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Efficient Conversion of Substituted Aryl Thioureas to 2-Aminobenzothiazoles Using Benzyltrimethylammonium Tribromide

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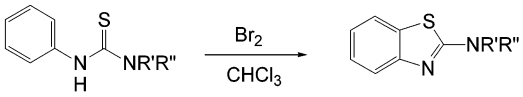
Abstract: The reaction of molecular bromine (Br_2) with arylthioureas is known to produce 2-aminobenzothiazoles (Hugerschoff reaction). We show here that benzyltrimethylammonium tribromide (**1**, $PhCH_2NMe_3Br_3$), a stable, crystalline organic ammonium tribromide (OATB), can be readily utilized as an alternative electrophilic bromine source. It is easier to control the stoichiometry of addition with an OATB, which minimizes aromatic bromination caused by excess reagent. We have developed a direct procedure from isothiocyanates and amines using tetrabutylammonium thiocyanate (Bu_4NSCN) and $PhCH_2NMe_3Br_3$ to afford functionalized 2-aminobenzothiazoles.

2-Aminobenzothiazoles are broadly found in bioorganic and medicinal chemistry with applications in drug discovery and development for the treatment of diabetes,[1] epilepsy,[2,3,4] inflammation,[5] amyotrophic lateral sclerosis,[6] analgesia,[7] tuberculosis,[8] and viral infections.[9] Investigations into the preparation of 2-aminobenzothiazoles can be traced to the early 1900s with the work of Hugerschoff, who found that an arylthiourea can be cyclized with liquid bromine in chloroform to form an 2-aminobenzothiazole (eq 1).[10,11] Although this reaction



(eq. 1)

usually proceeds efficiently at room temperature, several drawbacks are associated with the use of liquid bromine, which is a highly toxic and corrosive reagent, and can be difficult to manipulate on small scale. As an alternative reagent to liquid bromine, organic ammonium tribromides (OATBs) such as benzyltrimethylammonium tribromide (**1**, $PhCH_2NMe_3Br_3$) and tetrabutylammonium tribromide (**2**, Bu_4NBr_3) are high molecular weight, stable, crystalline solids, which can deliver a stoichiometric amount of bromine where small amounts are necessary for microscale reactions. For example, Bu_4NBr_3 and $PhCH_2NMe_3Br_3$ are effective alternatives to bromine for the bromination of activated aromatic substrates,[12−14] alkenes,[14] and ketones.[15] To date, OATBs have not been reported as a substitute for bromine in the preparation of 2-alkylaminobenzothiazoles from arylthioureas. Herein, we describe an efficient method for the facile conversion of aryl thioureas to 2-aminobenzothiazoles with an equimolar amount of $PhCH_2NMe_3Br_3$ under a variety of reaction conditions. In addition, this reagent has been used to prepare 2-aminobenzothiazoles via a one-pot procedure from isothiocyanates and amines or a substituted aniline and tetrabutylammonium thiocyanate (Bu_4NSCN).

Results and Discussion

During the course of a medicinal chemistry project, we needed to prepare a series of 2-aminobenzothiazoles and initially used the method of Ambati and co-workers who reported a facile synthesis from substituted arylthioureas and bromine in acetic acid at room temperature.[16] They had reported that *N*-methyl-*N*′-phenylthiourea **3** underwent oxidative cyclization with 1.95 molar equiv of bromine in acetic acid at room temperature to provide 2-(methylamino)benzothiazole **4** in 75% yield (Table 1, entry 1). When we repeated this experiment, we obtained 6-bromobenzothiazole **5**[18] in 46% isolated yield with only

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(17) We believe that the earlier work[16] had actually produced **5** and not **4** and that this product had been improperly characterized. Consistent with this analysis is our observation that the melting point we found for **5** (227−228 °C) is closer to what was reported (215 °C) than the melting point for **4** (140−141 °C).

