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Benzylation Reactions in DMF Lead to an Impurity Which Acts as an Organocatalyst Poison in Thiourea-Catalyzed Glycosylations

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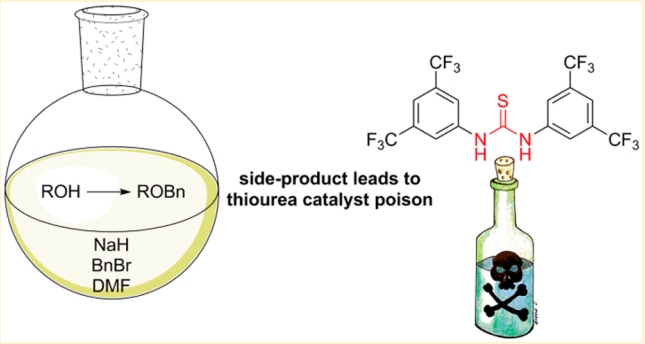
Supporting Information

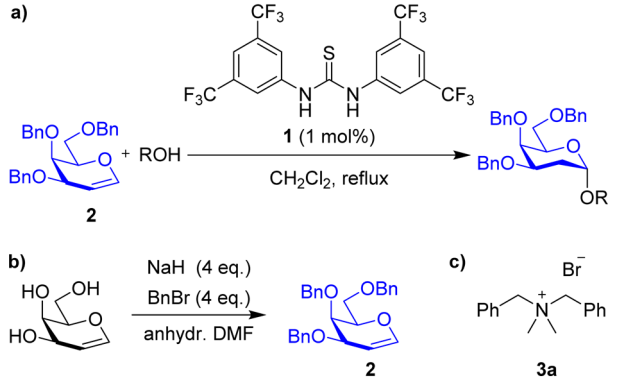
ABSTRACT: The benzylation of alcohols with the commonly used combination of benzyl bromide and sodium hydride in DMF can lead to the formation of an amine side product, *N*,*N*′-dimethyl-1-phenyl-1-(*o*-tolyl)methanamine. This amine coeluted with benzylated galactal during column chromatography and was found to be a catalyst poison in thiourea-catalyzed glycosylations of galactals. It may also be problematic for other base-sensitive reactions involving benzylated substrates. Solutions to this problem are described.



The benzylation of alcohols with benzyl bromide in DMF is an extremely common reaction, and sodium hydride is the base of choice (>50% of the time).[1] Herein, we describe a previously unreported impurity that can arise under these reaction conditions and report that it can act as a catalyst poison in thiourea-catalyzed reactions.[2]

Building on Schreiner's THP protection of alcohols,[3] in 2012, we[4] reported the use of Schreiner's catalyst **1** (Scheme 1a) in organocatalyzed glycosylations[5−13] forming 2-deoxygalactosides. Although we successfully synthesized 17 disaccharides with excellent α-selectivity and high yields, at the time, it was noted that the "*purity of precursors was crucial to obtaining reproducible results*", and at that time, we attributed this to "*small amounts of salts in the precursors*".[4] In our efforts to further develop this chemistry, we experienced capricious behavior, sometimes the reaction returned unreacted starting material, which we narrowed down to being due to differences between batches of benzyl galactal **2** (our standard test substrate). In an unremarkable standard protocol, galactal was benzylated using BnBr, NaH, and anhydrous DMF (Scheme 1b). Following column chromatography and subsequent recrystallization, benzylated galactal **2** was analyzed by mp and ^{1}H and ^{13}C NMR. We were unable to detect significant differences between "good" and "bad" batches of **2**. Since our glycosylations use just 1 mol % of catalyst, we were conscious that a catalyst poison could still be present but evade detection by NMR. HPLC revealed small amounts of an impurity eluting which was common among all "bad" batches examined. Following isolation of this impurity by preparative HPLC, we were able to determine that the impurity did not contain any glycal, so we deduced it must have originated from a reaction between DMF and BnBr; however, its structure remained unclear. ESI-MS gave an ion with m/z = 226. Mobashery and co-workers[14] reported the formation of dibenzyldimethylammonium bromide **3a** (m/z = 226) in the benzylation of a glycal; however, the NMR data for our impurity were inconsistent with **3a**.

