A Convenient Synthetic Method for Trisubstituted s-Triazines

Chen Chen,* Raymond Dagnino, Jr., and James R. McCarthy*

Department of Medicinal Chemistry, Neurocrine Biosciences, Inc., 3050 Science Park Road, San Diego, California 92121

Received July 3, 1995

Despite the fact that 1,3,5-triazines are one of the oldest known classes of organic molecules, synthetic methods for the preparation of analogs containing different substituents at each carbon are limited.[1] Cyanuric chloride has been the most valuable starting material for the preparation of trisubstituted triazines even though stepwise replacement of the three chlorines is often unreliable and leads to mixtures.[2] In 1965 Bader reported the first synthesis of s-triazines bearing three different substituents, albiet in low yields, by reaction of methyl or isopropyl *N*-acetimidates with amidines.[3] More recently, amidines were reported to undergo cyclization with *N*-ethoxycarbonyl thioamides to form fully substituted s-triazinones.[4]

We required a general method to 2-aryl- and 2-alkyl-4-alkyl-6-amino and alkyl s-triazines (**7**) that would be amenable to the rapid preparation of large numbers of analogs for biological testing and wish to report the development of a new method meeting these requirements. *N'*-Acyl-*N,N*-dimethylamidines (**4**, R_2 = H; **5**, R = CH_3) were prepared in excellent yields by heating amides **1** with dimethylformamide dimethyl acetal (**2**) or dimethylacetamide dimethyl acetal (**3**) as orginally reported by Lin and co-workers.[5] *N'*-Acyl-*N,N*-dimethylamidines **4** and **5** have previously been converted to triazines by a laborious three-step process that requires the use of hydrogen sulfide. The acyl amidines **4** and **5** were converted to the corresponding *N*-thioacylamidines by treatment with hydrogen sulfide.[6] The intermediate *N*-thioacylamidines were ethylated to form ethyl *N*-acylthioimidates that were reacted with amidines or guanidines to form the desired triazines.[7] We found that **4** and **5** condensed with amidines or guanidines (**6**) in aprotic solvents to give s-triazines in good to excellent yields. The simplified one-pot process we report provides the first general and facile synthetic route to a variety of trisubstituted s-triazines.[8]

Attempts to cyclize acylamidines **4** or **5** with *N,N*-dialkylguanidines **6** by a procedure that was successful with hydroxylamine[5] gave only diacylamines[10] (i.e. acetic acid as solvent with or without 1 equiv of 5 N aqueous NaOH). Thus *N'*-(2,4-dichlorobenzoyl)-*N,N*-dimethylformamidine (**4c**) and *N,N*-dimethylguanidine (**6d**) were heated in acetic acid at 100 °C for 1 h to give *N*-formylbenzamide in 85% yield. Reaction in ethanol with 1 equiv of potassium *tert*-butoxide at 80 °C gave benzamide. However, when the reaction was carried out in refluxing THF, the desired s-triazine **7k** was obtained in good yield. The yield was usually improved in refluxing 1,4-dioxane. Hydrolyzed amide was the only byproduct[3] in this reaction, and better yields could be obtained when 2 equiv of the acylamidine was used. The triazines synthesized are tabulated in Table 1.

Acetamidine (**6a**) gave lower yields of corresponding triazines than other amidines or guanidines. A possible explanation for the low yield is the poor solubility of this amidine in THF and dioxane. Attempts to run the reaction in DMSO gave no triazine and amide was the only isolated product. It should be noted that when the two alkyl groups were different on an amino group (i.e. **7a**, **7f**, **7m**, and **7n**), an equimolar mixture of two isomers which could not be separated by chromatography was identified by ^{1}H NMR in deuterochloroform.

In conclusion, cyclizations of acylamidines with amidines or guanidines gave s-triazines bearing three different substitutents. This is a convenient synthetic route to s-triazines via a simple procedure from readily available starting materials.

