Reaction of Orthoformates with Acidic Methines

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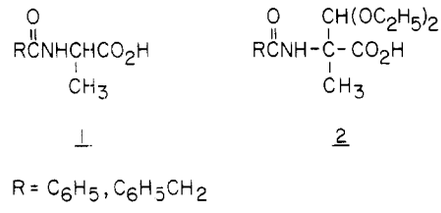
The previously little known reaction of acidic methines with orthoformates has been investigated. A variety of acidic methines have been found to react with orthoformates or with diethoxymethyl acetate to yield acetals, the product of C-alkylation. Some of these acetals are useful intermediates in synthesis. The acetals produced from the reactions of ethyl substituted benzylcyanoacetates and orthoformates have been reacted with guanidine to yield the medicinally important 2,4-diamino-5-benzylpyrimidines, trimethoprim, ormetoprim, and diaveridine.

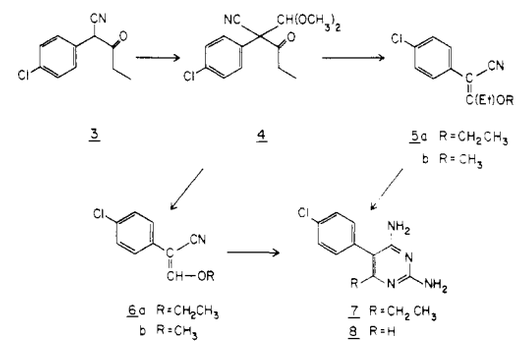
In contrast to the well-known reaction of orthoformates with reactive methylenes,[1] very little has been reported about the corresponding reaction with acidic methines.[2] One example is the reaction of phenylacetyl- and benzoylalanine, **1**, with triethyl orthoformate and acetic anhydride to form the acetals **2**.[3] Another example is the formation of 2,2-dinitropropionaldehyde diethyl acetal from 1,1-dinitroethane and triethyl orthoformate–acetic anhydride.[4] In this paper we describe additional examples of this type of reaction, comment upon its limitations, and demonstrate its utility in synthesis.[5]



In 1952 Russell and Whittaker reported that α-acylarylacetonitriles reacted with aliphatic orthoesters to yield the corresponding enol ethers, which reacted with guanidine to yield 2,4-diamino-5-arylpyrimidines.[6] They observed that if the crude product from the reaction of α-propionyl-*p*-chlorophenylacetonitrile (**3**) and triethyl orthoformate was condensed with guanidine, the 6-unsubstituted pyrimidine, **8**, was obtained in 7.7% yield in addition to the expected 6-ethylpyrimidine (pyrimethamine),[7] **7**, in 32% yield. The authors presented a mechanism for the conversion of **3** to the corresponding enol ether, **5a**, which involved an interaction of the orthoformate with the enolic form of **3**. It was further suggested that attack by triethyl orthoformate on the substituted α-carbon atom of the keto form of **3** gave rise to the α-aryl-β-ethoxyacrylonitrile, **6a**, as the contaminant responsible for the production of 6-unsubstituted pyrimidines. In some subsequent work by Logemann et al.[8] this reaction was repeated, and in contrast, not only was pyrimethamine (**7**) not isolated or found, but a 49% yield of **8** was obtained.

We have repeated the reaction of **3** with orthoformates. After an initial experiment with triethyl orthoformate, we

Scheme I

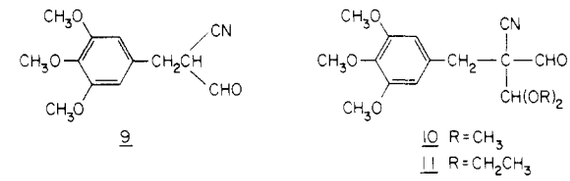


changed to trimethyl orthoformate to simplify the NMR analysis. A product of limited stability was isolated and characterized as the acetal **4** by a combination of ^{1}H NMR and IR spectra. The ^{1}H NMR spectrum showed an acetal group (3 H singlets at δ 3.27 and 3.57, 1 H singlet at δ 5.00); the IR spectrum showed an aliphatic nitrile (2260 cm^{-1}) and a nonconjugated ketone (1742 cm^{-1}).

The C-alkylated intermediate **4** can fragment in two ways to yield either of the enol ethers **5b** or **6b**. The divergent results in the literature may be explained by different handling of the unstable intermediate **4** (CH_3 replaced by CH_2CH_3). Attempted chromatography on alumina yielded **6b** whereas recrystallization (Russell and Whittaker[6]) yielded compounds analogous to **5**.

In an attempt to explore the generality of the reaction, a variety of acidic methines were allowed to react with orthoformates or related reagents. Although the reaction is quite general, some compounds reacted slowly, and a few gave no detectable reaction (Table I).

