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E. N. Beal^a & K. Turnbull^a ^a Department of Chemistry Wright, State University Dayton, Ohio, 45435 Published online: 23 Sep 2006.

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BROMINATION / DEBROMINATION OF 6-BENZOYL-3-ALKYL OR 3-ARYL SYDNONEIMINES

E.N. Beal and K. Turnbull*

Department of Chemistry Wright State University Dayton, Ohio 45435

ABSTRACT: 6-Benzoyl-3-alkyl or 3-aryl sydnoneimines (cf. 3) form the 4-bromo congeners 4 cleanly, in good yield using NBS in DMF. Subsequent debromination occurs efficiently with sodium borohydride or sodium sulfite but in variable yield (and / or complexity) using sodium dithionite.

6-Acyl-3-substituted sydnoneimines (cf. 1) undergo facile electrophilic aromatic substitution at the 4- position.¹ Bromination has been the most studied reaction of this type and, in this regard, a number of methods (inter alia Br₂ / NaHCO₃², dibromodioxane or NBS³) have been developed for the preparation of the 4-bromo-6-acyl species 1 (R = alk., Ar; R' = Br) from their unsubstituted precursors 1 (R = alk, Ar; R' = H). Surprisingly, the reagent most effective for the bromination of the congeneric, more studied sydnones 2 (X = O), viz. NBS in DMF⁴, has been utilized only in a handful of specialized cases for 4-bromosydnoneimine preparations and, reportedly³ gives low yields of the desired products. Thus, it was one goal of the present research to examine the generality and optimization of this approach for the bromination of 6-benzoyl-3-alkyl or 3-aryl sydnoneimines 3. In addition, we have shown that the 4-bromo substituent (in e.g. 2 (X = O), R = Ar, R' = Br) can be used to protect the sydnone 4-position from further reaction while allowing modification of substituents upon the 3-aryl ring.⁵ Subsequent facile removal of the bromine can be effected using sodium borohydride⁶, sodium dithionite⁷ or sodium sulfite.⁸ In order to extend the utility of these findings, we

^{*} To whom correspondence should be addressed

chose to examine the reactions of the closely related 6-benzoyl-4-bromo-3-aryl sydnoneimines 4 with each of the aforementioned reagents.



We now report that bromination of 3 with NBS / DMF occurs cleanly, in high yield under mild conditions (0°C to room temperature) [route a and Table 1].

With the 4-bromo products 4 in hand, we turned our attention to their reactivity towards the reagents previously employed for debromination of 4-bromo sydnones 2 $(X = O, R^1=Br)$ [route b and Table 2]. In the event, removal of the 4-bromo atom (*i.e.* 4 to 3) with sodium borohydride or sodium sulfite appears to be a general, high yield process which is unaffected by the nature of the 3-substituent. The variable yields and sometimes complex mixtures resulting from the reduction of 4 with sodium dithionite were surprising, especially since no such problems were encountered with the corresponding sydnones 2 (X = O, R=Ar, R¹=Br).⁷ This notwithstanding, it appears that the 4-bromo atom can be used as a protective group for the sydnoneimine ring since it can be attached and removed cleanly, in high yield.

EXPERIMENTAL

Preparation of Starting Materials: The requisite 6-benzoyl sydnoneimines **3** were prepared from the corresponding sydnoneimine hydrochlorides **2** (X = NH+HCl)⁹ by standard methods.¹⁰

General Procedure for the Bromination of 6-Benzoyl Sydnoneimines

With stirring, N-bromosuccinimide (0.23 g, 1.29 mmol) was added in small portions to an ice cooled solution of the 6-benzoyl-3-substituted sydnoneimine (1.08 mmol) in N, N-dimethylformamide (3 mL). After a further 3 h at 0°C and 14 h at room temperature, ice water (30 mL) was added. Generally, crystals formed rapidly.

4	R	Yield [%] ^a	4	R	Yield [%] ^a
a	i-Pr	80	d	4-MeC ₆ H ₄	89
b	Bn	79	e	4-MeOC ₆ H ₄	83
с	Ph	74		Û.	

Table 1. Bromination of 6-Benzoyl-3-Substituted Sydnoneimines 3 with NBS

^a Yields are of isolated and purified products

Table 2. Debromination of 4-Bromo-6-Benzoyl-3-Substituted Sydnoneimines 4

3	R	Yield [%]			
		NaBH ₄	Na ₂ SO ₃	$Na_2S_2O_4$	
a	i-Pr	81	82	a	
b	Bn	85	91	85	
c	Ph	91	77	39 ^b	
d	4-MeC ₆ H ₄	84	92	86	
e	4-MeOC ₆ H ₄	86	82	64	

^a reaction not done

^b plus unidentified products

If not, the solution was reduced *in vacuo* to about one third volume and cooled. The crystals obtained were removed by filtration, dried and recrystallized from dichloromethane / petroleum ether.