Experimental Section

General Methods. Analytical samples were homogeneous by TLC and afforded spectroscopic results consistent with the assigned structures. Solvents used for reactions or chromatography were either reagent grade or HPLC grade. Reactions were run under an argon atmosphere. Solutions were evaporated under reduced pressure on a rotary evaporator. Acetamidine hydrochloride (**6a**), benzamidine hydrochloride (**6b**), (4-methoxyphenyl)guanidine carbonate (**6c**), and *N,N*-dimethylguanidine sulfate (**6d**) were obtained from Aldrich. Morpholinoguanidine hydrobromide (**6e**) was purchased from Lancaster Synthesis, Inc. *N*-Propyl-*N*-(cyclopropylmethyl)guanidine hydrochloride (**6f**), and *N*-benzyl-*N*-butylguanidine hydrochloride (**6g**) were synthesized according to general methods.[11]

General Preparation of Acylamidines. A mixture of amide (**1**, 5.0 mmol) and *N,N*-dimethylformamide dimethyl acetal (**2**, 0.8 g, 6 mmol) or *N,N*-dimethylacetamide dimethyl acetal (**3**, 0.88 g, 6 mmol) was heated in an open flask with an air-cooled condenser at 80 °C for 1 h. The mixture was cooled and placed under high vacuum to provide an oil or solid product **4** or **5** which was used without further purification.

General Procedure for Triazine Synthesis. A mixture of the acylamidine (**4** or **5**, 2.0 mmol), guanidine or amidine (**6**, 0.8 mmol), and potassium *tert*-butoxide (0.8 mmol) in dioxane (10 mL) was heated to reflux under argon atmosphere. The

(1) (a) Smolin, E. M.; Papoport, L. S-Triazines and Derivatives *The Chemistry of Heterocyclic Compounds*; Interscience Publishers: New York, 1959. (b) Neunhoeffer, H. *Chemistry of 1,2,3-triazines, 1,2,4-triazines, tetrazines, and pentazines*; Wiley: New York, 1978.

(2) Quirke, J. M. E. 1,3,5-Triazines. *Comprehensive Heterocyclic Chemistry*; Katritzky, A., Ed.; Pergamon Press: London, 1984; pp 457–530.

(3) Bader, H. *J. Org. Chem.* **1965**, *30*, 707.

(4) Papadopoulos, E. P.; George, B. *J. Org. Chem.* **1977**, *42*, 2530.

(5) (a) Lin, Y.; Lang, S. A., Jr.; Lovell, M. F.; Perkinson, N. A. *J. Org. Chem.* **1979**, *44*, 4160. (b) Lin, Y.; Lang, S. A., Jr.; Ridge, D. N. Eur. Pat. 51084, 12 May, 182. *Chem. Abstr.* **1982**, *97*, 127644.

(6) (a) Lin, Y.; Fields, T. L.; Lee, V. J.; Lang, S. A., Jr. *J. Heterocycl. Chem.* **1982**, *19*, 613. Similar cyclizations were also reported: (b) Whitfield, L. L., Jr.; Papadopoulos, E. P. *J. Heterocycl. Chem.* **1981**, *18*, 1197. (c) Augustin, M.; Richter M.; Salas, S. *J. Prakt. Chem.* **1980**, *322*, 55.

(7) *N*-Thioacylamidines were also synthesized by (a) reactions of acylisothiocyanate with Grignard reagents; see Walter, W.; Krohn, J. *Ann. Chem.* **1973**, 476. (b) Friedel–Crafts reactions of acylisothiocyanates with benzenes; see Wheeler, H. R. *J. Am. Chem. Soc.* **1901**, *26*, 345. (c) Acylations of thioamides, see: (1) Goedeler, J.; Horstmenn., H. *Chem. Ber.* **1960**, *93*, 663. (2) Goedeler, J.; Stadelbauer, K. *Chem. Ber.* **1965**, *98*, 1556.

(8) Two papers related to triazine cyclization appeared recently, see: (a) Popovich, T. P.; Drach, B. S. *Zh. Org. Khim*, **1987**, *23*, 2443. *Chem. Abstr.* **1988**, *109*, 110376d. (b) Shmel'kova, T. K.; Ignatenko, A. V.; Krukovskii, S. P.; Ponomarenko, V. A. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1989**, 928. *Chem. Abstr.* **1989**, *111*, 194722r.

