Synthetic Communications

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Walter W. Zajac Jr. , Thomas R. Walters , John Buzby , Janet Gagnon & Marc Labroli (1994) N-Benzylidenebenzenesulfonamide as a Benzaldehyde Equivalent in the Knoevenagel Reaction, Synthetic Communications, 24:3, 427-432

To link to this article: http://dx.doi.org/10.1080/00397919408011202

SYNTHETIC COMMUNICATIONS, 24(3), 427-432 (1994)

N-BENZYLIDENEBENZENESULFONAMIDE AS A BENZALDEHYDE EQUIVALENT IN THE KNOEVENAGEL REACTION

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ABSTRACT: N-Benzylidenebenzenesulfonamide was shown to be a useful benzaldehyde equivalent in the Knoevenagel Reaction for cyana - containing active methylene compunds. The intermediate β-N-benzenesulfonylamino carbonyl derivatives from other active methylene compounds failed to undergo elimination.

Interest in the chemistry of sulfonimines is enjoying a resurgence owing to the unique addition chemistry associated with these electron-deficient imines[1,2] and their improved syntheses.[3] We previously exploited the potential utility of N-benzylidenebenzenesulfonamide (**1**) as a benzaldehyde equivalent during the course of our investigation into the oxidation of amines with 2-(phenylsulfonyl)-3-phenyloxaziridine (**2**).[4] This study revealed that the synthetic utility of **2** for effecting the amine to nitroso oxidation was limited by side reactions involving sulfonimine **1** which is generated stoichiometrically following oxygen transfer (Eq. 1). The displacement of benzenesulfonamide from **1** by the starting amine (Eq. 2) and intermediate hydroxylamine (Eq. 3) served to divert these substrates from the oxidation pathway.[5] The synthetic utility of this transimination process was established when it was determined that the displacement of

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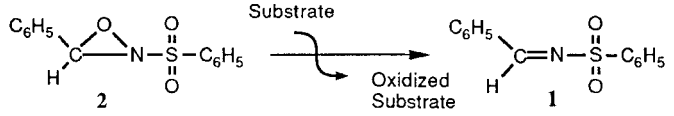
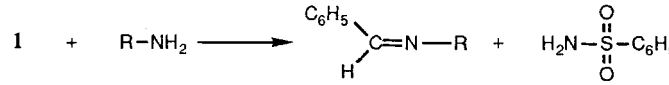
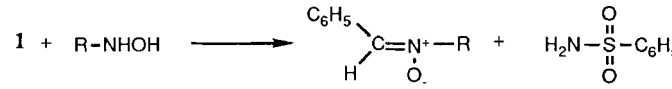
benzenesulfonamide from **1** by simple amines and hydroxylamines was a general reaction and the respective imine and nitrone derivatives could be isolated in high yields (~90-100%).[6] This reaction was shown to proceed rapidly and quantitatively (by NMR) at room temperature, without added catalyst. The use of chloroform as the solvent offered the additional advantage that the benzenesulfonamide precipitated during the reaction and could be separated by filtration to yield a crude product which could be used in subsequent reactions without further purification.



Eq. 1



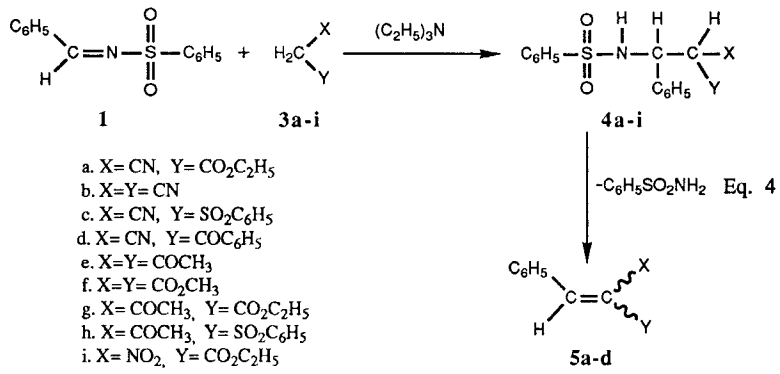
Eq. 2



Eq. 3

The facility with which these transimination reactions proceeded and the well-documented addition of organometallic reagents to sulfonimines,[2] either in a deliberate manner, or as an undesirable side reaction,[2d,e] prompted us to extend our evaluation of **1** as a benzaldehyde equivalent in the Knoevenagel reaction (Eq. 4).[7] Futhermore, the reactions of simple sulfonimines with active methylene compounds have recieved very limited attention[8] although the use of simple imines in place of aldehydes or ketones has been reported[9] and imines have been implicated as intermediates when the condensation is carried out using a primary amine catalyst.[7a]

The conditions examined involved stirring **1** and one of the active methylene compounds **3a-i** in chloroform containing triethylamine as a catalyst for 3-6 h at room temperature.[5] The reaction of **3a-e** proceeded with the formation of a copious white precipitate which was isolated by filtration. The solid was determined to be benzenesulfonamide in the cases of **3a-d** and the styrene



derivatives **4a-d** were obtained via chromatography of the filtrate (72%-94%). The solid obtained from the reaction mixture of **3e** was identified as the addition product **4e** (84%).[10] The initial products from the reactions of **3f-i** also proved relatively stable towards the elimination and **4f-i** were isolated from the reaction mixtures by pentane induced precipitation (65%-87%). However, the slow deposition of benzenesulfonamide was observed during prolonged reaction times (48h) and peaks supporting the formation of the corresponding elimination products were evident in the NMR spectra of the crude products.