2-Formyl-3-(3,4,5-trimethoxyphenyl)propionitrile[9] (**9**)



underwent C-alkylation with trimethyl and triethyl orthoformates yielding **10** and **11**, respectively. Acetals **10** and **11** were obtained as reasonably stable crystalline solids; however, upon prolonged storage at ambient temperature, they did revert to **9**. 2-Diethoxymethyl-2-formyl-3-(3,4,5-trimethoxyphenyl)propionitrile (**11**) was allowed to react with guanidine, giving a 67% yield of 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine (trimethoprim).[10]

(1) L. Claisen, *Chem. Ber.*, **26**, 2729 (1893).
(2) Robert H. De Wolfe, "Carboxylic Ortho Acid Derivatives", Academic Press, New York, 1970, p 234.
(3) H. E. Stavely and M. Berestecki, *J. Am. Chem. Soc.*, **73**, 3448 (1951). The actual acidic methines were the oxazolones from cyclization of the *N*-acylamino acids with acetic anhydride.
(4) N. A. Tikhonova, K. K. Babievskii, and V. M. Belikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 877 (1967).
(5) D. A. Yeowell and R. A. Swaringen, Jr., U.S. Patent 4144263 (1979).
(6) P. B. Russell and N. Whittaker, *J. Am. Chem. Soc.*, **74**, 1310 (1952).
(7) G. H. Hitchings, P. B. Russell, and E. A. Falco, U.S. Patent 2576939 (1951).
(8) W. Logemann, L. Almivante, and L. Capiro, *Chem. Ber.*, **87**, 435 (1954).
(9) R. M. Cresswell, J. W. Mentha, and R. L. Seaman, British Patent 1261455 (1972).

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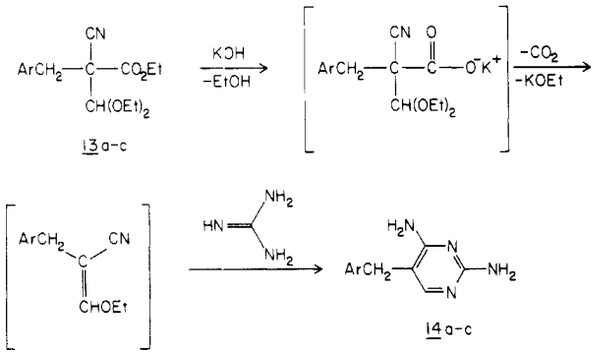
Table I. Acetals from Acidic Methines and Orthoformates or Related Reagents (RCHXY → RCXYCH(OR')$_2$)

compd no.	acidic methine (RCHXY) R	X	Y	orthoformate	reaction time, h/temp, °C	yield of acetal, %	mp (bp), °C
3	*p*-ClC$_6$H$_4$	CN	COEt	TMOF[a]	6 h/reflux	84[b]	
9	3,4,5-(MeO)$_3$C$_6$H$_2$CH$_2$	CN	CHO	TMOF	3 h/reflux	42	118–122
9	3,4,5-(MeO)$_3$C$_6$H$_2$CH$_2$	CN	CHO	TEOF[c]	0.5 h/reflux	78	117–121
12a	3,4,5-(MeO)$_3$C$_6$H$_2$CH$_2$	CN	CO$_2$Et	TEOF	18 h/reflux	82	95–97
12a	3,4,5-(MeO)$_3$C$_6$H$_2$CH$_2$	CN	CO$_2$Et	DEMA[d]	18 h/95	73	95–97
12b	2-Me-4,5(MeO)$_2$C$_6$H$_2$CH$_2$	CN	CO$_2$Et	TEOF	68 h/reflux	84	84–86
12c	3,4-(MeO)$_2$C$_6$H$_3$CH$_2$	CN	CO$_2$Et	DEMA	20 h/95	94	62–65
15	CH$_3$	NO$_2$	CO$_2$Et	TEOF/Ac$_2$O[e]	1 h/reflux	86	(128–131 (10 mm))
16	3,4,5-(MeO)$_3$C$_6$H$_2$CH$_2$	CN	CN	TEOF	7.5 h/reflux	89	110–112
16	3,4,5-(MeO)$_3$C$_6$H$_2$CH$_2$	CN	CN	TiPOF[f]	7.5 h/reflux	53	98–99
20	3,4,5-(MeO)$_3$C$_6$H$_2$CH$_2$	COCH$_3$	CO$_2$Et	DEMA	6 h/110	66	55–57
21	3,4,5-(MeO)$_3$C$_6$H$_2$CH$_2$	CN	COC$_6$H$_5$	DEMA	2.5 h/110	76	123–125
22	3,4,5-(MeO)$_3$C$_6$H$_2$CH$_2$	CN	*p*-MeC$_6$H$_4$SO$_2$	TEOF	48 h/reflux	70	97–98
23	CH$_3$	CO$_2$Me	*m*-ClC$_6$H$_4$CO	TEOF	96 h/reflux	77[b,g]	
24	CH$_3$	CN	C$_6$H$_5$CO	TMOF	45 h/reflux	81[b]	
25	CH$_3$	CO$_2$Et	COCO$_2$Et	TEOF	6 h/reflux	57	(100–102 (0.2 mm))
26	CH$_3$	CO$_2$Et	CO$_2$Et	TEOF	90 h/reflux	55[b]	
27	C$_6$H$_5$	CO$_2$Et	CO$_2$Et	TEOF	90 h/reflux	13[b]	
28	Br	CO$_2$Et	CO$_2$Et	TEOF	24 h/reflux	38[b,h]	
29	3,4,5-(MeO)$_3$C$_6$H$_2$CH$_2$	CN	$\overbrace{\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{NCO}}$	TEOF	57 h/reflux	0	
29	3,4,5-(MeO)$_3$C$_6$H$_2$CH$_2$	CN	$\overbrace{\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{NCO}}$	DEMA	88 h/110	0	
30	3,4,5-(MeO)$_3$C$_6$H$_2$CH$_2$	CN	COCO$_2$Et	TEOF	11 h/reflux	0[i]	
30	3,4,5-(MeO)$_3$C$_6$H$_2$CH$_2$	CN	COCO$_2$Et	DEMA	5 h/110	0[i]	
31	C$_6$H$_5$	CN	C$_6$H$_5$	TEOF	45 h/reflux	0	
32	CH$_3$	CO$_2$Et	PO(OEt)$_2$	TEOF	48 h/reflux	0	
33	*p*-ClC$_6$H$_4$	CCl$_3$	*p*-ClC$_6$H$_4$	TEOF	21.5 h/reflux	0[j]	
34	CH$_3$	*p*-NO$_2$C$_6$H$_4$	*p*-MeC$_6$H$_4$SO$_2$	TEOF	48 h/reflux	0	
35	3,4,5-(MeO)$_3$C$_6$H$_2$CH$_2$	CO$_2$Et	CO$_2$Et	TEOF	336 h/reflux	0	
35	3,4,5-(MeO)$_3$C$_6$H$_2$CH$_2$	CO$_2$Et	CO$_2$Et	DEMA	72 h/110–120	0	