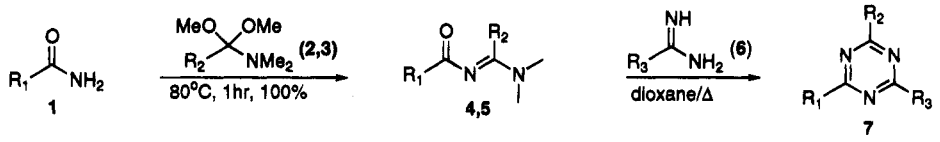
(9) **2** and **3** were purchased from Aldrich. Amide dialkyl acetals could be synthesized from various substrates, see Simchen, G. *Houben-Weyl Methoden der Organischen Chemie*; Falbe, J., Ed., Suppl. v. E5, part 1; pp 125–145, **1985**.

(10) The acidic hydrolysis of *N'*-acyl-*N,N*-dimethylamidine was reported: Lin, Y.; Lang, S. A., Jr. *Synthesis* **1980**, 119.

(11) For synthesis of guanidines, see Petersen, U. *Houben-Weyl Methoden der Organischen Chemie*; Hagemann, H., Ed., Band E4, pp 608–624, 1983.

0022-3263/95/1960-8428$09.00/0

Scheme 1



1a, R^1 = $PhCH_2CH_2$-
1b, R^1 = Ph-
1c, R^1 = 2,4-$(Cl)_2C_6H_3$-
1d, R^1 = 4-BrC_6H_4-

2, R^2 = H
3, R^2 = Me

4a, R^1 = $PhCH_2CH_2$-, R^2 = H
4b, R^1 = Ph, R^2 = H
4c, R^1 = 2,4-$(Cl)_2C_6H_3$-, R^2 = H
4d, R^1 = 4-BrC_6H_4-, R^2 = H

5a, R^1 = $PhCH_2CH_2$-, R^2 = Me
5b, R^1 = Ph, R^2 = Me
5c, R^1 = 2,4-$(Cl)_2C_6H_3$-, R^2 = Me

6a, R^3 = Me
6b, R^3 = Ph
6c, R^3 = 4-$MeOC_6H_4NH$-
6d, R^3 = Me_2N
6e, R^3 = $O(CH_2CH_2)_2N$-
6f, R^3 = c-$PrCH_2$(n-Pr)N-
6g, R^3 = Bn(n-Bu)N-

Table 1. Triazines (7) Synthesized from Acylamidines (4, 5) and Amidines or Guanidines (6)

		acylamidine (4, 5)		amidine/guanidine (6)[a]				
entry	compds 7	R^1	R^2	R^3	salt	solvent	*T*/time (°C/h)	yield (%)[b]
1	**7a**	phenethyl	H	c-$PrCH_2$(Pr)N	HCl	THF	67/4	64
2	**7b**	phenethyl	Me	4-MeOPh	H_2CO3	dioxane	100/14	81
3	**7c**	phenethyl	Me	morpholino	HBr	dioxane	100/14	94
4	**7d**	Ph	Me	Me	HCl	THF	67/16	40
5	**7e**	Ph	Me	4-MeOPh	H_2CO3	dioxane	100/16	76
6	**7f**	Ph	Me	Bn(n-Bu)N	HCl	dioxane	100/15	92
7	**7g**	4-BrPh	H	4-MeOPh	H_2CO3	dioxane	100/6	71
8	**7h**	4-BrPh	H	morpholino	HBr	dioxane	100/6	80
9	**7i**	2,4-$(Cl)_2$Ph	H	Me	HCl	THF	67/4	46
10	**7j**	2,4-$(Cl)_2$Ph	H	Ph	HCl	THF	67/5	87
11	**7k**	2,4-$(Cl)_2$Ph	H	Me_2N	H_2SO_4	THF	67/5	67
12	**7l**	2,4-$(Cl)_2$Ph	Me	Me_2N	H_2SO_4	THF	67/15	59
13	**7m**	2,4-$(Cl)_2$Ph	H	c-$PrCH_2$(Pr)N	HCl	dioxane	100/3	88
14	**7n**	2,4-$(Cl)_2$Ph	Me	Bn(n-Bu)N	HCl	dioxane	100/16	77

