Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Run-Tao Li [a] & Meng-Shen Cai [a]
[a] School of Pharmaceutical Sciences, Beijing Medical University, Beijing, 100083, China
Published online: 17 Sep 2007.

To cite this article: Run-Tao Li & Meng-Shen Cai (1999): Convenient Synthesis of 1,4-Di-(Alkyldithioate)Piperazines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:1, 65-71

To link to this article: http://dx.doi.org/10.1080/00397919908085736

SYNTHETIC COMMUNICATIONS, 29(1), 65-71 (1999)

CONVENIENT SYNTHESIS OF 1,4-DI-(ALKYLDITHIOATE)PIPERAZINES

Run-Tao Li * Meng-Shen Cai

School of Pharmaceutical Sciences,
Beijing Medical University, Beijing, 100083, China

Abstract A series of 1,4-di(alkyldithioate)-piperazine were prepared from the reaction of anhydrous piperazine with carbon disulfide and different alkyl halide in the presence of anhydrous potassium phosphate under mild condition in good to excellent yields.

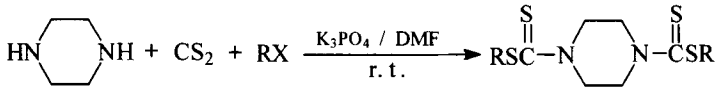
Piperazine derivatives are of great interest because of their potential biological properties including anticancer activities[1], atypical antipsychotic activities[2, 3], 5-HT. receptor antagonist[4], analgesic and anti-inflammatory activities[5] etc.. We have studied on the synthesis and biological activities of several kinds of piperazine derivatives[6-8]. Recently we found a convenient method for the preparation of dithiocarbamates in the presence of anhydrous potassium phosphate[9]. As the continuation of our works, we wish to report the use of this method in the synthesis of 1,4-di(alkyldithioate)-piperazine in this paper.

1,4-Di(alkyldithioate)-piperazines were prepared from the reaction of anhydrous piperazine with carbon disulfide and alkyl halide in the presence of anhydrous

*To whom correspondence should be addressed.

potassium phosphate in DMF at room temperature. Most of the reactions were completed within 1~2 hours. After reaction, the mixture was poured into cold water and extracted with ethyl acetate; the collected extract was washed with cold water, dried over anhydrous calcium chloride, evaporated the solvent and the residue was recrystallized to give the corresponding 1,4-di(alkyldithioate)-piperazine 3. The yields and physical properties were listed in the table.

Reaction of anhydrous piperazine with carbon disulfide and alkyl halide



1 2 3

Compd.	RX	Yield (%)	Compd.	RX	Yield (%)
3a	C_2H_5Br	84	**3g**	$C_6H_5CH_2Cl$	92
3b	n-$C_6H_{13}Br$	86	**3h**	p-NO_2-$C_6H_4CH_2Cl$	88
3c	$HOCH_2CH_2Cl$	87	**3I**	$(p\text{-F-}C_6H_4)_2CHCl$	91
3d	$CH_2=CHCH_2Cl$	93	**3j**	2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide	92
3e	$NCCH_2Cl$	84			
3f	$BrCH_2CO_2C_2H_5$	74	**3k**	2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide	91

It is better to use the DMF then to use the acetone[9], ethanol or DMSO as solvent in this reaction. The presence of -COOH, -CN, -OH, -COOEt , -CH=CH_2, -CON- and saccharide ring in the alkyl halides are not affected under this condition. The operation is simple and the yields are good to excellent.

EXPERIMENTAL

Anhydrous piperazine and anhydrous potassium phosphate were obtained from the dehydration of hexahydrate piperazine and $H_3PO_4 \cdot 7H_2O$ respectively. Di(4-fluorophenyl)methyl chloride was prepared from the chlorination of di(4-fluorophenyl)methanol. 2,3,4,6-Tetra-O-acetylglycopyranosyl bromide was prepared according to literature[10]. Other reagents were of commercial quality from freshly opened containers. Melting points were determined on X4 microscopic melting point apparatus and were uncorrected. IR spectra were recorded on Perkin-Elmer 298 instrument(KBr disk). ^{1}H NMR spectra were recorded on a VXR 300 spectrometer (300Mhz) with TMS as internal standard in $CDCl_3$ or DMSO-d_6. Elemental analyses were performed on PE-2400 instrument.