[a] TMOF = trimethyl orthoformate. [b] NMR assayed yield. [c] TEOF = triethyl orthoformate. [d] DEMA = diethoxymethyl acetate. [e] When acetic anhydride was omitted, the oxime of ethyl pyruvate was also obtained via O-alkylation and decomposition of the nitronate ester. [f] TiPOF = triisopropyl orthoformate. [g] The reaction was accompanied by transesterification. [h] NMR and mass spectrometry also indicated the presence of diethyl ethoxymethylenemalonate (20% yield) as a byproduct. [i] The enol ether was obtained. [j] 1,1-Bis(*p*-chlorophenyl)-2,2-dichloroethane was the product in 69% yield (recrystallized).

Scheme II



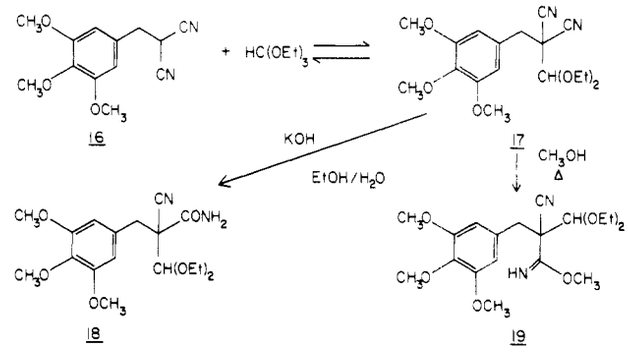
a, Ar = 3,4,5-trimethoxyphenyl
b, Ar = 2-methyl-3,4-dimethoxyphenyl
c, Ar = 3,4-dimethoxyphenyl

Since **11** contained both a free and a masked aldehyde in addition to a cyano group, the formation of a 2,4-diamino-5-benzylpyrimidine upon condensation with guanidine was not altogether unexpected. Of greater surprise and utility was the production of the 2,4-diamino-5-benzylpyrimidines, trimethoprim (**14a**), ormetoprim (**14b**), and diaveridine (**14c**), by treatment of the acetals, **13a–c**, derived from the cyanoesters, **12a–c**, with potassium hydroxide followed by reaction with guanidine. A reasonable mechanism for this transformation is presented in Scheme II. Saponification of the esters followed by decarboxylation yields the enol ether intermediates which react with guanidine in the normal manner. Since the cyanoesters are readily available (e.g., by condensation of the appropriate benzaldehyde with ethyl cyanoacetate followed by hydrogenation), and the yields are high, this sequence constitutes a useful new synthesis of the medicinally important 2,4-diamino-5-benzylpyrimidines. The acetal **13a** was also prepared from 3,4,5-trimethoxybenzylcyanoacetic acid by reaction with triethyl orthoformate at reflux or diethoxymethyl acetate at 90 °C.