[a] One equivalent of t-BuOK was used to generate the amidine or guanidine free base from the HCl or H_2CO_3 salt; 2 equiv from the H_2SO_4 salt. (b) Yield of purified material.

progress of the reaction was monitored by TLC. The mixture was cooled to room temperature and concentrated in vacuo. The residue was transferred to a silica gel column and chromatographed with 1:5 to 1:3 ethyl acetate–hexanes to give the s-triazine (**7**).

2-[*N*-(Cyclopropylmethyl)-*N*-propylamino]-4-(2-phenylethyl)-1,3,5-triazine (7a): colorless oil; 1:1 isomers; ^{1}H NMR δ 0.27 (m, 2H), 0.49 (m, 2H), 0.89 (t, J = 7.5 Hz, 0.5 × 3H), 0.91 (t, J = 7.5 Hz, 0.5 × 3H), 1.05 (m, 1H), 1.61 (m, 2H), 2.96 (m, 2H), 3.06 (m, 2H), 3.46 (d, J = 6.9 Hz, 0.5 × 2H), 3.47 (d, J = 6.9 Hz, 0.5 × 2H), 3.56 (m, 2H), 7.24 (m, 5H), 8.42 (s, 0.5 × 1H), 8.45 (s, 0.5 × 1H); MS (IS) *m*/*e* 297 (MH^+); HR FAB MS calcd for $C_{18}H_{25}N_4$ (M + H) 297.2079, found 297.2068.

2-Methyl-4-[(4-methoxyphenyl)amino]-6-(2-phenylethyl)-1,3,5-triazine (7b): colorless oil; ^{1}H NMR δ 2.24 (s, 3H, CH_3), 2.70 (t, J = 6.6 Hz, 2H), 2.87 (d, J = 6.6 Hz, 2H), 3.71 (s, 3H), 6.80 (d, J = 8.8 Hz, 2H), 7.14 (m, 5H), 7.38 (d, J = 8.8 Hz, 2H), 9.40 (br s, 1H); ^{13}C NMR δ 26.97, 34.74, 41.63, 56.84, 115.49, 124.13, 127.41, 129.74, 132.20, 142.47, 157.70, 165.38, 177.30, 177.43, 179.58; MS (IS) *m*/*e* 321 (MH^+); HR FAB MS calcd for $C_{19}H_{21}N_4O$ (M + H) 321.1715, found 321.1728.

2-Methyl-4-morpholino-6-phenethyl-1,3,5-triazine (7c): colorless oil; ^{1}H NMR δ 2.82 (s, 3H), 3.15–3.60 (m, 4H), 4.23 (m, 6H), 4.36 (m, 2H), 7.72 (m, 5H); IR (cm^{-1}) 2918, 1595, 1563, 1528, 1265, 738; MS (EI) *m*/*e* 285 (MH^+); HR FAB MS calcd for $C_{16}H_{21}N_4O$ (M + H) 285.1715, found 285.1724.

2,4-Dimethyl-6-phenyl-1,3,5-triazine (7d): colorless oil, (lit. bp 93–6 °C/1.5 torr);[12] ^{1}H NMR δ 2.69 (s, 6H), 7.52 (m, 3H), 8.50 (d, J = 7.5 Hz, 2H); MS (IS) *m*/*e* 186 (MH^+).

2-Methyl-4-[(4-methoxyphenyl)amino]-6-phenyl-1,3,5-triazine (7e): white solid, mp 142–144 °C; ^{1}H NMR δ 2.60 (s, 3H), 3.87 (s, 3H), 6.98 (d, J = 9.0 Hz, 2H), 7.30 (brs, 1H), 7.50–7.63 (m, 5H), 8.47 (d, J = 7.0 Hz, 2H); MS (IS) *m*/*e* 293 (MH^+). Anal. Calcd for $C_{17}H_{16}N_4O$ (292.34): C, 69.85; H, 5.52; N, 19.16. Found: C, 69.54; H, 5.62; N, 18.85.

