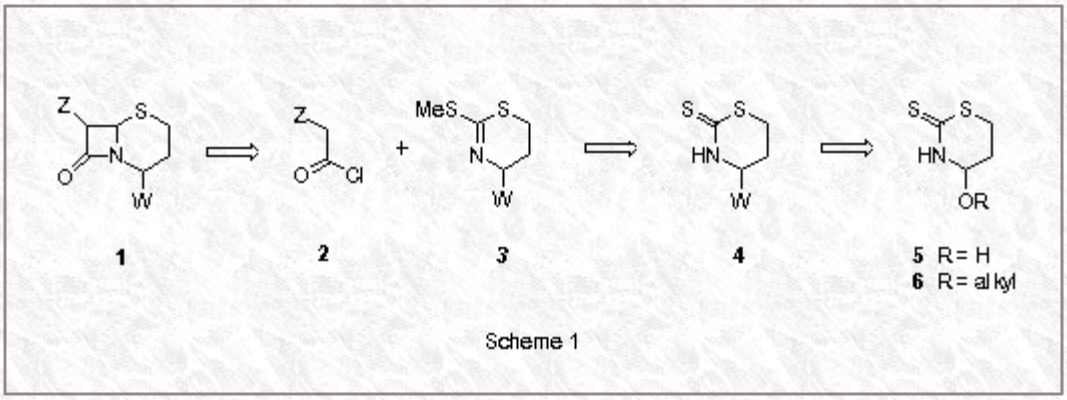
Department of Organic Chemistry, State Academy of Fine Chemical Technology, Vernadsky Avenue 86, Moscow 117571, Russia. Tel./Fax (095) 431-6332.

Abstract: A general approach to the synthesis of 4,7-disubstituted cephams is described starting from a,b-unsaturated aldehydes or ketones *via* 4-functionally substituted tetrahydro-1,3-thiazine-2-thiones.

Keywords: a,b-Unsaturated aldehydes or ketones, dithiocarbamic acid, 4-hydroxy- and 4-alkoxytetrahydro-1,3-thiazine-2-thiones, 4-functionally substituted tetrahydro-1,3-thiazine-2-thiones, 4-alkoxy-2-methylthio-5,6-dihydro-4H-1,3-thiazines, 4,7-disubstituted cephams.

Introduction

b-Lactam antibiotics are continuously of great interest owing to their antibacterial activity. Synthesis of new more effective and selective antibiotics is an important goal of the therapy of infectious diseases. In continuation of our studies on hydrogenated nitrogen containing heterocycles with two heteroatoms [1] we interested in synthesis of novel cephams bearing at the 4 position not only carboxylic group as in classical antibiotics but also other functional groups. The Scheme 1 outlines our retrosynthetic plan for the preparation of the cephams.



Scheme 1

Thus the synthesis includes the following principal steps:

- preparation of 4-hydroxy- **5** or 4-alkoxytetrahydro-1,3-thiazine-2-thiones **6**.
- synthesis of 4-functionally substituted tetrahydro-1,3-thiazine-2-thiones **4**.
- synthesis of 4-functionally substituted 2-methylthio-5,6-dihydro-4H-1,3-thiazines **3**.
- transformation of **3** into the target cephams **1**.

In the present communication we report some results of the investigation.

Results and Discussion

Synthesis of 4-hydroxy- and 4-alkoxytetrahydro-1,3-thiazine-2-thiones

Earlier it was shown that 4-hydroxytetrahydro-1,3-thiazine-2-thiones **5** could be prepared by addition of dithiocarbamic acids to a,b-unsaturated aldehydes or ketones in water or aqueous ethanol [2]. However, yields of the desired thiazines were rather low and usually did not exceed 30 %. Moreover formation of various by-products in these syntheses also complicated isolation and purification of the target compounds. Nevertheless the above method of construction of thiazine ring is very convenient and we decided to improve it. We proposed that this goal could be achieved by *in situ* transformation of the 4-hydroxythiazines **5** into more stable and crystalline 4-alkoxy derivatives **6**.