In theory this new pyrimidine synthesis could be quite general. It was hoped that a variety of functional groups other than ester and aldehyde (e.g., aliphatic and aromatic ketones, cyano, sulfonyl, etc.) would undergo cleavage with base and generate the enol ether intermediates. This hope has not been realized experimentally. Some of the intervening processes for 2-cyano-2-(diethoxymethyl)-3-(3,4,5-trimethoxyphenyl)propionitrile are depicted in Scheme III. Formation of the acetal **17** is actually an equilibrium situation in which the acetal product is favored. Prolonged reflux of **17** in anhydrous ethanol did regenerate 3,4,5-trimethoxybenzylmalononitrile (**16**) (71% after 28.5 h). Prolonged reflux of acetal **17** in dry 2-propanol gave a slower reversion to **16** (25% after 21 h), while in refluxing *tert*-butyl alcohol no fragmentation of **17** was seen after 48 h. The fragmentation is thought to proceed through ionization and reaction of the ion pair with solvent. The observed decrease in rates from ethyl to isopropyl to *tert*-butyl alcohol could be due to the decreasing dielectric constant of the solvent, which would retard ionization, and/or the increasing bulk of the nucleophile (alcohol). The isopropyl acetal corresponding to **17** was cleaved faster in refluxing ethanol (100% after 5 h) and probably is intrinsically less stable (crowding relieved by ionization). Fragmentation of acetal **17** to the malononitrile **16** was rapid in 50% aqueous ethanol. However, when potassium hydroxide was present, the major product (67.5%) was the amide **18**. Since the basic hydrolysis of amides to acids

(10) G. H. Hitchings and B. Roth, U.S. Patent 2909522 (1959).

Scheme III



is slower than the hydrolysis of nitriles to amides, it was not surprising that **18** did not serve as a trimethoprim precursor. In refluxing dry methanol, acetal **17** was rapidly converted to the imino ether **19**. Thus there seems to be a fine balance between reaction at the nitrile group and loss of the acetal moiety.

Conclusions

A variety of acidic methines have been found to react with orthoformates or diethoxymethyl acetate yielding acetals, the products of C-alkylation. The reaction has proved useful in introducing a masked aldehyde and provided intermediates for 2,4-diamino-5-benzylpyrimidines.

Experimental Section

Melting points are uncorrected. Infrared spectra were scanned on the neat smears or mineral oil mulls (NaCl plates), using a Pye Unicam SP1000 spectrophotometer. NMR spectra were obtained with a Varian Associates T-60, CFT-20 and Perkin Elmer R-24B spectrometers. Chemical shifts are in parts per million relative to internal Me_4Si (δ 0).

2-(*p*-Chlorophenyl)-2-(dimethoxymethyl)-3-oxovaleronitrile (4). To a solution of 10.4 g (0.05 mol) of α-propionyl-*p*-chlorophenylacetonitrile in 100 mL of trimethyl orthoformate was added 1.0 g of Rexyn 101(H) (strong cation exchange resin). The mixture was heated at reflux, using a steam jacketed column for continuous removal of methanol. After 2 h at reflux, 50 mL of trimethyl orthoformate was added dropwise, and reflux was continued for a total of 6 h. The mixture was cooled and filtered to remove the catalyst. The filtrate was rapidly concentrated in vacuo to yield 14.0 g of an oil, **4**: IR bands at 2260 (W, C≡N) and 1742 cm^{-1} (S, C=O); NMR ($CDCl_3$) δ 1.03 (t, 3, CH_3CH_2), 2.75 (q, 2, CH_3CH_2 C=O), 3.27 and 3.57 (singlets, 6, $CH(OCH_3)_2$), 5.00 (s, 1, $CH(OCH_3)_2$), and 7.5 (m, 4, *p*-ClC_6H_4). The NMR spectrum also showed small amounts of starting materials.

2-(*p*-Chlorophenyl)-3-methoxyacrylonitrile (6b). The product (27.1 g) from an uncatalyzed reaction of α-propionyl-*p*-chlorophenylacetonitrile (20.6 g) and trimethyl orthoformate (150 mL) was applied to an alumina column (aluminum oxide, Merck, 190 g) and eluted with ether–hexane in an unsuccessful attempt to remove unreacted starting material. A 17.1-g portion of the recovered mixture was then taken up in 500 mL of hexane; 250 g of alumina was added, and the mixture was stirred overnight. The mixture was filtered, and the filtrate was concentrated in vacuo to an oil. The process was repeated using 100 g of alumina. Concentration of the filtrate gave only 125 mg; therefore the alumina cake was washed with 200 mL of ether. Concentration of the ether extract gave 1.0 g of crude **6b**. Recrystallization from hexane gave colorless microcrystals of **6b**: mp 107–109 °C; NMR ($CDCl_3$) δ 3.98 (s, 3, OCH_3) and 7.30 (s, 5, *p*-ClC_6H_4 and CH= CCN).

Anal. Calcd for $C_{10}H_8ClNO$: C, 62.03; H, 4.16; N, 7.23. Found: C, 61.83; H, 4.18; N, 7.16.