The structures of adducts **4e-i** were assigned on the basis of their ^{13}C and ^{1}H NMR spectra[10] and by analogy to the one example reported previously.[8] The ^{13}C NMR spectra of the products from the reaction of 2,4-pentanedione (**3e**) and dimethyl malonate (**3f**) each showed two distinct carbonyl and methyl resonances suggesting that one of the carbonyls may be involved in an intramolecular hydrogen bond with the sulfamido proton. The non-equivalence of the methyl groups was also apparent in the ^{1}H NMR spectra. The adducts arising from unsymmetrical active methylene compounds were present as a mixture of diastereomers.

It is interesting to note that the facile elimination of benzenesulfonamide under the conditions investigated was observed to occur only in those cases where the active methylene compound possesses a cyano group. The lack of correlation between the pKa's of the methylene groups and their propensity towards elimination suggests that this phenomenon may be related to greater accessibility of the base to the methine proton of **4** in the presence of the linear cyano substituent.[11]

In conclusion, we have demonstrated that **1** may be successfully used as an alternative to benzaldehyde in the Knoevenagel reaction. The very mild conditions and the failure to generate water during the reaction suggests that this method may be preferable for substrates possessing hydrolytically labile functional groups.

Typical procedure (with elimination): Triethylamine (5 drops) was added to a well stirred solution of ethyl cyanoacetate (**3a**) (0.23 g, 2 mmol) and N-benzylidenebenzenesulfonamide (**1**) (0.49 g, 2 mmol) in chloroform (5 mL). A copious white precipitate formed after 30 min and stirring was continued for an additional 2.5 h at room temperature. The solid was removed by filtration and the residue obtained upon concentration of the filtrate was subjected to preparative TLC (silica gel, $CHCl_3$). Isolation of the material from the prominent band at R_f=0.78 afforded *trans*-ethyl-α-cyanocinnamate (**4a**) (0.38 g, 94%) as a colorless solid. Mp 49-51°C; ^{13}C NMR ($CDCl_3$) δ 162.2, 154.7, 133.1, 131.2, 130.8, 129.1, 115.3, 102.8, 62.5, 13.9. ^1H NMR ($CDCl_3$) δ 8.28 (s, 1H), 8.06-7.97 (m, 2H), 7.61-7.48 (m, 3H), 4.41 (q, 2H), 1.42 (t, 3H). This product was compared with an authentic sample of commercially available material (Aldrich) and was found to be identical in all respects.[12a]

Characteristic ^{13}C NMR resonances for other elimination products:
5b: 159.9, 113.6, 112.4, 82.6.[12b] **5c**: 151.5, 114.6, 113.0.[13] **5d**: 188.9, 155.4, 116.6, 110.0.[14]

Typical procedure (without elimination): Triethylamine (5 drops) was added to a well stirred solution of dimethyl malonate (**3f**) (0.26 g, 2 mmol) and N-benzylidenebenzenesulfonamide (**1**) (0.49 g, 2 mmol) in chloroform (5 mL). The reaction was stirred for 3 h at room temperature and pentane (5 mL) was added to induce precipitation. The solid was isolated by filtration (0.49 g, 65%) and was assigned the structure of adduct (**4f**) on the basis of literature precedent[7] and spectroscopic evidence. Mp 94-96°C, mixture of diastereomers; ^{13}C NMR ($CDCl_3$) δ 167.9 (C=O), 166.6 (C=O), 140.6, 137.3, 132.1, 128.5, 128.3, 127.8, 126.8, 126.4, 57.4 (C-H), 56.8 (C-H), 52.8 (OCH_3), 52.6 (OCH_3). ^1H NMR ($CDCl_3$) δ 7.73-7.04 (ArH), 6.45 (d, 1H, *J*=9.6, N-H), 5.18 (dd, 1H, *J*=9.6, 5.4, C-H), 3.83 (d, 1H, *J*=5.4, C-H), 3.62 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3).
Characteristic ^{13}C NMR resonances for other adducts:

4e: 203.9, 201.3, 73.4, 57.4, 30.4, 29.4. **4g**: 202.4, 200.1, 168.1, 166.4, 65.1, 64.4, 61.7, 61.6, 57.3, 56.7, 30.0, 29.1, 13.7, 13.6. **4i**: 163.1, 161.7, 91.6, 88.9, 63.8, 63.6, 57.6, 57.4, 13.6, 13.5.

