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TECHNICAL NOTE

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Development of an Optimized Process for the Preparation of 1-Benzylazetidin-3-ol: An Industrially Important Intermediate for Substituted Azetidine

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Supporting Information

ABSTRACT: A thoroughly optimized and robust process for the synthesis of 1-benzylazetidin-3-ol has been emphasized. 1-Benzylazetidin-3-ol has been utilized as a starting material in the commercial synthesis of azetidin-3-ol hydrochloride. Synthesis of azetidin-3-ol hydrochloride involves the usage of very low cost and commercially available starting material (benzylamine) and with reduced formation of di(3-chloro-2-hydroxypropyl) benzylamine significantly resulting in an economical process that allows the effective production of 1-benzyl azetidin-3-ol as well as azetidin-3-ol hydrochloride.

1. INTRODUCTION

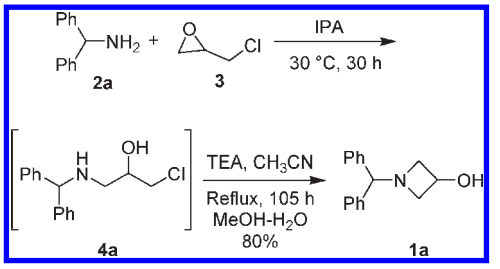
Drugs comprising azetidine derivatives have been thoroughly investigated for their pharmacological and biological effects.[1] The number of recent research articles provides evidence of the large use of the azetidine ring system in medicinally important molecules.[1] Among the various derivatives of azetidines, 3-substituted azetidine is most important constituent in various potential therapeutic moieties.[1] The required synthetic azetidine compounds are gaining much attention in the pharmaceutical industry as well as drug discovery for the synthesis of drugs comprising azetidine derivatives. Several research articles describe the synthesis of 3-substituted azetidines.[1,2] Recently, we reported an improved, one-pot, and multikilogram-scale synthesis of 1-benzhydrylazetidin-3-ol, **1a** (Scheme 1) starting from benzhydrylamine, **2a** and epichlorohydrin **3** via 3-chloro-1-diphenylmethylamino-2-hydroxypropane, **4a**.[3] 1-Benzhydrylazetidin-3-ol **1a** is utilized as a starting material in the commercial synthesis of an industrially important key structural motif, azetidin-3-ol hydrochloride **5** (Figure 1).[3,4]

Although the reported synthesis of **1a** is efficient, the total cost for the preparation of azetidin-3-ol hydrochloride **5** has not reached our expectation (even though the overall yield in preparing **5** is about 77% starting from **2a**). Upon a raw-material cost exercise, we evaluated that the contribution of benzhydrylamine **2a** (starting material for preparation of either **1a** or **5**) is more than 55% in total cost of **5**, and we simultaneously evaluated possibilities to replace the benzhydrylamine **2a** with other amines.

Our interest in replacing **2a** to synthesize azetidin-3-ol hydrochloride **5** was thus renewed due to the low cost of benzylamine **2b** (commercial cost of benzylamine **2b** is about 25 times lower than that of benzhydrylamine **2a**). Even if we achieve an overall yield as low as 15% while preparing compound **5** starting from benzylamine **2b**, the raw-material cost (RMC) of **5** will be similar to 80% overall yield of **5** starting from benzhydrylamine **2a**. This gave us incentive to develop the process to prepare compound **5** staring from benzylamine via 1-benzylazetidin-3-ol **1b**. Another advantage of using benzylamine **2b** instead of benzhydrylamine **2a** is the byproduct during hydrogenolysis is toluene (in the case of benzylamine) that can be very easily removed by simple atmospheric distillation when compared to diphenylmethane, the byproduct in the case of benzhydrylamine.

Initially, the compounds **4b** and **1b** were synthesized as per the literature-documented process.[5] Numerous procedures were reported for **4b** including minor process modifications with varied yields ranging from 40 to 95%.[5] However, we often observed lower yields and formation of di(3-chloro-2-hydroxypropyl)benzylamine **6b** (bis impurity) in major proportion (Figure 2). The reaction of epichlorohydrin **3** with benzylamine

Scheme 1. Synthesis of 1-benzhydrylazetidin-3-ol, 1a



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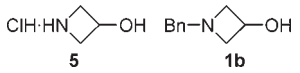


5 1b

Figure 1. Structures of azetidin-3-ol hydrochloride **5** and 1-benzylazetidin-3-ol **1b**.