2-(Dimethoxymethyl)-2-formyl-3-(3,4,5-trimethoxyphenyl)propionitrile (10). A solution of 17.2 g (0.069 mol) of 2-formyl-3-(3,4,5-trimethoxyphenyl)propionitrile (**9**)[9] in 100 mL

of trimethyl orthoformate was heated at reflux for 3 h, using a steam jacketed column for continuous removal of methanol. The solution was cooled, and most of the excess orthoformate was removed in vacuo. The residual oil was taken up in 100 mL of ether, and crystallization began almost immediately. The mixture was filtered to yield 9.4 g (42%) of light tan crystals, mp 117–121 °C. Recrystallization from cyclohexane–chloroform gave colorless needles of **10**: mp 118–122 °C; IR bands at 2250 (C≡N) and 1738 cm^{-1} (CHO); NMR ($CDCl_3$) δ 3.15 (s, 2, $ArCH_2C$), 3.57 and 3.62 (singlets, 6, $CH(OCH_3)_2$), 3.87 (s, 9, $C_6H_2(OCH_3)_3$), 4.50 (s, 1, $CH(OCH_3)_2$), 6.53 (s, 2, aromatic H), and 9.53 (s, 1, CHO).

Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.44; H, 6.60; N, 4.33.

2-(Diethoxymethyl)-2-formyl-3-(3,4,5-trimethoxyphenyl)propionitrile (11). By the same procedure as was used in the preparation of **10**, there was obtained a 78% yield of **11**, mp 109–115 °C. Recrystallization from ether–acetone gave the analytical sample, mp 117–121 °C.

Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.31; H, 7.21; N, 3.87.

2,4-Diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine (14a). Reaction of 11 with Guanidine. To an ethanolic solution of guanidine (from 0.35 mol of guanidine hydrochloride) was added 35.1 g (0.10 mol) of **11**. The mixture was heated at reflux for a total of 6.5 h, during which time enough ethanol was allowed to boil off to bring the reaction temperature up to 85 °C. The dark solution was allowed to cool and stand overnight. The mixture was filtered, and the solid was washed with cold ethanol and dried to yield 24.4 g of crude product. Purification was effected by dissolving the crude product in hot aqueous acetic acid and reprecipitation with concentrated ammonium hydroxide. The precipitate was washed twice with water and once with cold acetone and dried to yield 19.5 g (67.2%) of 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine, mp 197–198 °C (identity confirmed by NMR). The acetone wash was concentrated in vacuo to dryness, yielding an additional 2.5 g of somewhat less pure trimethoprim, mp 194–196 °C.

Ethyl 2-(Diethoxymethyl)-2-nitropropionate. A mixture of 14.7 g (0.10 mol) of ethyl 2-nitropropionate, 29.6 g (0.20 mol) of triethyl orthoformate, and 40.8 g (0.40 mol) of acetic anhydride was heated at reflux for 1 h, using a steam-jacketed column for continuous removal of any low-boiling products (ethanol, ethyl acetate). The reaction solution was then fractionally distilled to yield 21.4 g (86%) of the title compound: bp 128–131 °C (10 mm); NMR ($CDCl_3$) δ 1.17, 1.20, and 1.30 (3 triplets, 9, CH_3CH_2O), 1.80 (s, 3, CH_3C), ca. 3.83 (2 overlapping quartets, 4, CH_3CH_2O), 4.40 (q, 2, CH_3CH_2OCO), and 5.30 (s, 1, $CH(OEt)_2$).

Anal. Calcd for $C_{10}H_{19}NO_6$: C, 48.18; H, 7.68; N, 5.62. Found: C, 48.52; H, 7.57; N, 5.61.

2-(Ethoxycarbonyl)-2-(diethoxymethyl)-3-(3,4,5-trimethoxyphenyl)propionitrile (13a). A solution of ethyl 3,4,5-trimethoxybenzylcyanoacetate (14.7 g, 0.050 mol) in triethyl orthoformate (100 mL) was heated at reflux for 18 h, using a steam-jacketed column for continuous removal of ethanol. The solution was cooled, and most of the excess orthoformate was removed in vacuo. The crystals obtained were washed with ether and dried to yield colorless crystals of 2-(ethoxycarbonyl)-2-(diethoxymethyl)-3-(3,4,5-trimethoxyphenyl)propionitrile (16.3 g, 82%): mp 95–97 °C; NMR ($CDCl_3$) δ 1.13, 1.20, and 1.32 (triplets, 9, CH_3CH_2O), 3.15 (s, 2, $ArCH_2C$), 3.4–4.0 (quartets, 4, CH_3CH_2O), 3.85 (s, 9, $C_6H_2(OCH_3)_3$), 4.13 (q, 2, CH_3CH_2OCO), 4.80 (s, 1, $CH(OEt)_2$), and 6.55 (s, 2, aromatic H).

Anal. Calcd for $C_{20}H_{29}NO_7$: C, 60.74; H, 7.39; N, 3.54. Found: C, 60.56; H, 7.33; N, 3.64.

