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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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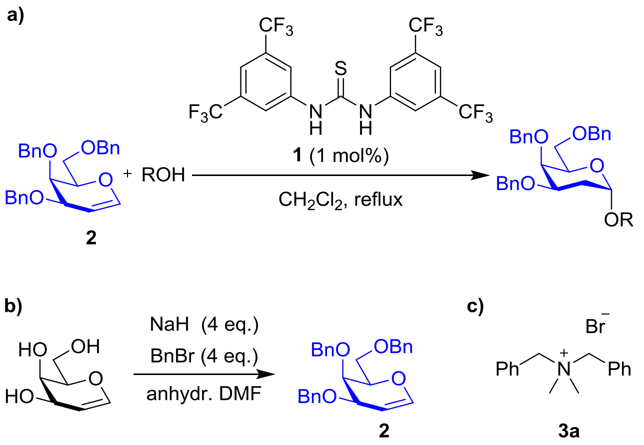
ABSTRACT: The benzylation of alcohols with the commonly used combination of benzyl bromide and sodium hydride in DMF can lead to the formation of an amine side-product, *N,N'*-dimethyl-1-phenyl-1-(*o*-tolyl)methanamine. This amine co-eluted with benzylated galactal during column chromatography and was 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, ^{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 amongst 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] had 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. (c) Ammonium salt side-product identified by Mobashery and co-workers.[14]

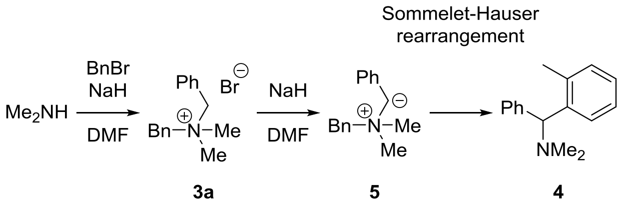


The reaction of BnBr with NaH in DMF was carried out in the absence of the alcohol component (Method 1). TLC analysis (cyclohexane:ethyl acetate; 4:1) following reaction showed a complex mixture with 5 spots evident upon UV visualization (R_f = 0.66, 0.5, 0.33, 0.14 and 0.03). The spot with R_f = 0.33 matched the R_f of perbenzylated galactal **2**, and thus could co-elute during attempted column chromatographic 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. Crucially, 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.

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 'ageing' (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.

Scheme 2: Formation of 4 from Me2NH, BnBr in the presence of NaH via Sommelet-Hauser rearrangement of ylide 5.



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 7 mol% of **4** was added. The control reaction went to completion after 18 h and the glycosylation with added amine **4** did not proceed at all i.e. 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] ^1H 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 work-up 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 Across 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). ^1H 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 residual solvent peak (referenced) and coupling constants (*J*) 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 (ice:water; 50:50). 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 hours. TLC analysis (cyclohexane:EtOAc; (4:1)) 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 (cyclohexane:ethyl acetate; 95:5-60:40) 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 one week (time un-optimized). 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 (approx. 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). ^1H 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); $^{13}C\{^1H\}$ 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 anhydr. 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 three hours. TLC analysis (cyclohexane: EtOAc; 4:1) showed 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 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, ArCH$_3$), 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 N2 atmosphere, D-galactal (1.75 g, 12 mmol) was dissolved in anhydrous DMF (50 ml). The flask was cooled to 0 °C (ice:water; 50:50) 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 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; H2SO4 stain (15-10% EtOH)) showed 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 1M HCl (2 × 30 ml), then sat. $NaHCO_3$ (1 × 30 ml) and deionized H_2O (30 ml). The organic layer was dried using $MgSO_4$, 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

NMR spectra for compounds **3b**, **4**, and glycosylation reactions, NMR titration of **1** vs **4**, HPLC chromatograms for compound **2** contaminated with impurity **4**, X-ray crystal structure and a CIF file for compound **4** (CCDC 1496558). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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