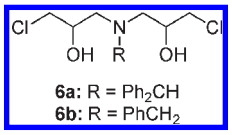
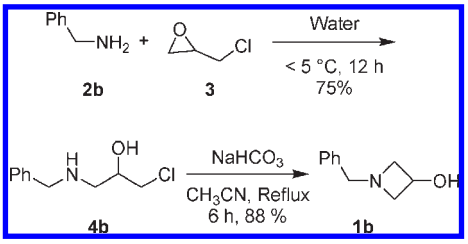


Figure 2. Structure of bis impurity **6**.

Scheme 2. Synthesis of 1-benzylazetidin-3-ol, 1b



2b was not greatly encouraging even when subjected to the conditions described for **1a**, and the formation of bis impurity **6b** was about 20−22%, whereas 7−9% of **6a** in case of benzhydrylamine **2a**. Probably steric factors could be the reason for formation of **6b** in enriched levels as compared to that of **6a**. Attempts were unsuccessful to recrystallize 1-(benzylamino)-3-chloropropan-2-ol **4b** (step 1 product in preparation of 1-benzylazetidin-3-ol **1b**) when associated with bis impurity **6b** in larger portions (20−25%). This conclusively indicated that the reaction conditions previously described (for 1-benzhydrylazetidin-3-ol, Scheme 1) are not suitable or applicable to 1-benzylazetidin-3-ol **1b**. Therefore, we took on the task of reducing the formation of **6b** in the preparation of 1-(benzylamino)-3-chloropropan-2-ol **4b** by optimizing the reaction conditions (critical process parameters and robustness testing).

2. RESULTS AND DISCUSSION

To develop an efficient and robust process for 1-benzyl azetidin-3-ol **1b**, the synthesis of **1b** was studied as a two-step process i.e., the formation of respective chlorohydrin **4b** followed by intramolecular cyclisaiton to get **1b**. First step involves the opening of oxirane ring in epichlorohydrin using benzylamine to give **4b**. Initially, we studied the impact of mole ratio of both the starting materials (epichlorohydrin and benzylamine), rate of addition of epichlorohydrin, effect of solvent, temperature and reaction time on the formation of bis impurity **6b** during preparation of **4b** (Scheme 2).

Equimolar ratio of benzylamine and epichlorohydrin resulted in incomplete reaction. Increasing epichlorohydrin mole ratio increases the formation of bis impurity **6b** as expected, but the results are not vice versa. Excess benzylamine did not reduce **6b** formation and also the reaction encountered difficulty in isolation of **4b**. Summarizing the study, the optimized molar ratio of benzylamine and epichlorohydrin is arrived at 1:1.16 respectively. Addition time was studied. Epichlorohydrin is added in to the stirred solution of isopropanol and benzylamine over a period of more than 1 h. Upon decreasing the addition time to its half (about 30 min), observed the enrichment of formation of **6b** to about 5−6% but upon increasing, there is not much impact on formation of **6b**.

Table 1. Effect of solvent and temperature on reaction progress and impurity 6b formation

	reaction conditions		content (%)[a]	
entry no.	solvent[b]	temperature (°C)	SM	**6b**
1	water	0−5	1.2	5.1
2	water	25−30	4.9	42.7
3	acetonitrile	0−5	no reaction	
4	acetonitrile	15−20	35.2	8.5
5	acetonitrile	25−30	22.5	12.7
6	toluene	0−5	no reaction	
7	toluene	15−20	52.0	7.9
8	toluene	25−30	44.0	10.0
9	hexane	0−5	no reaction	
10	hexane	15−20	7.2	28.0
11	hexane	25−30	7.3	43.8

[a] Area % by HPLC (216 nm) in the reaction mass. Remaining major portion in reaction mixture was identified as product, i.e., 3-chloro-1-phenylmethyl amino-2-hydroxypropane, **4b**. Any other major single maximum impurity (>1.0%) was not observed. Each reaction was maintained in its respective conditions for more than 24 h. [b] Note. No reaction has been observed at below 0 °C in any of the above-mentioned solvents.