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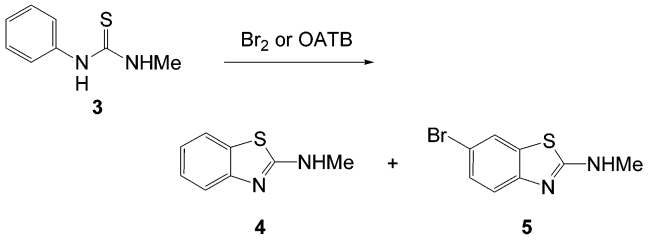
TABLE 1. Hugerschoff Reaction Using Br_2 and OATBs in Acetic Acid



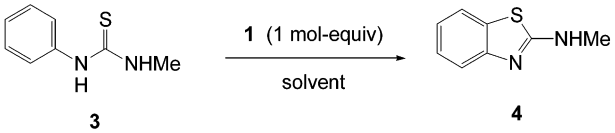
entry	reagent	reaction conditions	% yield of **4**	% yield of **5**
1	Br_2 (1.95 molar equiv)[16,17]	AcOH/rt	75	0
2	Br_2 (1.95 molar equiv)	AcOH/rt	<5	46
3	Br_2 (1 molar equiv)	AcOH/rt/3 h	83	0
4	$PhCH_2NMe_3Br_3$ (1 molar equiv)	AcOH/rt/5 h	81	0
5	$PhCH_2NMe_3Br_3$ (2.2 molar equiv)	AcOH/rt /18 h	0	70

a trace (<5%) of **4** (Table 1, entry 2).[17] Compound **5** was prepared independently in order to unambiguously assign the structure by reacting *N*-4-bromophenyl-*N*′-methylthiourea **6** with one molar equiv of $PhCH_2NMe_3Br_3$. It is known for the Hugerschoff reaction that excess bromine will produce the perbromide of the aminobenzothiazole, which can then brominate the benzene ring under prolonged reaction conditions.[10,11] We conducted the reaction with 1 molar equiv of either liquid bromine (3 h) or $PhCH_2NMe_3Br_3$ (5 h) in acetic acid at room temperature to provide **4** in 83% or 81% yields, respectively (Table 1, entries 3 and 4). Furthermore, reaction of **3** with 2.2 molar equiv of $PhCH_2NMe_3Br_3$ provided 2-methylamino-6-bromobenzothiazole **5** in 70% yield (Table 1, entry 5). We were encouraged by the initial finding that $PhCH_2NMe_3Br_3$ could substitute for liquid bromine in the reaction because it is easier to control the stoichiometry of addition of $PhCH_2NMe_3Br_3$ which would minimize the formation of brominated side products when the reaction is conducted with an excess of reagent.

The arylthioureas used in this study were prepared by reacting the appropriate aryl isothiocyanate and alkylamine in refluxing methanol, and subsequent conversion of the resulting arylthioureas with $PhCH_2NMe_3Br_3$ in acetic acid provided the 2-alkylamino benzothiazoles as hydrobromide salts.

We investigated the effects of varying solvent in this reaction. Compound **3** was reacted with 1 molar equiv of $PhCH_2NMe_3Br_3$ (Table 2, entry 2) in CH_2Cl_2 at room temperature for 1 day to give desired product **4** in 80% yield. Acetonitrile, 1,2-dimethoxyethane, and tetrahydrofuran were also found to be effective (Table 2, entries 3−5), whereas polar solvents, such as methanol and dimethylformamide, gave little (<5%) or no product (Table 2, entries 6 and 7). To investigate the compatibility of the ester functional group, thiourea **7** was prepared from aniline and methyl 3-(isothiocyanato)propionate in refluxing methanol and reacted with $PhCH_2NMe_3Br_3$ in acetic acid to give an 84% yield of aminobenzothiazole **8**[19] (Table 3, entry 1). When the cyclization was conducted