2-(Ethoxycarbonyl)-2-(diethoxymethyl)-3-(3,4,5-trimethoxyphenyl)propionitrile (13a). Ethyl 3,4,5-trimethoxybenzylcyanoacetate (5 g, 17.1 mmol) and diethoxymethyl acetate (15 g, 92.5 mmol) were heated at 95 °C overnight. The mixture was cooled and crystallized by addition of 25 mL of ether–hexane (1:1). The product was filtered and dried under reduced pressure, giving 4.9 g (73%) of colorless crystals, mp 95–97 °C.

2-(Ethoxycarbonyl)-2-(diethoxymethyl)-3-(3,4,5-trimethoxyphenyl)propionitrile (13a). 3,4,5-Trimethoxybenzylcyanoacetic acid monohydrate (5.0 g, 17.65 mmol) and triethyl orthoformate (42 mL) were heated at reflux for 21 h. Excess orthoformate was removed in vacuo, and the residue was crystallized from ether–hexane to yield 4.4 g (63.0%) of colorless crystals, mp 95–96.5 °C.

The cyanoacetic acid was also allowed to react with diethoxymethyl acetate in a couple of small scale (NMR tube) reactions. After 4 h at 90 °C or 19 days at ambient temperature, conversion to the acetal **13a** was >95% complete.

2,4-Diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine (14a). Reaction of 13a with Guanidine. A solution of 2-carbethoxy-2-(diethoxymethyl)-3-(3,4,5-trimethoxyphenyl)propionitrile (7.9 g, 0.02 mol) and an equivalent amount of potassium hydroxide in ethanol (50 mL) was heated at reflux for 1 h. A solution of guanidine (0.07 mol) in ethanol (50 mL) was added, and reflux was resumed. Some ethanol was allowed to boil off, bringing the reaction temperature up to 85 °C. After about 20 h at reflux, the mixture was allowed to cool, and the product was filtered and washed with ethanol. The crude product was purified by treating it with hot aqueous acetic acid and reprecipitating with ammonium hydroxide. The yield of purified trimethoprim (mp 197–198 °C) was 3.6 g (62%); its identity was confirmed by an NMR spectrum.

2-Cyano-3-(3,4,5-trimethoxyphenyl)acrylonitrile. 3,4,5-Trimethoxybenzaldehyde (78.0 g, 0.398 mol) and malononitrile (30.0 g, 0.454 mol) were combined in 800 mL of *n*-butyl alcohol, and 1 mL of piperidine was added dropwise with stirring. After being stirred for 2 h at ambient temperature, the mixture was allowed to stand for 30 min and then filtered. The yellow crystals were collected, washed with denatured ethanol (SD3A), and dried in vacuo to yield 94.0 g (96.8%) of crude product, mp 134–136 °C. Two recrystallizations from ethanol gave 67 g (69%) of yellow needles: mp 149–150 °C; NMR ($CDCl_3$) δ 3.90 (s, 6, OCH_3), 3.98 (s, 3, OCH_3), 7.20 (s, 2, aromatic H), and 7.67 (s, 1, vinyl H). Concentration of the mother liquors gave a second crop of 6.5 g (6.7%), mp 147–148 °C.

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.71; H, 5.04; N, 11.54.

3,4,5-Trimethoxybenzylmalononitrile (16). Sodium borohydride (14 g, 0.37 mol) was added in small portions to a stirred suspension of 2-cyano-3-(3,4,5-trimethoxyphenyl)acrylonitrile (68 g, 0.278 mol) in 1000 mL of absolute ethanol at 0–5 °C. The mixture was allowed to stir for 70 min at 0–5 °C and then was filtered. The colorless crystals were washed with cold ethanol and dried in vacuo (40 °C) to yield 55.7 g (81.2%) of the title compound: mp 144–146 °C [lit.[11] mp 145–147 °C]; NMR ($CDCl_3$) δ 3.20 (d, 2, benzyl CH_2), 3.85 (s, 9, OCH_3), 4.00 (t, 1, methine), and 6.52 (s, 2, aromatic H).

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.06; H, 5.60; N, 11.33.

2-Cyano-2-(diethoxymethyl)-3-(3,4,5-trimethoxyphenyl)propionitrile (17). 3,4,5-Trimethoxybenzylmalononitrile (24.6 g, 0.10 mol) and 100 mL of triethyl orthoformate were heated at reflux for 7.5 h, using a steam jacketed condenser for removal of ethanol. The dark reaction solution crystallized upon cooling. The product was collected by filtration, washed with cold ether, and dried in vacuo to yield 26.4 g (75.8%) of colorless crystals: mp 110–112 °C; NMR ($CDCl_3$) δ 1.33 (t, 6, CH_3CH_2O), 3.23 (s, 2, benzyl CH_2), ~3.82 (q, 4, CH_3CH_2O), 3.88 (s, 9, OCH_3), 4.72 (s, 1, $CH(OEt)_2$), and 6.63 (s, 2, aromatic H). Concentration of the mother liquor to ~25 mL gave a second crop, 4.5 g (12.9%). Recrystallization from methanol gave the analytical sample, mp 114–116 °C.