Preparation of 4-Bromo-6-benzoyl-3-isopropylsydnoneimine (4a)

Using 6-benzoyl-3-isopropyl sydnoneimine (3a)[0.25 g] in the general procedure gave the title compound as colourless needles, 0.28 g (83%); mp 165-6°C; IR (KBr) 1632 (C=O str.), 1595 (C=N str.), 1337, 1209,1006 and 718 cm⁻¹; ¹H-NMR ∂ (CDCl₃) 1.71 (d, 6H), 4.96 (septet, 1H), 7.45 (m, 3H), 8.26 (m, 2H); analysis: calculated for C₁₂H₁₂BrN₃O₂: C, 46.45; H, 3.87; N, 13.55. Found: C, 46.56; H, 3.87; N, 13.49.

Preparation of 4-Bromo-6-benzoyl-3-benzylsydnoneimine (4b)

Using 6-benzoyl-3-benzyl sydnoneimine (**3b**) [0.32 g] in the general procedure gave the title compound as colourless crystals, 0.31 g (79%); mp 138-40°C; IR (KBr) 1615 (C=O str.), 1583 (C=N str.), 1565, 1379, 1340, 1006 and 708 cm⁻¹; ¹H-NMR ∂ (CDCl₃) 5.57 (s, 2H), 7.41 (s, 8H), 8.23 (m, 2H); analysis: calculated for C₁₆H₁₂BrN₃O₂: C, 53.63; H, 3.35; N, 11.73. Found: C, 53.51; H, 3.37; N, 11.53.

Preparation of 4-Bromo-6-benzoyl-3-phenylsydnoneimine (4c)

Using 6-benzoyl-3-phenylsydnoneimine (3c) [0.32 g] in the general procedure gave the title compound as tan crystals, 0.27 g (74%); mp 126-8°C; IR (KBr) 1627 (C=O str.), 1583 (C=N str.), 1360, 1316, 1213 and 1022 cm⁻¹; ¹H-NMR ∂ (CDCl₃) 7.59 (m, 8H), 8.30 (m, 2H); analysis: calculated for C₁₅H₁₀BrN₃O₂: C, 52.33; H, 2.91; N, 12.21 Found: C, 52.75; H, 3.11; N, 11.95.

Preparation of 4-Bromo-6-benzoyl-3-(p-tolyl)sydnoneimine (4d)

Using 6-benzoyl-3-(*p*-tolyl)sydnoneimine (**3d**) [0.31 g] in the general procedure gave the title compound as pale yellow crystals, 0.34 g (89%); mp 156-7°C; IR (KBr) 1633 (carbonyl str.), 1588 (C=N str.), 1358, 1347, 1212, 1035, 1015 and 989cm⁻¹; ¹H-NMR ∂ (CDCl₃) 2.51 (s, 3H), 7.48 (s, 7H), 8.30 (m, 2H); analysis: calculated for C₁₆H₁₂BrN₃O₂: C, 53.63; H, 3.35; N, 11.73. Found: C, 53.54; H, 3.35; N, 11.61.

Preparation of 4-Bromo-6-benzoyl-3-(p-anisyl)sydnoneimine (4e)

Using 6-benzoyl-3-(*p*-anisyl)sydnoneimine (3e) [0.32 g] in the general procedure gave the title compound as tan crystals, 0.34 g (83%); mp 123-4°C; IR (KBr) 1637 (C=O str.), 1583 (C=N str.), 1317, 1215, 1170 and 708 cm⁻¹; ¹H-NMR ∂ (CDCl₃) 3.91 (s, 3H), 7.10 (m, 2H), 7.47 (m, 5H), 8.29 (m, 2H); analysis: calculated for C₁₆H₁₂BrN₃O₃: C, 51.34; H, 3.21; N, 11.23. Found: C, 51.09; H, 3.15; N, 10.94.

Debromination of 4-Bromo-6-benzoyl-3-substituted sydnoneimines (4) i) with Sodium Borohydride in Methanol

General Procedure:

To a stirred solution (or suspension) of the bromosydnoneimine (4) [0.11 mmol] in methanol (2 mL) was added sodium borohydride (0.04 g, 1.1 mmol) in portions with stirring. The reaction was complete in 10-15 min as indicated by T.L.C whereupon the solvent was removed under a stream of air and water added (5-10mL). The insoluble product was removed by filtration in vacuo, dried, and compared to an authentic sample using T.L.C., IR and mp.