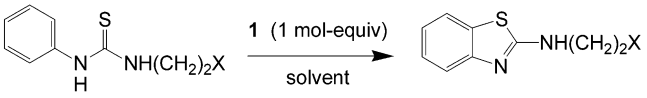
TABLE 2. Variation of Solvent in the Hugerschoff Reaction with $Ph_2CH_2NMe_3Br_3$ (1)



entry	solvent	reaction conditions	% yield
1	AcOH	rt/5 h	81
2	CH_2Cl_2	rt/1 d	80
3	CH_3CN	rt/1 d	61
4	1,2-DME	rt/1 d	68
5	THF	rt/1 d	41
6	MeOH	rt/1 d	<5
7	DMF	rt/1 h	<5

in dichloromethane, **8** was isolated in 77% yield (Table 3, entry 2). The compatibilities of amino and hydroxyl functionalities were also studied. 2-*N*-Dimethylaminoethyl-*N*′-phenylthiourea **9** was treated with $PhCH_2NMe_3Br_3$ to give the corresponding aminobenzothiazole **10**[20] in 29% yield in acetic acid and in 73% in dichloromethane at room temperature (Table 3, entries 3 and 4). Reaction of *N*-2-hydroxyethyl-*N*′-phenylthiourea **11** with **1** in acetic acid provided 2-[2-(acetoxy)ethylamino]benzothiazole **12** in 73% yield in which the hydroxyl group was acetylated, whereas the use of dichloromethane as the solvent provided 2-[2-(hydroxy)ethylamino]benzothiazole **13** in 76% yield (Table 3, entries 5 and 6).

TABLE 3. Compatibility of Different Functional Groups in the Hugerschoff Reaction Using 1



entry	starting material	X in **7**, **9**, and **11**	solvent	product	X in **8**, **10**, **12**, and **13**	% yield
1	7	CO_2Me	AcOH	8	CO_2Me	84
2	7	CO_2Me	CH_2Cl_2	8	CO_2Me	77
3	9	NMe_2	AcOH	10	NMe_2	29
4	9	NMe_2	CH_2Cl_2	10	NMe_2	73
5	11	OH	AcOH	12	OAc	73
6	11	OH	CH_2Cl_2	13	OH	76

We then examined the effects of aromatic substitution involving electron-donating (methoxy and methyl) and electron-withdrawing (bromo and nitro) groups. The reaction of 3-methoxyphenylthiourea analogue **14** and **1** in acetic acid proceeded readily (<30 min) to give product **15**[21] in 87% yield (Table 4, entry 1). However, the reaction of 3-methylphenylthiourea **16** and **1** in acetic acid produced a 3:2 inseparable mixture of products **17** and **18** in 88% yield as evidenced by doubling of key aromatic resonances in the ^1H and ^{13}C NMR (Table 4, entry 2). The reaction of 3-bromophenylthiourea **19** and **1** produced a 1:1 mixture of isomeric products **20** and **21** in 70% yield (Table 4, entry 3). The reaction of 3-nitrophenylthiourea compound **22** was slower (2 days) and

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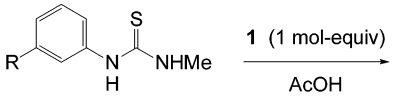
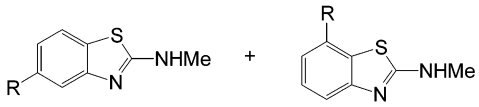
TABLE 4. Influence of 3-Phenyl Substitution in the Hugerschoff Reaction Using 1



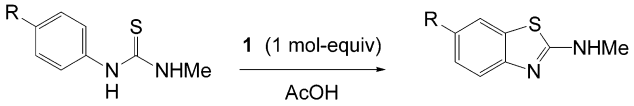
14, 16, 19, 22



15, 17, 20, 23 **18, 21**

entry	starting material	R	reaction conditions	product	% yield
1	14	MeO	AcOH/rt/30 min	15	87
2	16	Me	AcOH/rt/30 min	17, 18	88 (mixture)
3	19	Br	AcOH/rt/18 h	20, 21	70 (mixture)
4	22	NO_2	AcOH/rt/2d	23	<5