Thus 4-alkoxytetrahydro-1,3-thiazine-2-thiones **6** were synthesized by reaction of dithiocarbamic acid with a,b-unsaturated aldehydes or ketones **7** in alcoholic solutions in the presence of HCl (Scheme 2). We found that the treatment of the unsaturated aldehydes or ketones **7a-e** and ammonium dithiocarbamate **8** in methanol with conc. HCl (1.2-1.5 equiv.) followed by refluxing of the reaction mixtures for 1-2 h gave the 4-methoxytetrahydro-1,3-thiazine-2-thiones **6a-e** in 31-75 % yields (Table 1). Similarly the 4-ethoxythiazines **6f,g** were prepared from **7a,b** and **8** in ethanolic solution in 53-54 % yields. It should be noted that the 4,6-disubstituted thiazines **6b,d,g** are obtained as a single *trans*-diastereomer in each case.

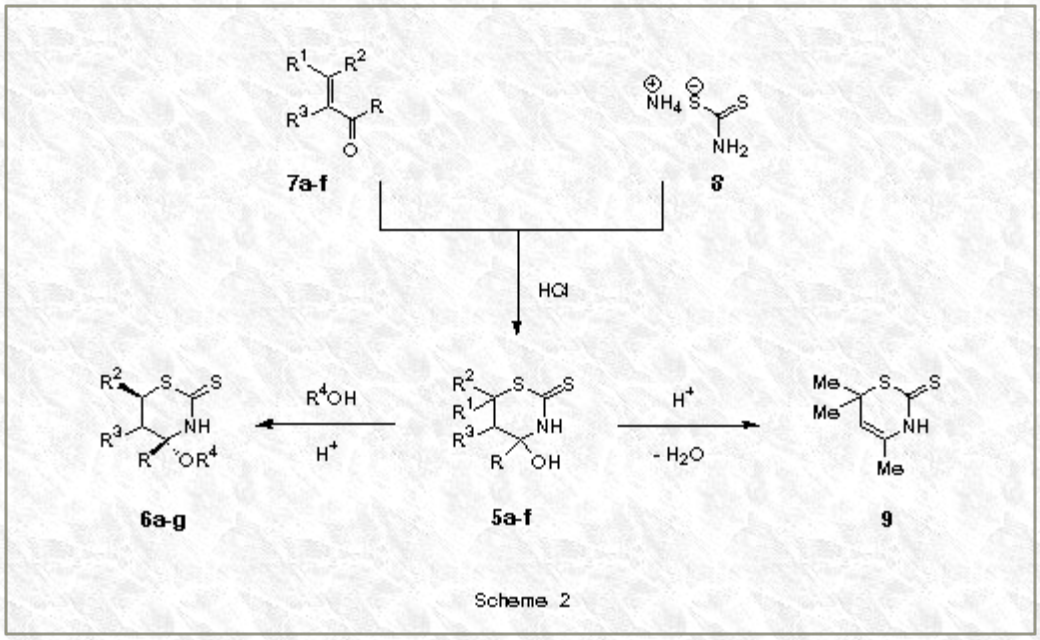


Table 1. *Synthesis of 4-alkoxytetrahydro-1,3-thiazine-2-thiones* **6a-g**

a,b-Unsaturated aldehyde or ketone	Product **6**	R	R^2	R^3	R^4	Isolated yield, %
7a	**6a**	H	H	H	Me	60
7b	**6b**	H	Me	H	Me	75
7c	**6c**	H	H	Me	Me	65
7d	**6d**	H	Ph	H	Me	31
7e	**6e**	Me	H	H	Me	60
7a	**6f**	H	H	H	Et	53
7b	**6g**	H	Me	H	Et	54

The described synthesis can serve as a convenient method for construction of tetrahydro-1,3-thiazine ring. Advantages of this method in comparison with the literature procedure [2] are more high yields of the heterocyclic products (in 1.5-4.0 times) as well as their easy isolation and purification.

We found that reaction of mesityl oxide **7f** with dithiocarbamic acid in methanol failed to give the desired 4-methoxy-4,6,6-trimethyltetrahydro-1,3-thiazine-2-thione. Instead of it we obtained 4,6,6-trimethyl-2,3-dihydro-6H-1,3-thiazine-2-thione **9** in 73 % yield.