REFERENCES AND NOTES

(1) For representative examples of cycloaddition reactions, see: (a) McFarlane, A.K.; Thomas, G.; Whiting, A. Tetrahedron Lett. 1993, 34, 2379. (b) Hamley, P.; Helmchen, G.; Holmes, A.B.; Marshall, D.R.; MacKinnon, J.M.W.; Smith, D.F.; Ziller, J.W. J. Chem. Soc. Chem. Commun. 1992, 786. (c) Hamley, P.; Holmes, A.B.; Kee, A.; Ladduwahetty, T.; Smith, D.F. Synlett 1991, 29. (d) Maggini, M.; Prato, M.; Scorrano, G. Tetrahedron Lett. 1990, 31, 6243. (e) Weinreb, S.M.; Sisko, J. Tetrahedron Lett. 1989, 30, 3037. (f) Boger, D.L.; Weinreb, S.M. "Hetero Diels-Alder Methodology in Organic Synthesis," Academic Press, Inc., San Diego, 1987, 36-38.

(2) For examples of the addition of organometallic reagents to sulfonimines, see: (a) Reetz, M.T.; Jaeger, R.; Drewlies, R.; Hubel, M. Angew. Chem., Int. Ed. Engl., 1991, 30, 103. (b) Weinreb, S.M.; Sisko, J. J. Org. Chem. 1990, 55, 393. (c) Pearce, H.L.; Bach, N.J.; Cramer, T.L. Tetrahedron Lett. 1989, 30, 907. (d) Belletire, J.L.; Fry, D.F. J. Org. Chem. 1988, 53, 4724. (e) Evans, D.A.; Morrissey, M.M.; Dorow, R.L. J. Am. Chem. Soc. 1985, 107, 4346. (f) Nadir, U.K.; Koul, V.K. Synthesis 1983, 554. (g) Stetter, H.; Thiesen, D. Chem. Ber. 1969, 102, 1641.

(3) (a) Boger, D.L.; Corbett, W.L. J. Org. Chem. 1992, 57, 4777. (b) Trost, B.M.; Marrs, C. J. Org. Chem. 1991, 56, 6468. (c) Kresze, G.; Albrecht, R.; Mlakar, B. Chem. Ber. 1964, 97, 483. See also references 1a, c, and d.

(4) Zajac, W.W., Jr.; Walters, T.R.; Darcy, M.G. J. Org. Chem. 1988, 53, 5856.

(5) Precedence for these processes may be found in: (a) Paquette, L.A.; Waykole, B.H.; Shen, C.C. J. Org. Chem. 1988, 53, 4969. (b) Adams, R.; Braun, B.H.; Pomerantz, S.H. J. Am. Chem. Soc. 1953, 75, 4642. (c) Adams, R.; Schowalter, K.A. Ibid. 1952, 74, 2597.

(6) We and others (ref 5a) have observed that sterically crowded amines and hydroxylamines may require more forcing conditions, if they react at all. We have found that the reaction of 2 equivalents of **1** with 2,3-diamino-2,3-dimethylbutane results in the formation of the mono imine instead of the diimine which is readily available from the reaction of diamine with 2 equivalents of benzaldehyde. This result is believed to arise due steric considerations with the large size of the N-sulfonylimino group of **1**, relative to the oxygen of benzaldehyde, inhibiting the reaction of the second equivalent of **1** with the more sterically encumbered amino group of the mono imine. This observation suggests that **1** may be a selective benzylideneating agent when a molecule possesses two sterically differentiable amine or hydroxylamine functions.

(7) (a) Knoevenagel, E. Chem. Ber. 1898, 31, 2585. (b) For a discussion of the Knoevenagel reaction. See: March, J. "Advanced Organic Chemistry; Reactions, Mechanisms and Structure", John Wiley & Sons, New York, 1992, 945-951.

(8) Reference 3c reports the addition of the anion of dimethyl malonate to N-benzylidene-p-toluenesulfonamide.

(9) (a) Charles, G. Bull. Soc. Chim. (France), 1963, 1573. (b) Ibid. 1963, 1566. (c) Ibid. 1963, 1573. (d) Ibid. 1963, 1576. (See also: Chem. Abstr. 1964, 60, 471d for an extensive abstract.)

(10) The addition products obtained in this study were contaminated with small amounts of benzenesulfonamide. Analytically pure samples were difficult to obtain as either chromatography or recrystallization resulted in some decomposition. However the ^{1}H and ^{13}C NMR spectra are fully consistent with the structure proposed in reference 8.

(11) The anomalous behavior of cyano containing active methylene compounds in the Knoevenagel reaction has been described previously, see: Patai, S.; Israel, Y. J. Chem. Soc. 1960, 2025. Patai, S.; Zabicki, Z. Ibid. 1960, 2030.

(12) (a) The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra, Edition I. Aldrich Chemical Co., 1993, Vol. 2, 1507B. (b) Ibid. Vol 2, 1504C.

(13) Kani, D.; Kohn, D.H. J. Appl. Polym. Sci. 1991, 43, 1941.

(14) Barchiesi, E.; Bradamante, S.; Ferraccioli, R.; Pagani, G.A. J. Chem. Soc. Perkin Trans. 2, 1990, 375.

(Received in the USA 24 May 1993)