With 4-Bromo-6-benzoyl-3-isoproylsydnoneimine (4a)

Using the bromosydnoneimine (4a) [0.034 g] in the general procedure gave the debrominated product (3a), 0.021 g (81%); identical (mp, TLC, and IR) to an authentic sample.¹⁰

With 4-Bromo-6-benzoyl-3-benzylsydnoneimine (4b)

Using the bromosydnoneimine (4b) [0.041 g] in the general procedure gave the debrominated product (3b), 0.026 g (85%); identical (mp, TLC, and IR) to an authentic sample.¹⁰

With 4-Bromo-6-benzoyl-3-phenylsydnoneimine (4c)

Using the bromosydnoneimine (4c) [0.03 g] in the general procedure gave the debrominated product (3c), 0.027 g (91%); identical (mp, TLC, and IR) to an authentic sample.¹⁰

With 4-Bromo-6-benzoyl-3-(p-tolyl)sydnoneimine (4d)

Using the bromosydnoneimine (4d) [0.04 g] in the general procedure gave the debrominated product (3d), 0.026 g (84%); identical (mp, TLC, and IR) to an authentic sample.¹⁰

With 4-Bromo-6-benzoyl-3-(p-anisyl)sydnoneimine (4e)

Using the bromosydnoneimine (4e) [0.04 g] in the general procedure gave the debrominated product (3e), 0.028 g (86%); identical (mp, TLC, and IR) to an authentic sample.¹⁰

ii) with Sodium Sulfite in Methanol / Water

General Procedure:

To the bromosydnoneimine (4) (0.14 mmol) in methanol (1 mL) was added sodium sulfite (0.071 g, 0.56 mmol) in water (1mL). After the reaction was

complete (usually half to one and a half hours, TLC) more water was added (7-10 mL) to form a precipitate. The insoluble product was removed by filtration in vacuo, dried, and compared to an authentic sample using T.L.C., IR and mp.

With 4-Bromo-6-benzoyl-3-isopropylsydnoneimine (4a)

Using the bromosydnoneimine (4a) [0.034 g] in the general procedure gave the debrominated product (3a), 0.027 g (82%); identical (mp, TLC, IR) to an authentic sample.¹⁰

With 4-Bromo-6-benzoyl-3-benzylsydnoneimine (4b)

Using the bromosydnoneimine (4b) [0.053 g] in the general procedure gave the debrominated product (3b), 0.036 g (91%); identical (mp, TLC, IR) to an authentic sample.¹⁰

With 4-Bromo-6-benzoyl-3-phenylsydnoneimine (4c)

Using the bromosydnoneimine (4c) [0.053 g] in the general procedure gave the debrominated product (3c), 0.029g (77%); identical (mp, TLC, IR) to an authentic sample.¹⁰

With 4-Bromo-6-benzoyl-3-(p-tolyl)sydnoneimine (4d)

Using the bromosydnoneimine (4d) [0.051g] in the general procedure gave the debrominated product (3d), 0.036g (92%); identical (mp, TLC, IR) to an authentic sample.¹⁰

With 4-Bromo-6-benzoyl-3-(p-anisyl)sydnoneimine (4e)

Using the bromosydnoneimine (4e) [0.053 g] in the general procedure gave the debrominated product (3e), 0.034g (82%); identical (mp, TLC, IR) to an authentic sample.¹⁰

iii) with Sodium Dithionite in Water / Dimethylformamide General Procedure:

To the bromosydnoneimine (4) [0.14 mmol] in water / DMF (1:1, 0.5 mL) was added sodium dithionite (0.049 g, 0.28 mmol) and the mixture was stirred for 1.5 hours at room temperature. After the reaction was complete (TLC) more water was added (7-10 mL) to form a precipitate. The insoluble product was removed by

filtration *in vacuo*, dried, and compared to authentic sample using T.L.C., IR and mp.

With 4-Bromo-6-benzoyl-3-benzylsydnoneimine (4b)

Using the bromosydnoneimine (4b) [0.053 g] in the general procedure gave the debrominated product (3b), 0.033g (85%); identical (mp, TLC, IR) to an authentic sample.¹⁰

With 4-Bromo-6-benzoyl-3-phenylsydnoneimine (4c)

Using the bromosydnoneimine (4c) [0.048 g] in the general procedure gave the debrominated product (3c), 0.014g (39%); identical (mp, TLC, IR) to an authentic sample.¹⁰

With 4-Bromo-6-benzoyl-3-(p-tolyl)sydnoneimine (4d)

Using the bromosydnoneimine (4d) [0.051g] in the general procedure gave the debrominated product (3d), 0.036g (86%); identical (mp, TLC, IR) to an authentic sample.¹⁰

With 4-Bromo-6-benzoyl-3-(p-anisyl)sydnoneimine (4e)

Using the bromosydnoneimine (4e) [0.053 g] in the general procedure gave the debrominated product (3e), 0.026g (64%); identical (mp, TLC, IR) to an authentic sample.¹⁰

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