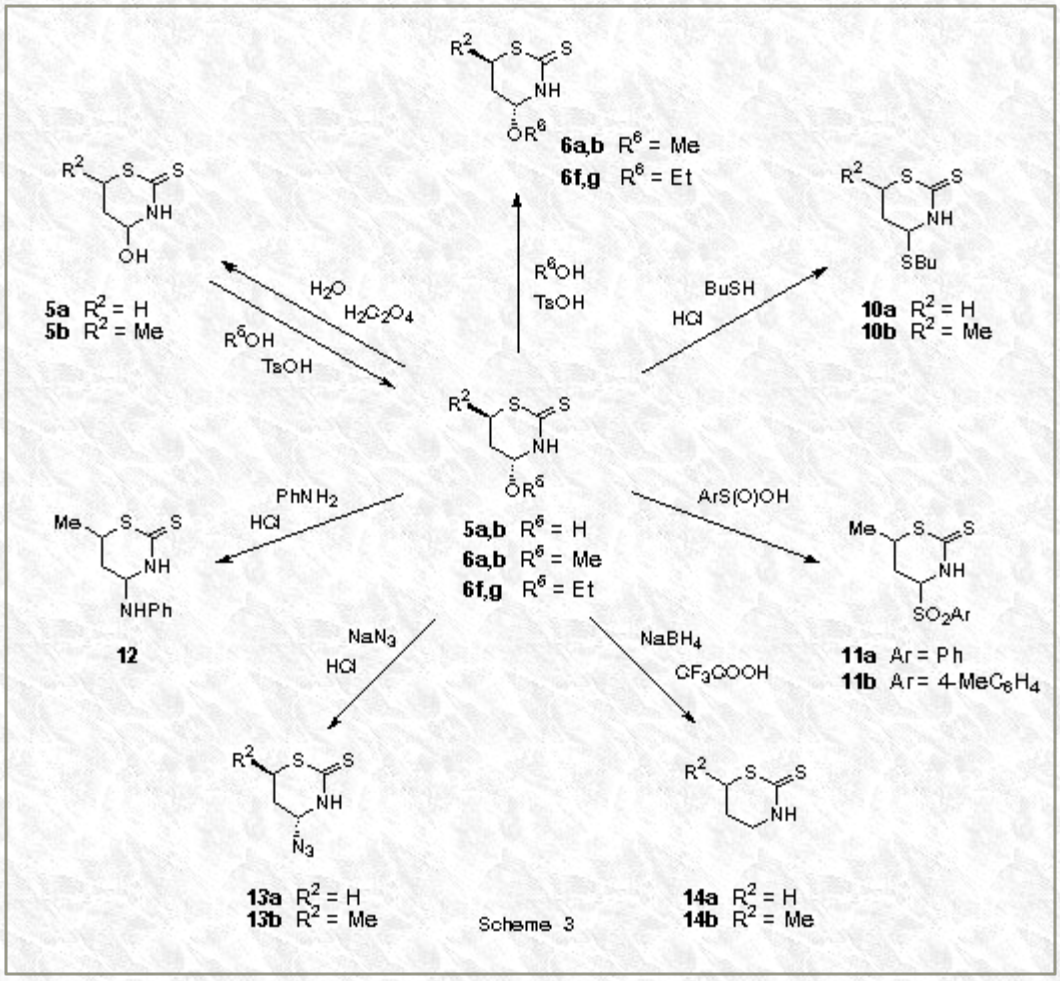
We also showed that the obtained 4-alkoxythiazines **6** by heating in water in the presence of oxalic acid readily gave the 4-hydroxythiazines **5** (see below) in 76-77 % yields. Thus synthesis of hydroxythiazines **5** can be performed in two steps from unsaturated aldehydes and ketones *via* 4-alkoxythiazines **6** in good overall yields. For example, Garraway reported 16 and 26 % yields for the compounds **5a,b** correspondingly [2] whereas we obtained these compounds in 46 and 58 % overall yields from the aldehydes **7a,b**. It should be noted that 4-hydroxytetrahydro-1,3-thiazine-2-thiones themselves are of great interest owing to their biological activity [3] and other useful properties [4].

• Synthesis of 4-functionally substituted tetrahydro-1,3-thiazine-2-thiones

A few years ago we developed some general methods for the synthesis of various 4-functionally substituted hexahydropyrimidine-2-thiones/ones starting from 4-hydroxy or 4-alkoxy substituted hexahydropyrimidine-

2-thiones/ones [5]. We proposed that the similar methods could be also applied to the synthesis of 4-functionally substituted tetrahydro-1,3-thiazine-2-thiones.

Really we found that the 4-hydroxy- **5** and 4-alkoxytetrahydro-1,3-thiazine-2-thiones **6** reacted with various O- (water, alcohols), S- (alkanethiols, arylsulfinic acids), N- (arylamines, hydrazoic acid) and H-nucleophiles (sodium tetrahydroborate - trifluoroacetic acid) in acidic media to give the corresponding 4-substituted products (Scheme 3). The Table 2 shows some of the obtained results.