SCHEME 1

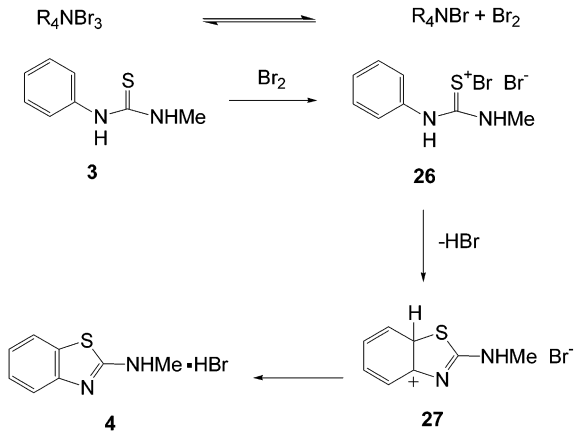


6: R = Br
24: R = Me

5: R = Br
25: R = Me

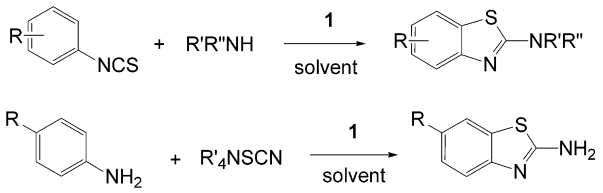
provided a minor amount (<5%) of 2-(methylamino)-nitrobenzothiazole **23** (uncharacterized regioisomeric ratio, Table 4, entry 4). 4-Methylphenylthiourea **24** was reacted with **1** in acetic acid for 18 h to provide aminobenzothiazole **25**[22] in 69% yield, and 2-methylamino-6-bromobenzothiazole **5** was also prepared in 75% yield (Scheme 1). The substituent effects we observed support a bromine-mediated cyclization process involving electrophilic addition to the thiocarbonyl of the thiourea to afford **26** as a transient intermediate, which is then attacked by the π system of the aromatic ring to give **27** followed by rapid formation of **4** (Scheme 2).[23,24]

SCHEME 2



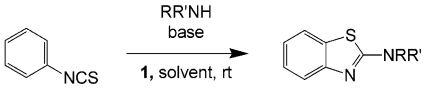
We extended this synthetic methodology to the direct (one-pot) synthesis of aminobenzothiazoles (Scheme 3).

SCHEME 3



We initially reacted substituted anilines, methyl isothiocyanate, and **1**, but the only products detected were brominated aniline hydrobromide salts **28** because aniline is highly activated for electrophilic bromination and protonated bromoanilines are inert to further reaction with alkyl isothiocyanate. Therefore, we adopted an alternative strategy in which **4** was prepared by the reaction of phenyl isothiocyanate and methylamine hydrochloride in the presence of DBU and **1** in either CH_2Cl_2 or THF (Table 5, entries 1 and 2). We anticipated that the arylthioureas would form in situ from aryl isothiocyanates and amines and then spontaneously convert to the desired 2-aminobenzothiazoles in the presence of **1**. The treatment of phenyl isothiocyanate with propylamine and **1** in methylene chloride was complete in 18 h to give **29** in 73% yield (Table 5, entry 3). Similarly, reaction of phenyl isothiocyanate and piperidine afforded aminobenzothiazole **30**[20,27] in 69% yield (Table 5, entry 4). Phenyl isothiocyanate was stirred with methyl 4-aminobutyrate hydrochloride, triethylamine, and **1** furnishing amino ester **31** in 38% yield (Table 5, entry 5).

TABLE 5. Direct Synthesis of 2-Alkylaminobenzothiazoles from Arylisothiocyanates



4, **29-31**

Entry	Amine (RR'NH)	Reaction Conditions	Product	% Yield
1	$MeNH_2$ HCl	DBU/CH_2Cl_2	**4**	40
2	$MeNH_2$	THF	**4**	42
3	$PrNH_2$	CH_2Cl_2	**29**	73
4		CH_2Cl_2	**30**	69
5	$H_2N(CH_2)_3CO_2Me$ HCl	TEA/CH_2Cl_2	**31**	38