Scheme 1. (a) Thiourea-Catalyzed Glycosylation, (b) Standard Benzyl Ether Protection of Galactal Using NaH, BnBr, and DMF, and (c) Ammonium Salt Side Product Identified by Mobashery and Co-workers[14]



The reaction of BnBr with NaH in DMF was carried out in the absence of the alcohol component (Method 1). TLC analysis (cyclohexane/ethyl acetate; 4:1) following reaction showed a complex mixture with five spots evident upon UV visualization (R_f = 0.66, 0.5, 0.33, 0.14, and 0.03). The spot with R_f = 0.33 matched the R_f of perbenzylated galactal **2** and thus could coelute during attempted column chromatographic

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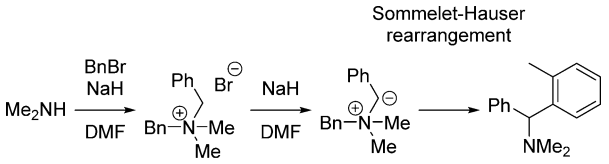
purification of **2**. Following isolation of this unknown by column chromatography, NMR, MS, and HPLC data for this compound were consistent with the impurity we had previously isolated by preparative HPLC. The material was crystalline, and the structure was determined by X-ray analysis to be tertiary amine **4** (Scheme 2; see Supporting Information for X-ray data). To the best of our knowledge, there are no previous reports of this impurity arising from these popular benzylation conditions.

Scheme 2. Formation of 4 from Me_2NH and BnBr in the Presence of NaH via Sommelet−Hauser Rearrangement of Ylide 5



We propose that under the reaction conditions, amine **4** is formed as follows (Scheme 2): DMF is known to decompose, giving dimethylamine and carbon monoxide.[15] This decomposition is catalyzed by acids or bases. It is noted to be particularly prevalent when DMF is allowed to stand for long periods at room temperature in dehydrative agents such as KOH, NaOH, or CaH_2. The commercially available anhydrous DMF used in our laboratory may contain some dimethylamine.[16] Reaction of dimethylamine with BnBr in the presence of NaH would give salt **3a**, followed by deprotonation to give ylide **5**. Sommelet−Hauser rearrangement of ylide **5** would then give **4**.[17−19] We note that increasing the amount of NaH used in Method 1 did not increase the amount of compound **4** generated, so we do not believe that dimethylamine is forming from a reaction of NaH with DMF under our conditions. We dried DMF[15] over $CaCl_2$, distilled it, and explored whether "aging" (1, 3, 23 days) or storing the DMF over molecular sieves affected the levels of impurity obtained in our benzylation reaction. However, we saw similar levels of **4** in all cases.

To confirm that amine **4** poisoned reactions involving catalyst **1**, two parallel glycosylations were set up using our previously reported glycosylation conditions with benzyl galactal free of **4** (see below) (Scheme 1a). To one of the reactions was added 7 mol % of **4**. The control reaction went to completion after 18 h, and the glycosylation with added amine **4** did not proceed at all; that is, the catalyst was poisoned. For completion, we then synthesized **4** by an alternative route which was free of DMF, BnBr, and NaH (Method 2), and once again, it was shown to be a competent catalyst poison. In line with the literature reported pK_a of 8.5 in DMSO for **1**,[20,21] ^{1}H NMR in CD_2Cl_2 showed the disappearance of the N−H protons (8.1 ppm) of catalyst **1** upon addition of tertiary amine **4**. The catalyst is poisoned by deprotonation of the acidic N−H proton by amine **4**. In the case of our reaction, these problems can be avoided by changing the solvent for benzylation from DMF to THF.[22] However, we found that including an acid wash in the workup of the reactions carried out in DMF was a preferable solution in our hands and is likely to be broadly applicable to any benzylation in DMF where **4** is a problem. Benzyl galactal **2** made in these ways showed no batch-to-batch variation.

In summary, we have identified a previously unreported side product that can arise under standard benzylation conditions using benzyl bromide, sodium hydride, and DMF. We have shown that this compound can poison thiourea catalysts. This should serve as a reminder that, like metal-based catalysts, organocatalysts are susceptible to poisoning by low-level impurities—something that does not garner that much attention. It is our hope that by documenting this reaction, other workers will be able to avoid similar problems when using benzylated substrates in thiourea-catalyzed and other base-sensitive reactions.