Anal. Calcd for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found: C, 61.71; H, 6.89; N, 7.95.

2-Cyano-2-(diisopropoxymethyl)-3-(3,4,5-trimethoxyphenyl)propionitrile. 3,4,5-Trimethoxybenzylmalononitrile (2.0 g, 8.1 mmol) and triisopropyl orthoformate (4.6 g, 24.2 mmol) were heated at reflux for 10.5 h, using a steam-jacketed condenser for removal of isopropyl alcohol. The reaction mixture was allowed to cool and stand overnight. The solid product was collected and recrystallized twice from methanol to yield 1.6 g (52.3%) of colorless crystals: mp 151–156 °C (trace of starting material seen by TLC); NMR ($CDCl_3$) δ 1.30 (d, 12, $CH(CH_3)_2$), 3.20 (s, 2, benzyl CH_2), 3.86 (s, 9, OCH_3), 4.05 (m, 2, $CH(CH_3)_2$), 4.93 (s, 1, CH-(O-*i*-Pr)$_2$), and 6.61 (s, 2, aromatic H); mass spectrum (70 eV), *m/e* (relative intensity, assignment) 376 (1.9 M), 317 (0.5, M –

(11) L. Fuentes, A. Lorente, and J. L. Soto, *J. Heterocycl. Chem.*, **16**, 273 (1979).

C_3H_7O), 288 (1.9, M – $HCOOC_3H_7$), 181 (66.7, 3,4,5-trimethoxybenzyl), 131 (25, $C_3H_7OCHOC_3H_7$), and 89 (100, $HOCHOC_3H_7$).

2-Cyano-2-(diethoxymethyl)-3-(3,4,5-trimethoxyphenyl)propionamide (18). 2-Cyano-2-(diethoxymethyl)-3-(3,4,5-trimethoxyphenyl)propionitrile (10 g, 28.7 mmol) was combined with 200 mL of ethanol–water (1:1) containing 3.6 g of potassium hydroxide. The solid dissolved upon warming, and the solution was heated at reflux for 35 min. The mixture was cooled and concentrated in vacuo to dryness. The residue was triturated with water and filtered. The solid was slurried in water, filtered, and dried to yield 7.1 g (67.5%) of a buff-colored solid: mp 125–127 °C; NMR ($CDCl_3$) δ 1.26, 1.33 (t's, 6, J = 7 Hz, CH_2CH_3), 3.11, 3.22 (ABq, 2, J = 13 Hz, benzyl CH_2), 3.74, 3.77 (q's, 4, J = 7 Hz, OCH_2CH_3), 4.74 (s, 1, $CH(OEt)_2$), 5.59, 6.24 (br s, 2, $CONH_2$), and 6.59 (s, 2, aromatic H); mass spectrum (70 eV), m/e (relative intensity, assignment) 366 (2, M), 323 (11.7, M – CONH), 277 (8.2, M – NH_2CO_2Et), 181 (55, 3,4,5-trimethoxybenzyl), and 103 (100, $C_2H_5OCHOC_2H_5$).

Methyl 2-Cyano-2-(diethoxymethyl)-3-(3,4,5-trimethoxyphenyl)propionimidate (19). 2-Cyano-2-(diethoxymethyl)-3-(3,4,5-trimethoxyphenyl)propionitrile (2.5 g, 7.2 mmol) was dissolved in 27 mL of dry methanol, and the solution was heated at reflux for 1 h. A 2-mL aliquot was concentrated in vacuo to an oil: NMR ($CDCl_3$) δ 1.14 and 1.25 (t's, 6, J = 7 Hz, CH_2CH_3), 3.07 (s, 2, benzyl CH_2), ~3.6 (q's, 4, CH_2CH_3), ~3.8 (s, 12, OCH_3), 4.65 (s, 1, $CH(OEt)_2$), 6.40 (s, 2, aromatic H), and 7.7 (s, 1, NH (exchanges with D_2O)); IR bands at 2255 (C≡N) and 1505, 1509, and 1610 cm^{-1} (C=NH); mass spectrum (70 eV), m/e (relative intensity, assignment) 380 (1.8, M), 334 (1.3, M – C_2H_5OH), 277 (7.4, M – $C_2H_5OC(NH)OCH_3$), 181 (23, 3,4,5-trimethoxybenzyl), and 103 (100, $C_2H_5OCHOC_2H_5$).