We investigated the direct reaction of substituted anilines with tetrabutylammonium thiocyanate and prepared riluzole (**32**), a marketed therapeutic for the treatment of amylotrophic lateral sclerosis (ALS).[25] Compound **32** was synthesized in 61% isolated yield by condensing equimolar amounts of 4-(trifluoromethoxy)-aniline, tetrabutylammonium thiocyanate, and **1** in dichloromethane at room temperature (Table 6, entry 1). We also prepared **32** by reaction of the aniline with 1 molar equiv of ammonium thiocyanate and **1** in acetonitrile in 71% yield (Table 6, entry 2). In addition, *p*-toluidine and 4-bromoaniline were reacted with *n*Bu_4-SCN and **1** in methylene chloride to provide 2-aminoben-

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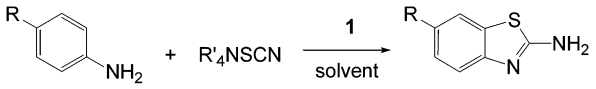
TABLE 6. Direct Synthesis of 2-Alkylaminobenzothiazoles Using R_4NSCN



32-34

entry	R	R′	solvent	product	% yield
1	CF_3O	Bu	CH_2Cl_2	32	61
2	CF_3O	H	CH_3CN	32	71
3	Me	Bu	CH_2Cl_2	33	40
4	Br	Bu	CH_2Cl_2	34	41

zothiazoles **33** and **34**[3] in 40 and 41% yields, respectively (Table 6, entries 3 and 4).

Conclusion

$PhCH_2NMe_3Br_3$ (**1**) is a stable, electrophilic bromine source for the conversion of substituted arylthioureas to 2-aminobenzothiazoles (Hugerschoff reaction) under mild conditions in a variety of solvents with good yields. One of the key benefits for this reagent when compared with molecular bromine is ease of addition and handling, which minimizes the risk of forming brominated side products.[16,17] We have extended the use of this reagent to a direct, one-pot synthesis of 2-aminobenzothiazoles from either aryl isothiocyanates and amines or tetrabutylammonium thiocyanate and anilines in the presence of a stoichiometric amount of $PhCH_2NMe_3Br_3$.

Experimental Section

Synthesis of 2-(Methylamino)benzothiazole (4). General Procedure for the Hugerschoff Reaction Using $PhCH_2NMe_3Br_3$. *N*-Methyl-*N*′-phenylthiourea **3** (164.6 mg, 1.000 mmol) was dissolved in acetic acid (5 mL) and treated with **1** (390.6 mg, 1.002 mmol) at ambient temperature. The reaction mixture was stirred for 5 h and was slowly poured into ice-cold saturated $NaHCO_3$ and extracted into EtOAc (3 × 40 mL) The organic extracts were dried over Na_2SO_4, filtered, and concentrated. The isolated residue was purified by preparative TLC eluting with 2% MeOH in $CHCl_3$ and gave 131.4 mg (81%) of **4** as a white solid: mp 140−141 °C (lit.[16] 215 °C); ^{1}H NMR (DMSO-d_6 300 MHz) δ 7.93−7.91 (m. 1H), 7.67−7.64 (m, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.24−7.19 (m, 1H), 7.03−6.98 (m, 1H), 2.94−2.93 (m, 3H); ^{13}C NMR (DMSO-d_6 75.5 MHz) δ 166.72, 152.60, 130.23, 125.41, 120.80, 120.68, 117.87, 30.39; MS MH^+ (rel int) 165.2 (100). Anal. Calcd for $C_8H_8N_2S$: C, 58.51; H, 4.91; N, 17.06; S, 19.52. Found: C, 58.27; H, 4.95; N, 17.07; S, 19.41.