Table 2. Dilution effect on impurity 6b formation

	reaction conditions		
entry no.	solvent	volumes[a] (vol)	% of impurity 6b[b]
1.	water	5	15.1
2.	water	10	8.2
3.	water	15	7.5
4.	water	20	5.1

[a] Solvent volumes with respect to benzylamine. [b] Area % in HPLC (216 nm) in the reaction mass. In all the experiments, the absence of benzylamine was observed by HPLC.

Further, we studied the effect of solvent and reaction temperature on formation of **6b**. The solvent isopropanol at reflux temperature (identified as better solvent as in the case of preparation of **4a**) resulted 20−25% of **6b**. Therefore, we studied the impact of formation of **6b** in less polar and more polar solvents than isopropanol as well as at temperatures ranging from 0 to 30 °C. The results are quite encouraging and tabulated in Table 1.

From these studies it has been identified that formation of **6b** is in reduced level comparatively at low temperatures in water, acetonitrile or toluene as solvent while no reaction has been observed at 0−5 °C in acetonitrile, toluene and hexane. The best condition among the results tabulated is water as solvent at 0−5 °C for the reaction of benzylamine with epichlorohydrin with respect to reaction progress. On the other hand, the dilution (concentration) of the reaction mixture (solvent volume/quantity) is also playing a key role in the formation of impurity **6b** and therefore the dilution effect has been studied by using water as a solvent. These results are summarized in Table 2.

Reaction time is one of the most important parameters. If the step 1 reaction mixture is maintained at reaction conditions even

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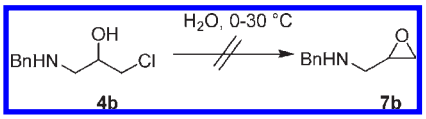
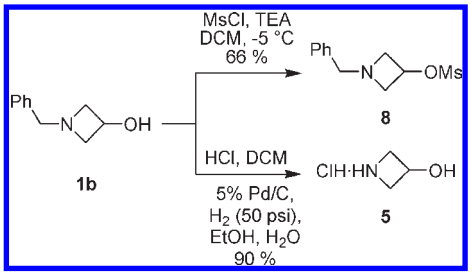
Scheme 3. *N*-Benzyl(oxiran-2-yl)methanamine 7b



Scheme 4. Synthesis of compound 8 and compound 5 from compound 1b



after consumption of the benzylamine (12−14 h), the enriched level of bis impurity is observed as expected. Finally optimized reaction conditions for the opening of the oxirane ring in epichlorohydrin using benzylamine is water as a solvent (20 times with respect to benzylamine), at 0−5 °C with 12−14 h.

We also planned to develop a reprocessing method to remove impurity **6b** (from **4b**) which could be useful in unanticipated situations since the formation of impurity **6b** is dependent on many parameters such as solvent volume, temperature, addition time, and reaction time. The development of the reprocessing method for the product (even though not necessary) is a general practice while performing critical reactions in pilot plant or production. In this case, various solvents and solvent mixtures were screened, and toluene was identified as a better solvent. However, this reprocessing method could be useful in cases where impurity **6b** is less than 15% in the crude **4b**.

Additionally, the formation of *N*-benzyl(oxiran-2-yl)methanamine **7b** has not been observed in step 2 in the case of benzylamine as the starting material compared to that of benzhydrylamine. No further conversion of **4b** into *N*-benzyl-(oxiran-2-yl)methanamine **7b** was confirmed by reaction of 3-chloro-1-phenylmethylamino-2-hydroxy propane **4b** in step 1 conditions and also at ambient temperature (Scheme 3).

Progress of the later step (cyclization of compound **4b**) was also studied thoroughly using different bases such as Na_2CO_3, $NaHCO_3$, K_2CO_3, $KHCO_3$, *N,N*-diisopropylethylamine (DIPEA), or triethylamine (TEA) in different solvents such as methanol, isopropanol, *N,N*-dimethylformamide (DMF), or acetonitrile at reflux temperature. While monitoring of all the described reactions using HPLC, the identified better condition among all the attempts was $NaHCO_3$ with acetonitrile as solvent in a period of 5−7 h at reflux temperature followed by isolation in hexane yielding the targeted compound **1b** with appropriate quality and quantity.