Scheme 3

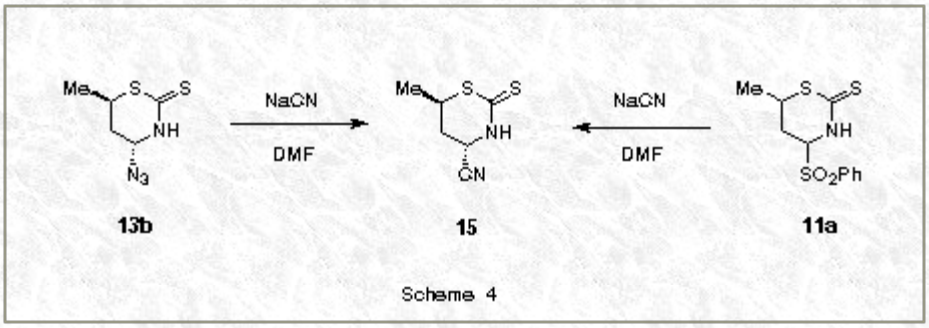
Table 2. *Synthesis of 4-functionally substituted tetrahydro-1,3-thiazine-2-thiones*

Starting compound	Nucleophile	Solvent	Catalyst	Reaction Temp. ^oC	Reaction Time, h	Product	Yield, %
6a	H_2O	H_2O	$H_2C_2O_4$	95	0.5	**5a**	76
6b	H_2O	H_2O	$H_2C_2O_4$	95	0.5	**5b**	77
5b	MeOH	MeOH	TsOH	65	1.0	**6b**	97
6b	EtOH	EtOH	TsOH	78	5.0	**6g**	79
6f	MeOH	MeOH	TsOH	65	2.5	**6a**	76
6a	BuSH	H_2O	HCl	80	0.2	**10a**	62
6b	BuSH	H_2O	HCl	80	0.3	**10b**	89
5b	PhS(O)OH	H O	-	95	0.3	**11a**	79

		H_2O					
6b	PhS(O)OH	H_2O	-	95	0.3	**11a**	81
6b	4-$MeC_6H_4S(O)OH$	H_2O	-	20	120	**11b**	91
5b	$PhNH_2$	H_2O	HCl	95	0.5	**12**	62
6a	HN_3	H_2O	-	76	4.0	**13a**	24
6b	HN_3	H_2O	-	80	6.0	**13b**	91
6a	$NaBH_4$-CF_3COOH	Dioxane	CF_3COOH	20	6.0	**14a**	79
6b	$NaBH_4$-CF_3COOH	Dioxane	CF_3COOH	20	5.5	**14b**	93

It is interesting to note that the reactivity of 4-hydroxy- and 4-alkoxytetrahydro-1,3-thiazine-2-thiones toward nucleophiles is less than the reactivity of 4-hydroxy- and 4-alkoxyhexahydropyrimidine-2-thiones. For example, reaction of *trans*-4-methoxy-6-methylhexahydropyrimidine-2-thione with hydrazoic acid in water at 20 ^{o}C for 24 h produce *trans*-4-azido-6-methylhexahydropyrimidine-2-thione in 97 % yield [6]. To obtain *trans*-4-azido-6-methyltetrahydro-1,3-thiazine-2-thione **13b** from the 4-methoxythiazine **6b** it is necessary to heat the reaction mixture in a sealed tube at 70-80 ^{o}C for 6 h (Table 2).

Earlier we shown that 4-azido- and 4-arylsulfonylhexahydropyrimidine-2-thiones/ones [7] are very effective amidoalkylation reagents and can be widely used in syntheses of other 4-substituted hexahydropyrimidines. Now we found that the similar properties manifest 4-azido- and 4-arylsulfonyltetrahydro-1,3-thiazine-2-thiones. For example, the 4-azidothiazine **13b** reacted with NaCN in DMF at r.t. for 1 h to give *trans*-4-cyano-6-methyltetrahydro-1,3-thiazine-2-thione **15** in 44 % yield.