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Registry No. **3**, 55474-40-3; **4**, 71870-92-3; **66**, 71870-93-4; **9**, 65430-22-0; **10**, 65743-11-5; **11**, 65743-12-6; **12a**, 29958-02-9; **12b**, 57941-89-6; **12c**, 37389-84-7; **13a**, 65708-35-2; **13b**, 71870-94-5; **13c**, 65708-36-3; **14a**, 738-70-5; **15**, 2531-80-8; **16**, 71870-95-6; **17**, 71870-96-7; **18**, 71870-97-8; **19**, 71870-98-9; **20**, 71870-99-0; **21**, 71871-00-6; **22**, 71885-39-7; **23**, 71871-01-7; **24**, 7391-29-9; **25**, 759-65-9; **26**, 609-08-5; **27**, 83-13-6; **28**, 685-87-0; **29**, 71870-80-9; **30**, 40988-36-1; **31**, 86-29-3; **32**, 3699-66-9; **33**, 50-29-3; **34**, 71870-81-0; **35**, 7402-30-4; ethyl 2-(diethoxymethyl)-2-nitropropanoate, 71870-82-1; 2-cyano-2-(diisopropoxymethyl)-3-(3,4,5-trimethoxyphenyl)propionitrile, 71870-83-2; ethyl 2-acetyl-2-(diethoxymethyl)-3-(3,4,5-trimethoxyphenyl)propanoate, 71870-84-3; 2-benzoyl-2-(diethoxymethyl)-3-(3,4,5-trimethoxyphenyl)propionitrile, 71870-85-4; 2-(diethoxymethyl)-2-tosyl-3-(3,4,5-trimethoxyphenyl)propionitrile, 71870-86-5; methyl 2-(*m*-chlorobenzoyl)-2-(diethoxymethyl)propanoate, 71870-87-6; 2-benzoyl-2-(dimethoxymethyl)propionitrile, 71870-88-7; ethyl 2-oxo-2-ethoxycarbonyl-2-(diethoxymethyl)butanoate, 71870-89-8; diethyl 2-(diethoxymethyl)-2-methylpropanedioate, 40364-91-8; diethyl 2-(diethoxymethyl)-2-phenylpropanedioate, 71870-90-1; diethyl 2-bromo-2-(diethoxymethyl)propanedioate, 71870-91-2; diethyl ethoxymethylenemalonate, 87-13-8; 1,1-bis(*p*-chlorophenyl)-2,2-dichloroethane, 72-54-8; TMOF, 149-73-5; TEOF, 122-51-0; DEMA, 14036-06-7; TiPOF, 4447-60-3; guanidine, 113-00-8; 3,4,5-trimethoxybenzylcyanoacetic acid, 42864-52-8; 3,4,5-trimethoxybenzaldehyde, 86-81-7; malonitrile, 109-77-3; 2-cyano-3-(3,4,5-trimethoxyphenyl)acrylonitrile, 5688-82-4.

Rates of Ionization of 1,1-Dinitroethane in 50% Dimethyl Sulfoxide–50% Water. Solvent Effect on Proton Transfer

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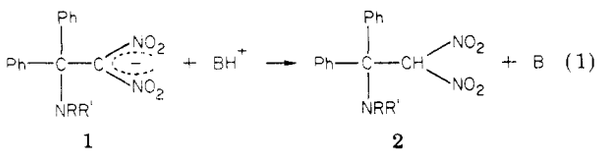
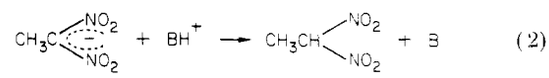
The rates of ionization of 1,1-dinitroethane have been measured in 50% Me_2SO–50% water (v/v) in the presence of various buffers. For a given pK difference between 1,1-dinitroethane and the buffer, the rates are up to ten times higher than those in pure water. This increase is consistent with the notion that solvational reorganization is at least partly responsible for the slow rates of proton transfer involving nitroalkanes, but it also shows that the rate enhancing effect of Me_2SO is relatively small as long as there is a significant protic component in the solvent. The data refute the hypothesis that the recently reported high rate of protonation of 1 on carbon by the hydronium ion is due to a solvent effect and support the notion of an intramolecular proton transfer **5** → **2**.

While studying nucleophilic additions of amines to 1,1-dinitro-2,2-diphenylethylene in 50% Me_2SO–50% water (v/v), we also measured the rates of proton transfer



1 2 (1)

to the carbon of the amine–olefin addition complex **1**.[1] With BH^+ = piperidinium ion, morpholinium ion, *n*-$BuNH_3^+$, $PhNH_3^+$, and cacodylic acid, the rate constants are of the same order of magnitude as the rate constants for the protonation of the anion of 1,1-dinitroethane (**3**) in aqueous solution by general acids of comparable pK_a.[2]



3 4 (2)

On the other hand, the rate constant for protonation of **1** by the *hydronium ion* is about 10^4 times higher than that for the protonation of **3**. This high rate was explained by initial protonation of **1** on *nitrogen*, followed by an intramolecular proton switch to form **2**[1] (eq 3).

In view of the known rate enhancing effect of Me_2SO on proton transfers involving carbon acids,[3-5] the possibility

(1) C. F. Bernasconi and D. J. Carré, *J. Am. Chem. Soc.*, **101**, 2698 (1979).

(2) R. P. Bell and R. L. Tranter, *Proc. R. Soc. London, Ser. A*, **337**, 518 (1974).

0022-3263/79/1944-4829$01.00/0