Azetidin-3-ol hydrochloride **5** can be prepared from 1-benzhydrylazetidin-3-ol **1a** but it was tedious to remove the by product, diphenylmethane by high vacuum distillation. However, the byproduct in deprotection of benzyl group of 1-bezhydrylazetidin-3-ol **1b** is toluene which can be easily removed from the reaction mixture either by distillation or filtration. Manufacturing cost of azetidin-3-ol hydrochloride **5** prepared from benzylamine as starting material via 1-benzylazetidin-3-ol **1b** reduced over 75% (Scheme 4). This showed a remarkable improvement in the reduction of RMC for **5**. In the similar way prepared *O*-mesyl derivative **8** of **1b** by following the reported procedure.[5d] As explained, the azetidine ring inclusion used to be done by 1-benzhydrylazetidinine-3-ol **1a**. Instead of 1-benzhydrylazetidinine-3-ol **1a**, 1-benzylazetidine-3-ol **1b** can be utilized for such kinds of purposes which give more atom economy as well as lower manufacturing cost.

Table 3. RT and RRT of compounds 1b, 2b, 4b, and 5

compound	RT	RRT
1b	5.81	1.00
2b	5.52	0.95
4b	6.58	1.13
5	7.53	1.29

HPLC Method. Nonchiral RP-HPLC method for the analysis of compounds **1**, **2**, **4**, and **5**: A Waters model Alliance 2690-separation module equipped with a Waters 996-photodiode array UV detector was used. ZORBAX ECLIPSE XDB C18 4.6 × 150 mm, 5.0 μ, injection volume 10 μL, Solvent A: 0.05% TFA (trifluoroacetic acid) in water, Solvent B: 0.05% TFA in acetonitrile, gradient 10−90% B in 25 min, then 10% B for 10 min, at 0.8 mL/min and detection at 216 nm using a ultraviolet visible detector. Samples were dissolved in acetonitrile. The approximate retention time (RT) and relative retention time (RRT) of compounds **1b**, **2b**, **4b**, and **5** are given in Table 3. RRT of each compound was specified relative to that of compound **1b**.

The robustness of the optimized process of 1-benzylazetidin-3-ol **1b** has been checked in various scales initially in the lab by conducting three process consistency batches (200-g scale) and also demonstrated to pilot plant by executing the process on >10-kg scale. The results are as expected, and the Hazard and Operability (HAZOP) studies were also carried out for existing process and operations in order to evaluate potential hazards and operability problems before execution of the final process on >10-kg level. However, we have not identified any possible deviations from normal operations and also placed appropriate safeguards to prevent accidents.

CONCLUSION

Herein we report an optimized and robust process for the synthesis of 1-benzylazetidin-3-ol **1b** and also demonstrated the synthesis of azetidine-3-ol hydrochloride **5** which involves the use of commercially available starting material and benzylamine and also reduces the formation of di(3-chloro-2-hydroxypropyl)benzylamine significantly. The optimized process is more economical and allows effective production of 1-benzylazetidin-3-ol **1b** as well as azetidine-3-ol hydrochloride **5**.

EXPERIMENTAL SECTION

Benzylamine and epichlorohydrin were obtained from commercial sources and used without further purification. All reagents and solvents employed were of commercial grade and were used as such, unless otherwise specified. Reaction flasks were oven-dried at 200 °C, flame-dried, and flushed with dry nitrogen prior to use. All moisture- and air-sensitive reactions were carried out under an atmosphere of dry nitrogen. Organic extracts were dried over anhydrous Na_2SO_4. Flash chromatography was performed using Kieselgel 60 brand silica gel (230−400 mesh). The melting points were determined in an

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open capillary tube using a Büchi B-540 melting point instrument and were uncorrected. The IR spectra were obtained on a Nicolet 380 FT-IR instrument (neat for liquids and as KBr pellets for solids). NMR spectra were recorded with a Varian 300 MHz Mercury Plus spectrometer at 300 MHz (^{1}H) and at 75 MHz (^{13}C). Chemical shifts were given in ppm relative to trimethylsilane (TMS). Mass spectra were recorded on Waters quattro premier XE triple quadrupole spectrometer using either electron spray ionisation (ESI) or atmospheric pressure chemical ionization (APCI) technique.