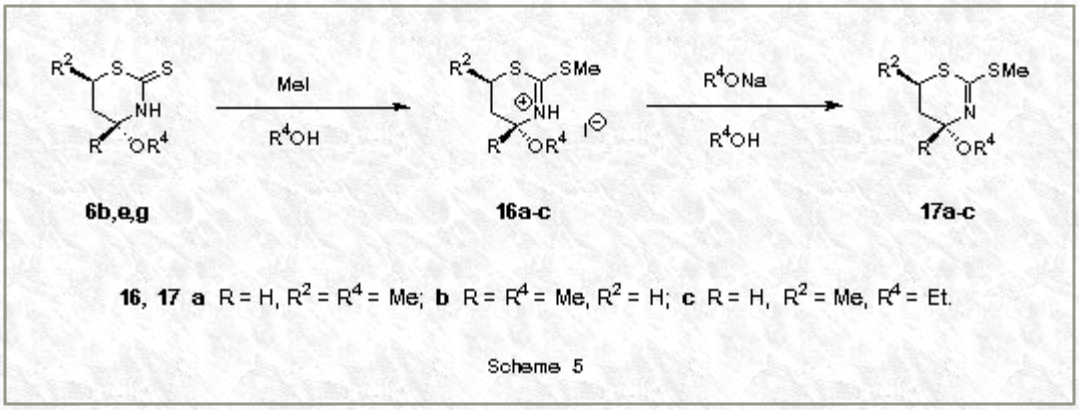


Scheme 4

The obtained 4-substituted tetrahydro-1,3-thiazine-2-thiones can be used as starting compounds in the synthesis of the corresponding 4-substituted cephams. As an example, hereafter we report the preparation of some 4-alkoxycephams from 4-alkoxytetrahydro-1,3-thiazine-2-thiones.

• Synthesis of 4-alkoxy-2-methylthio-5,6-dihydro-4H-1,3-thiazines

The next step of the cepham synthesis was transformation of the obtained 4-alkoxythiazines **6** into 4-alkoxy-2-methylthio-5,6-dihydro-4H-1,3-thiazines. We showed that the thiazines **6b,e** readily reacted with methyl iodide in methanol at r.t. (Scheme 5) to give the hydroiodides of 4-methoxythiazines **16a,b**.



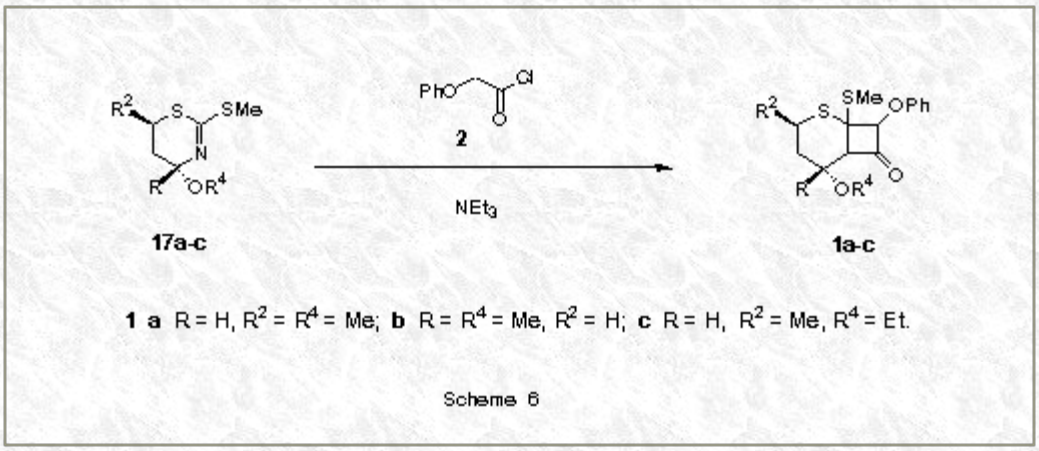
16, 17 a R = H, $R^2 = R^4$ = Me; **b** R = R^4 = Me, R^2 = H; **c** R = H, R^2 = Me, R^4 = Et.

Scheme 5

Similarly we prepared the hydroiodide of 4-ethoxythiazine **16c** by reaction of **6g** with methyl iodide in ethanol. The synthesized thiazines **16a-c** were treated without their isolation with the corresponding sodium alcoholate (MeONa for **16a,b** or EtONa for **16c**). Thus we obtained 4-alkoxy-2-methylthio-5,6-dihydro-4H-1,3-thiazines **17a-c** in 87-100 % overall yields.