EXPERIMENTAL SECTION

General. Chemicals were purchased and used without further purification. Anhydrous DMF was obtained from Acros Organics (99.8%, extra dry, stored over MS, AcroSeal). Reactions requiring anhydrous conditions were performed under nitrogen; glassware and needles were placed in an oven (107 °C) for at least 30 min, flame-dried immediately prior to use, and allowed to cool under reduced pressure. Reactions were monitored by TLC on Kieselgel 60 F254 (Merck). Detection was by examination under UV light (254 nm). ^{1}H NMR and ^{13}C NMR spectra were measured in the solvent stated at 400 or 500 MHz. Chemical shifts are quoted in parts per million from the residual solvent peak (referenced), and coupling constants (J) are given in hertz. Multiplicities are abbreviated as b (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or combinations thereof.

Method 1: *N,N′*-Dimethyl-1-phenyl-1-(*o*-tolyl)methanamine (4). Under a N_2 atmosphere, anhydrous DMF (10 mL) and BnBr (0.5 mL, 4 mmol) were added to the reaction flask. The solution was cooled to 0 °C using 50:50 ice/water. NaH (60% dispersion in mineral oil) (0.28 g, 7 mmol) was added to the reaction mixture. The ice bath was removed, and the reaction mixture was left to stir at room temperature for 24 h. TLC analysis (4:1 cyclohexane/EtOAc) showed five spots (R_f = 0.66, 0.5, 0.33, 0.14, and 0.03). The reaction was quenched with MeOH (3 mL). The mixture was diluted using heptane (30 mL). All solvents were removed using rotary evaporation, which gave a brown solid (4.4 g). $CHCl_3$ (10 mL) was added, which dissolved some material and left a brown precipitate. The mixture was filtered using Büchner filtration, and the filtrate was concentrated using rotary evaporation, giving an orange/brown oil (1.7 g). Purification by column chromatography (95:5−60:40 cyclohexane/ethyl acetate) gave the desired product as an off-white solid (46 mg, 10% yield (based on BnBr)).

Method 2: *N,N′*-Dimethyl-1-phenyl-1-(*o*-tolyl)methanamine (4).[23] Dimethylamine (0.22 mL, 1.9 mmol, 8.6 M in H_2O) was added to a round-bottom flask containing EtOH (10 mL). The flask was cooled using ice/water. K_2CO_3 (130 mg, 0.94 mmol) and benzyl chloride (0.44 mL, 3.8 mmol) were added, and the mixture was stirred at room temperature for 1 week (time unoptimized). The mixture was filtered using Büchner filtration to remove a white precipitate. The filtrate was concentrated using a rotary evaporator to give a clear oil. The oil was dissolved in EtOAc (10−15 mL), and Et_2O (approximately 100 mL) was added slowly with stirring until a white precipitate formed. The precipitate was isolated using Hirsch filtration. This gave *N,N′*-dimethyl-*N,N′*-dibenzylammonium chloride **3b** (100 mg, 20% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.56 (m, 4H), 7.50−7.33 (m, 6H), 5.11 (s, 4H), 3.12 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, chloroform-*d*) δ 133.6, 130.8, 129.3, 127.6, 68.1, 48.4. These data were consistent with literature data.[24]

Under a N_2 atmosphere, chloride salt **3b** (50 mg, 0.22 mmol) was suspended in dry THF (2 mL) and was cooled to −5 °C (ice/ammonium chloride). KO*t*Bu in anhydrous THF (0.13 mL, 0.23 mmol, 1.8 M) was added to the reaction flask, upon which the chloride salt **3b** dissolved. The reaction was stirred at −5 °C for 3 h. TLC analysis (4:1 cyclohexane/EtOAc) showed that the desired product had formed (R_f = 0.33). The mixture was quenched with saturated sodium chloride (1 mL) and extracted with EtOAc (3 × 10 mL). The

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combined organic layers were washed with saturated $NaHCO_3$ (10 mL) followed by saturated sodium chloride (10 mL). The solution was dried with Na_2SO_4 and concentrated using rotary evaporation, which gave a whitish oil. Purification by column chromatography gave a white solid (24 mg, 48% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 7.8 Hz, 1H, C*H*), 7.45−7.34 (m, 2H, C*H*), 7.27−7.19 (m, 3H, C*H*), 7.19−7.13 (m, 1H, C*H*), 7.11−7.02 (m, 2H, C*H*), 4.26 (s, 1H, ArPhC*H*NMe$_2$), 2.34 (s, 3H, ArC*H*$_3$), 2.18 (s, 6H, 2 x C*H*$_3$); ^{13}C{^{1}H} NMR (126 MHz, chloroform-*d*) δ 142.6 (4 °C), 141.6 (4 °C), 135.6 (4 °C), 130.6 (CH), 128.6 (CH), 128.5 (CH), 127.2 (CH), 127.0 (CH), 126.5 (CH), 126.4 (CH), 73.0 (ArPhCHNMe$_2$), 45.1 (ArCH$_3$), 20.1 (NCH$_3$); HRMS (ESI-TOF) m/z calcd for $C_{16}H_{20}N$ 226.1596 ([M + H]$^+$); found 226.1601; crystals suitable for X-ray crystallography were obtained by evaporation from $CDCl_3$ (CCDC 1496558). Spectroscopic data were in agreement with literature data.[25]