Direct Preparation of 2-(Propylamino)benzothiazole (29). A mixture of phenyl isocyanate (120 μL, 1.00 mmol) and propylamine (85 μL, 1.03 mmol) was dissolved in CH_2Cl_2 (5 mL), stirred for 30 min, and then treated with **1** (390.2 mg, 1.00 mmol) at room temperature. The reaction mixture was stirred overnight. The reaction was diluted with CH_2Cl_2 (25 mL) and neutralized with aqueous $NaHCO_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, filtered, and concentrated to provide a residue. The crude product was purified by tapered preparative TLC (2% MeOH in $CHCl_3$) and furnished 140.2 mg (73%) of **29** as an off-white crystalline solid: mp 79−80 °C; ^{1}H NMR (DMSO-d_6 300 MHz) δ 8.00−7.98 (m. 1H, NH), 7.64 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.23−7.18 (m, 1H), 7.02−6.97 (m, 1H), 3.3 (q, J = 6.8 Hz, 2H), 1.66−1.54 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (DMSO-d_6 75.5 MHz) δ 166.05, 152.63, 130.10, 125.37, 120.73, 120.61, 117.78, 45.65, 21.93, 11.31; MS MH^+ (rel int) 193.1 (100). Anal. Calcd for $C_{10}H_{12}N_2S$: C, 62.47; H, 6.29; N, 14.57; S, 16.68. Found: C, 62.29; H, 6.25; N, 14.47; S, 16.50.

Methyl 2-[(3-Carboxypropyl)amino]benzothiazole (31). A mixture of methyl 4-aminobutyrate (154.1 mg, 1.003 mmol) and triethylamine 155 μL, 1.11 mmol) in CH_2Cl_2 (5 mL) was stirred for 15 min and then treated with phenyl isocyanate (120 μL, 1.00 mmol). The resultant mixture was stirred for 1 h at room temperature, treated with **1** (390.5 mg, 1.00 mmol), and stirred overnight. The reaction was diluted with CH_2Cl_2 (25 mL) and neutralized with aqueous $NaHCO_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, filtered, and concentrated to provide a residue. The crude product was purified by tapered preparative TLC (2% MeOH in $CHCl_3$) and furnished 95.0 mg (38%) of **31** as an off-white solid: mp 110−111 °C; ^{1}H NMR (DMSO-d_6 300 MHz) δ 8.02 (t, J = 5.2 Hz, 1H, NH), 7.65 (d, J = 7.7 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.00 (t, J = 8.0 Hz, 1H), 3.59 (s, 3H), 3.40−3.32 (m, 2H), 2.41 (t, J = 7.4 Hz, 2H), 1.90−1.80 (m, 2H); ^{13}C NMR (DMSO-d_6 75.5 MHz) δ 172.94, 165.97, 152.52, 130.14, 125.40, 120.78, 120.74, 117.88, 51.19, 43.01, 30.59, 24.08; MS MH^+ (rel int) 251.1 (100). Anal. Calcd for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.64; N, 11.19; S, 12.81. Found: C, 57.54; H, 5.73; N, 11.13; S, 12.62.

2-Amino-6-methylbenzothiazole (33). To a mixture of *p*-toluidine (215.6 mg, 2.01 mmol) and tetrabutylammonium thiocyanate (604.8 mg, 2.01 mmol) in CH_2Cl_2 (12 mL) was added **1** (784.3 mg, 2.01 mmol) at ambient temperature. The reaction mixture was stirred for 1 d. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and neutralized with aqueous $NaHCO_3$, and the organic layer was washed with H_2O (50 mL), dried over Na_2SO_4, filtered, and concentrated to provide a residue. The crude product was purified by tapered preparative TLC (50% EtOAc in heptane) and yielded 131.0 mg (40%) of **33** as a white crystalline solid: mp 132.5−133.5 °C; ^{1}H NMR (DMSO-d_6 300 MHz) δ 7.43 (s, 1H), 7.31 (s, 2H, 2NH), 7.21 (d, J = 8.2 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (DMSO-d_6 75.5 MHz) δ 166.02, 151.03, 131.39, 130.22, 126.76, 121.15, 117.77, 21.08; MS MH^+ (rel int) 165.2 (100). Anal. Calcd for $C_8H_8N_2S$: C, 58.51; H, 4.91; N, 17.06; S, 19.52. Found: C, 58.47; H, 4.94; N, 16.99; S, 19.57.

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Supporting Information Available: General experimental methods and experimental procedures to prepare **5**, **8**, **10**, **12**, **13**, **15**, **17**/**18**, **20**/**21**, **25**, **32**, and **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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