3-Chloro-1-phenylmethylamino-2-hydroxypropane (4b). A 250-L glass-lined reactor was charged with demineralized water (150 L) and benzylamine **2b** (10 kg, 93.33 mol). To this stirred solution was added epichlorohydrin **3** (10 kg, 108.08 mol) over a period of 1 h, maintaining the batch temperature <5 °C. After the addition, the mixture was agitated for an additional 10−12 h at 0−5 °C and then sampled for HPLC analysis. HPLC typically indicated less than 2.0 area % of **2b** remaining in the reaction mixture. At this point the obtained white solids were filtered, and the wet cake was washed with additional demineralized water (25 L) followed by *n*-heptane (50 L). The wet cake was dried under vacuum at <45 °C (LOD = 0.5%) to give 3-chloro-1-phenylmethylamino-2-hydroxy propane **4b** as a white crystalline solid in 75% yield (14 kg) with an HPLC purity of 98.2 area %. Mp 72−73 °C; ^{1}H NMR ($CDCl_3$): δ 2.56−2.7 (m, 2H), 3.5−3.6 (m, 2H), 3.62−3.7 (m, 1H), 3.72−3.88 (m, 3H), 5.2 (br s, 1H), 7.2−7.4 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 47.4, 51.5, 53.5, 69.3, 127.2, 128.1, 128.4, 139.1. IR (KBr): 3290, 2900, 1449, 1340, 1254, 1073, 882 cm^{-1}. ESI-MS *m*/*z*: 199.8 [$M^+ + 1$].

1-Benzylazetidne-3-ol (1b). A 250-L glass-lined reactor was purged with nitrogen and charged with acetonitrile (170 L) and 3-chloro-1-phenylmethylamino-2-hydroxy propane **4b** (14 kg, 70.11 mol). To this stirred solution was added sodium bicarbonate (14.7 kg, 175 mol) at <30 °C. The temperature of the reaction mixture was raised to reflux, stirred for 5−7 h, and then sampled for HPLC analysis. HPLC indicated less than 2.0 area % of **4b** remaining in the reaction mixture. The temperature of reaction mixture was cooled to room temperature, the inorganic salts were filtered, and the wet cake was washed with acetonitrile (30 L). The majority of the organic volatiles (acetonitrile) from the filtrate were removed by distillation at <50 °C under reduced pressure (80−100 Torr), giving crude compound **1b**. *n*-Heptane (2 × 100 L) was added to the crude **1b** and codistilled at <50 °C under reduced pressure (80−100 Torr). The resulted residue was triturated with *n*-heptane (28 L) and stirred for 2 h at 25 °C. The obtained solids were filtered, the wet cake was washed with *n*-heptnae (10 L) and dried under vacuum at <45 °C to give 1-benzylazetidne-3-ol **1b** as a white crystalline solid in 88% yield (10.07 kg) with an HPLC purity of 94.98 area %. Mp 64−65 °C; ^{1}H NMR ($CDCl_3$): δ 3.0 (m, 2H), 3.54−3.60 (m, 2H), 3.62−6.64 (m, 2H), 3.7−4.0 (br s 1H), 4.4 (m, 1H), 7.23−7.33 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 61.1, 63.1, 63.4, 127.1, 127.6, 128.0, 128.1, 128.3, 136.8. IR (KBr): 3387, 2838, 1493, 1451, 1341, 1176, 1082, 743 cm^{-1}. ESI-MS *m*/*z*: 164.1 [$M^+ + 1$].