Synthesis of 3,4,6-tri-*O*-benzyl-D-galactal 2 Free of Impurity 4. Under a N_2 atm, D-galactal (1.75 g, 12 mmol) was dissolved in anhydrous DMF (50 mL). The flask was cooled to 0 °C (50:50 ice/water), and NaH (60% dispersion in mineral oil) (2.14 g, 53.5 mmol) was added to the reaction flask. The ice bath was removed, and the reaction was left to stir at room temperature for 30 min. The flask was again cooled to 0 °C, and BnBr (5.5 mL, 46 mmol) was added dropwise to the reaction mixture. The ice bath was removed, and the reaction mixture was left to stir at room temperature for 36 h. TLC analysis (4:1 cyclohexane/ethyl acetate; H_2SO_4 stain (15−10% EtOH)) showed that the starting galactal (baseline spot) was consumed and three spots were present in the reaction mixture (R_f = 0.67, 0.33, 0.03). The reaction was quenched with MeOH (2 mL), and the solvents were removed using rotary evaporation. The crude mixture was dissolved in cyclohexane (100 mL) and washed with 1 M HCl (2 × 30 mL), then saturated $NaHCO_3$ (1 × 30 mL) and deionized H_2O (30 mL). The organic layer was dried using $MgSO_4$ and filtered using Büchner filtration, and the solvent was removed using rotary evaporation. Purification by column chromatography (cyclohexane/ethyl acetate) gave a white solid (3.1 g, 62% yield): mp 51−53 °C (cyclohexane/ethyl acetate) (lit.[26] 49.6−52.0 °C (cyclohexane/ethyl acetate)); ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.47−7.13 (m, 15H), 6.36 (dd, J = 6.3, 1.5 Hz, 1H), 4.90−4.83 (m, 2H), 4.65 (d, J = 12.1 Hz, 1H), 4.64 (d, J = 12.4 Hz, 1H), 4.60 (d, J = 12.2 Hz, 1H), 4.50 (d, J = 11.9 Hz, 1H), 4.42 (d, J = 11.9 Hz, 1H), 4.22−4.16 (m, 2H), 3.97−3.92 (m, 1H), 3.78 (dd, J = 10.2, 7.2 Hz, 1H), 3.65 (dd, J = 10.1, 5.1 Hz, 1H); ^{13}C NMR (101 MHz, chloroform-*d*) δ 144.3, 138.6, 138.5, 138.1, 128.5, 128.5, 128.3, 128.0, 127.8, 127.7, 127.6, 100.1, 75.8, 73.6, 73.5, 71.4, 71.0, 70.9, 68.6. NMR data were consistent with literature data.[26] Compound **4** was not detected as an impurity by HPLC (Chiralpak IA column (250 mm length, 4.6 mm diameter), heptane/EtOH (95:5), 0.5 mL/min; 20 min run; R_t of **4** = 7.2 min, R_t of **2** = 14.5 min).

Control Experiments for Glycosylation. Two parallel glycosylations were set up as per the standard thiourea-catalyzed glycosylation procedure.[4] The reactions contained galactal **2** (149 mg, 0.36 mmol, 1.2 equiv),[22] diacetone galactose acceptor (78 mg, 0.3 mmol, 1 equiv), and thiourea catalyst **1** (1.5 mg, 0.003 mmol, 1 mol %). Amine **4** (5 mg, 0.022 mmol, 7 mol %) was added to the second reaction. After 18 h, the first reaction was shown to be complete by ^{1}H NMR analysis. The second reaction mixture showed only the starting materials after 18 h.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01914.

NMR spectra for compounds **3b** and **4**, glycosylation reactions, NMR titration of **1** vs **4**, HPLC chromatograms for compound **2** contaminated with impurity **4**, and X-ray crystal structure for compound **4** (PDF)

X-ray data for **4** (CIF)

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Notes

The authors declare no competing financial interest.

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