General procedure: The mixture of anhydrous piperazine (86mg, 1mmole) and anhydrous potassium phosphate (430mg, 4mmole) in 20ml DMF was stirred for 20min at room temperature, and than carbon disulfide (20drops, ~10mmole) was added. After the mixture was stirred further 20 min, the alkyl halide(2.2mmole) was added. The reaction was maintained at this condition until TLC (GF_{254}, acetone) showed the reaction to be completed. The mixture was poured into cold water(100 ml), extracted with ethyl acetate(20ml×3), the organic phase was washed 1 time with water(30ml) and dried over anhydrous calcium chloride. The solvent was evaporated under reduced pressure and the residue was recrystallized to give the pure 1,4-di(alkyldithiocarbate) piperazine **3**.

1,4-Di(ethyldithioate)piperazine 3a Recrystallization from ethyl acetate-petrol ether. mp. 127-128°C. IR(KBr, cm^{-1}) 1457, 1271, 1053, 993, 922; ^{1}HNMR ($CDCl_3$). 1.37(t, 6H,

J=7.5Hz, CH_3), 3.33 (q, 4H, J=7.5Hz, CH2), 4.00-4.60 (br, 8H, pip). Anal. calc. for $C_{10}H_{18}N_2S_4$ C 40.78, H 6.16, N 9.51; Found C 40.51, H5.95, N 9.10.

1,4-Di(hexyldithioate)piperazine 3b. Recrystallization from ethyl acetate-petrol ether. mp 78-79°C. IR(KBr, cm^{-1}) 1444, 1274, 1047, 992, 926, 726; ^{1}HNMR ($CDCl_3$) 1.29(t, 6H, J=7.2Hz, CH_3), 1.31-1.45(m, 12H, CH_2), 1.71(m, 4H, CH_2), 3.31(t, 4H, SCH_2), 3.90-4.60(br, 8H, pip); Anal. calc. for $C_{18}H_{34}N_2S_4$ C 53.15, H8.43, N 6.89; Found C 52.92, H 8.34, N 6.66.

1,4-Di(2-hydroxyethyldithioate)piperazine 3c. Recrystallization from ethyl acetate-methanol. mp 128-129°C. IR(KBr, cm^{-1}) 3365, 1444, 1280, 1056, 1002, 927; ^{1}HNMR (DMSO) 3.37(t, 4H, J=6.3Hz, CH_2), 3.59(t, 4H, J=6.3Hz, CH_2), 4.29(br, 4H, pip), 4.31(br, 4H, pip), 5.00(br, 2H, OH); Anal. calc. for $C_{10}H_{18}N_2S_4O_2$ C 36.78, H 5.56, N 8.58; Found C37.10, H 5.48, N 8.25.

1,4-Di(allyldithioate)piperazine 3d. Recrystallization from ethyl acetate-methanol. mp 84-85°C. IR(KBr, cm^{-1}) 3075, 1628, 1446, 1273, 1040, 992, 921; ^{1}HNMR ($CDCl_3$) 4.01(d, 4H, SCH_2), 4.00-4.58(br, 8H, pip), 5.30(dd, 2H, CH=), 5.36(dd, 2H, CH=), 5.91(dd, 2H, =CH); Anal. calc. for $C_{12}H_{18}N_2S_4$ C 45.24, H 5.69, N 8.80; Found C 44.78, H 5.45, N 8.48.

1,4-Di(cyanomethyldithioate)piperazine 3e. Recrystallization from ethyl acetate-methanol. mp 194-195°C. IR(KBr, cm^{-1}) 2243, 1462, 1274, 1024, 991, 921; ^{1}HNMR ($CDCl_3$) 4.12 (br, 4H, pip), 4.39(br, 4H, pip), 4.43(s, 4H, CH_2CN); Anal. calc. for $C_{10}H_{12}N_4S_4O_2$ C37.95, H 3.82, N 17.70; Found C38.14, H 3.70, N 17.48.