Synthesis of 4-alkoxy-7-phenoxycephams

For construction of b-lactam cycle we used the known method based on reaction of acylchlorides with imines in the presence of bases [7]. Phenoxyacetyl chloride **2** was chosen as one of the reagents for the present investigation. We found that the thiazines **17a-c** reacted easily with phenoxyacetyl chloride **2** in the presence of NEt_3 (CH_2Cl_2, 0 °C) to form the target 4-alkoxy-6-methylthio-7-phenoxycephams **1a-c** (Scheme 6) in 47-87 % yields.



1 a R = H, $R^2 = R^4$ = Me; **b** R = R^4 = Me, R^2 = H; **c** R = H, R^2 = Me, R^4 = Et.

Scheme 6

It should be noted that this reaction proceeded in complete stereoselectivity and the cephams **1a-c** were obtained as a single diastereomer.

Conclusion

Thus we have developed a convenient one-pot synthesis of 4-alkoxytetrahydro-1,3-thiazine-2-thiones from a,b-unsaturated aldehydes or ketones. We have also shown that these compounds can be used in syntheses of various multifunctional heterocycles containing 1,3-thiazine ring. Stereoselective preparation of 4-alkoxy-6-methylthio-7-phenoxycephams can serve as an example of synthetic applications of 4-alkoxytetrahydro-1,3-thiazine-2-thiones. The usage in the cepham synthesis of various 4-functionally substituted tetrahydro-1,3-thiazine-2-thiones and acylchlorides could give access to a large number of 4,7-disubstituted cephams. Our further studies on the cepham synthesis are in progress.

References

1. Shutalev, A.D.; Kishko, E.A.; Sivova, N.V.; Kuznetsov, A.Yu. *Molecules* **1998**, *3*, 100-106; Shutalev, A.D.; Kuksa, V.A. *Khim. Geterotsikl. Soedin.* **1997**, 105-109; Shutalev, A.D.; Alekseeva, S.G. *Khim. Geterotsikl. Soedin.* **1995**, 377-380; Sivova, N.V; Shutalev, A.D. *Khim. Geterotsikl. Soedin.* **1995**, 273-274; Shutalev, A.D.; Kuksa, V.A. *Khim. Geterotsikl. Soedin.* **1995**, 97-103.

2. Jansen, J.E.; Mathes, R.A. *J. Amer. Chem. Soc.* **1955**, *77*, 2866-2868; Garraway, J.L. *J. Chem. Soc.* **1964**, 4004-4007.

3. *Ger. Patent* 2,946,409 (Cl C07D417/04), 29 May 1980 - *Chem. Abstr.*, **1980**, *93*, 204674.

4. *Ger. Patent* 2,205,029 (Cl G03C), 29 Aug 1973 - *Chem. Abstr.*, **1973**, *79*, 120466; *Ger. Patent* 2,013,423 (Cl G03C), 07 Oct 1971 - *Chem. Abstr.*, **1972**, *76*, 20023.

5. Shutalev, A.D.; Pagaev, M.T.; Ignatova, L.A. *Khim. Geterotsikl. Soedin.* **1994**, 1093-1104; Shutalev, A.D. *Khim. Geterotsikl. Soedin*. **1993**, 1389-1397; Shutalev, A.D.; Komarova, E.N.; Ignatova, L.A. *Khim. Geterotsikl. Soedin*. **1993**, 1378-1388; Shutalev, A.D.; Ignatova, L.A. *Khim. Geterotsikl. Soedin*. **1991**, 228-236; Shutalev, A.D.; Ignatova, L.A.; Unkovsky, B.V. *Khim. Geterotsikl. Soedin*. **1990**, 133-134; Ignatova, L.A.; Shutalev, A.D.; Pagaev, M.T.; Unkovsky, B.V. *Khim. Geterotsikl. Soedin*. **1988**, 234-240.

6. Our unpublished data.

7. Bose, A.K.; Dayal, B.; Manhas, M.S. *Tetrahedron Letters*, **1972**, 2823; Bose, A.K.; Manhas, M.S.; Chib, J.; Chawla, H.; Dayal, B. *J. Org. Chem.*, **1974**, *39*, 2877; Sharma, S.D.; Arora, S.K.; Mehra, U. *Indian J. Chem.* **1985**, *24B*, 895-901.

Comments

During 1-30 September 1998, all comments on this poster should be sent by e-mail to ecsoc@listserv.arizona.edu with a0009 as the message subject of your e-mail. After the conference, please send all the comments and reprints requests to the author.