Azetidin-3-ol Hydrochloride (5). A 250-L glass-lined reactor was charged with dichloromethane (100 L) and 1-benzylazetidne-3-ol **1b** (10 kg, 61.3 mol). From this stirred solution was purged HCl gas over a period of 30 min. The precipitated solids were filtered, and the wet cake was washed with excess of dichloromethane. The wet solid was dried at <45 °C and gave 11.4 kg of the hydrochloride salt of **1b**. In a 200-L, hydrogenation reactor, the hydrochloride salt of **1b** (11.4 kg) was diluted with ethanol (90 L), followed by water (10 L), and was charged with 5% Pd/C (0.5 kg) and H_2 (50 psi). After 24 h at room temperature, the reaction was complete. The catalyst was filtered off, and the filtrate was concentrated to an oily solid. The crude product was slurried in ethyl acetate (25 L) overnight and then filtered to give azetidin-3-ol hydrochloride (**5**) as a white crystalline solid in 90% yield over two steps, 6.07 kg, with an HPLC purity of 99.3 area %. Mp 86−88 °C; ^{1}H NMR (DMSO-d_6): δ 3.7 (m, 2H), 4.0 (m, 2H), 4.5 (m, 1H), 6.2 (br s, 1H, D_2O exchangable), 9.1 (br s, 2H, D_2O exchangable); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.0, 61.3; ESI-MS: *m*/*z* 74.1 [$M^+ + 1$].

1-Benzylazetidin-3-yl Methanesulfonate Hydrochloride (8). To a solution of 1-benzylazetidne-3-ol **1b** (100 g, 0.613 mol) in dichloromethane (1 L) was added triethylamine (86.7 g, 0.858 mol) at <5 °C under nitrogen atmosphere. Methanesulfonyl chloride (82 g, 0.713 mol) was added slowly at <5 °C over a period of 1 h, and the reaction mixture was maintained another 1 h at the same temperature (<5 °C) and then sampled for HPLC analysis. HPLC typically indicated less than 2.0 area % of **1b** remaining in the reaction mixture. The temperature of reaction mixture **was raised** to room temperature, the inorganic salts were filtered, and the wet cake was washed with dichloromethane (150 mL). Dry HCl gas was slowly purged from the filtrate at <5 °C from pH 1.0 up to pH 2.0. The reaction mixture was maintained for an additional 1 h at the same temperature. The resulted solids were filtered, and the wet cake was washed with dichloromethane (200 mL) and dried at <60 °C under vacuum to give 1-benzylazetidin-3-yl methane sulfonate hydrochloride (**8**) as a white crystalline solid in 66% yield, 112 g, with an HPLC purity of 98 area %. Mp 137−138 °C; ^{1}H NMR (CD_3OD): δ 2.8 (s, 3H), 3.54−3.7 (m, 3H), 3.8 (m, 1H), 4.4 (d, 1H), 4.55−4.6 (d, 1H), 4.82 (m, 1H), 7.48 (m, 5H). IR (KBr): 2975, 2676, 2491, 1350, 1172 cm^{-1}. MS *m*/*z*: 242 [$M^+ + 1$].

Di(3-chloro-2-hydroxypropyl)benzylamine (Bis Impurity, 6b). To a stirred mixture of benzylamine (10 g, 0.09 mol) in water (50 mL) was added epichlorohydrin (20.0 g, 0.19 mol) at <5 °C over a period of 1 h, and then the temperature of the reaction mixture was allowed to reach room temperature. The reaction mixture was stirred for an additional 24 h at the same temperature. After completion of the reaction (by TLC), solids were filtered and purified by column chromatography eluting with ethyl acetate/hexane (1:9) to give **6b** as a white solid in 60% yield, 9.0 g. Mp 93−95 °C; ^{1}H NMR ($CDCl_3$): δ 2.7−2.9 (m, 4H), 3.3−3.5 (m, 6H), 3.7−3.8 (m, 2H), 3.85−4.0 (m, 2H), 7.2−7.4 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 30.9, 47.3, 57.8, 58.4, 60.1, 60.2, 68.4, 69.1, 127.7, 128.6, 129.0, 129.1, 137.5; IR (KBr): ν 3261, 2955, 1452, 1090, 746, 703 cm^{-1}; ESI-MS: *m*/*z* 292 [$M^+ + 1$].

■ ASSOCIATED CONTENT

Supporting Information. Characterization data of compound **4b**, **1b**, **5**, **6b**, **8** and HPLC chromatogram of **4b**, **1b**, **5**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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