1,4-Di(ethoxycarbonylmethyldithioate)piperazine 3f. Recrystallization from ethyl

acetate-petrol ether. mp 140-141°C. IR(KBr, cm^{-1}) 1709, 1462, 1278, 1046, 994, 931; ^{1}HNMR ($CDCl_3$) 1.31 (t, 6H, J=6.9Hz, CH_3), 4.17(s, 4H, SCH_2), 4.24(q, 4H, J=7.2Hz, CH_2), 4.10-4.50(br, 8H, pip); Anal. calc. for $C_{14}H_{22}N_2S_4O_4$ C 40.95, H 5.40, N 6.82; Found C 40.95, H 5.00, N 6.64.

1,4-Di(benzyldithioate)piperazine 3g. Recrystallization from ethyl acetate-methanol. mp 126-127°C. IR(KBr, cm^{-1}) 3021, 1595, 1462, 1273, 1040, 994, 925; ^{1}HNMR ($CDCl_3$) 3.90-4.50(br, 8H, pip), 4.57(s, 4H, CH_2), 7.26-7.40(m, 10H, Ar); Anal. calc. for $C_{20}H_{22}N_2S_4$ C 57.37, H 5.30, N 6.69; Found C 57.17, H 4.93, N 6.22.

1,4-Di(4-nitrobenzyldithioate)piperazine 3h. Recrystallization from ethyl acetate-methanol. mp 230-231°C. IR(KBr, cm^{-1}) 3014, 1606, 1446, 1269, 1046, 997, 926; ^{1}HNMR (DMSO) 4.10(br, 4H, pip), 4.32(br, 4H, pip), 4.74(s, 4H, CH_2), 7.65(d, 4H, Ar), 8.17(d, 4H, Ar); Anal. calc. for $C_{20}H_{20}N_4S_4O_4$ C 47.22, H 3.96, N 11.02; Found C 47.30, H 3.64, N 10.74.

1,4-Di[bi(4-fluorophenyl)methyldithioate]piperazine 3i. Recrystallization from ethyl acetate-i-propanol. mp 187-188°C. IR(KBr, cm^{-1}) 3039, 1597, 1457, 1278, 1048, 997, 925; ^{1}HNMR ($CDCl_3$) 3.90-4.50(br, 8H, pip), 6.51(s, 2H, SCH), 7.00(m, 8H, Ar), 7.32(m, 8H, Ar); Anal. calc. for $C_{32}H_{26}F_4N_2S_4$ C 59.79, H 4.08, N 4.36; Found C 60.15, H 3.98, N 4.26.

1,4-Di(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyldithioate)piperazine 3j. Recrystallization from ethyl acetate-methanol. mp 222-223°C. IR(KBr, cm^{-1}) 1742, 1411, 1272, 1219, 989, 916; ^{1}HNMR ($CDCl_3$) 2.03-2.08 (m×s, 24H, CH_3), 3.90(m, 2H, sugar ring), 4.10-4.48(br, 12H, pip, sugar ring), 5.15(t, 2H, sugar ring), 5.35(m, 4H, sugar ring),

5.85(dd, 2H, sugar ring); Anal. calc. for $C_{34}H_{46}N_2O_{18}S_4$ C45.42, H 5.16, N 3.12; Found C 45.23, H 5.31, N 3.37.

1,4-Di(2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyldithioate)piperazine 3k. Recrystallization from ethyl acetate-methanol. mp 131-133°C. IR(KBr, cm^{-1}) 1742, 1409, 1367, 1218, 1055, 916; ^{1}HNMR ($CDCl_3$) 2.09-2.15(m×s, 24H, CH_3), 4.05-4.50(br, 14H, pip, sugar ring), 5.22 (m, 2H, 5-H), 5.50(m, 4H, sugar ring), 5.83(dd, 2H, sugar ring); Anal. calc. for $C_{34}H_{46}N_2O_{18}S_4$ C45.42, H 5.16, N 3.12; Found C 45.08, H 4.97, N 3.16.

Acknowledgments We acknowledge the financial support of this work by the National Key Laboratory of New Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

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Accepted April 25, 1998