2-(*N*-Benzyl-*N*-butylamino)-4-methyl-6-phenyl-1,3,5-triazine (7f): colorless oil; 1:1 isomers; ^{1}H NMR δ 0.96 (m, 3H), 1.37 (m, 2H), 1.64 (m, 2H), 2.51 (s, 0.5 × 3H), 2.54 (s, 0.5 × 3H), 3.65 (m, 2H), 4.97 (s, 0.5 × 2H), 5.03 (s, 0.5 × 2H), 7.25–7.52 (m, 8H), 8.40 (d, J = 6.9 Hz, 0.5 × 2H), 8.46 (d, J = 7.0 Hz, 0.5 × 2H); MS (IS) *m*/*e* 333 (MH^+); HR FAB MS calcd for $C_{21}H_{25}N_4$ (M + H) 333.2079, found 333.2065.

2-(4-Bromophenyl)-4-[(4-methoxyphenyl)amino]-1,3,5-triazine (7g): white solid, mp 194–197 °C; ^{1}H NMR δ 3.84 (s, 3H), 6.50 (d, J = 8.5 Hz, 2H), 7.30 (br s, 1H), 7.50 (br s, 2H), 7.62 (d, J = 8.2 Hz, 2H), 8.29 (d, J = 8.2 Hz, 2H), 8.70 (br s, 1H); MS (EI) *m*/*e* 357, 359 (MH^+). Anal. Calcd for $C_{16}H_{13}BrN_4O$ (357.21): C, 53.80; H, 3.67; N, 15.68. Found: C, 53.82; H, 3.82; N, 15.27.

2-(4-Bromophenyl)-4-morpholine-1,3,5-triazine (7h):[13] white solid, mp160–161 °C; ^{1}H NMR δ 3.79 (br s, 4H), 3.90–4.05 (m, 4H), 7.60 (d, J = 8.4 Hz, 2H), 8.28 (d, J = 8.4 Hz, 2H), 8.64 (s, 1H); MS (IS) *m*/*e* 321, 323 (MH^+).

2-(2,4-Dichlorophenyl)-4-methyl-1,3,5-triazine (7i): white solid, mp 69–70 °C; ^{1}H NMR δ 2.75 (s, 3H), 7.37 (dd, J = 1.9, 8.2 Hz, 1H), 7.53 (d, J = 1.9 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 9.16 (s, 1H); MS (IS) *m*/*e* 240, 242 (MH^+). Anal. Calcd for $C_{10}H_7Cl_2N_3$ (240.09): C, 50.03; H, 2.94; N, 17.50. Found: C, 50.01; H, 3.08; N, 17.61.

2-(2,4-Dichlorophenyl)-4-phenyl-1,3,5-triazine (7j): white solid, mp 105–106 °C; ^{1}H NMR δ 7.43 (dd, J = 2.1, 8.4 Hz, 1H), 7.54–7.62 (m, 4H), 8.03 (d, J = 8.4 Hz, 1H), 8.60 (m, 2H), 9.33 (s, 1H); ^{13}C NMR δ 128.70, 130.20, 130.45, 132.48, 134.51, 134.60, 134.91, 135.96, 136.41, 138.89, 167.90, 172.67, 172.87; IR (cm^{-1}) 2916, 1586, 1560, 1539, 1511, 1415; MS (IS) *m*/*e* 302, 304 (MH^+). Anal. Calcd for $C_{15}H_9Cl_2N_3$ (302.17): C, 59.63; H, 3.00; N, 13.91. Found: C, 59.98; H, 3.05; N, 13.55.

2-(2,4-Dichlorophenyl)-4-(dimethylamino)-1,3,5-triazine (7k): white solid, mp 71 °C; ^{1}H NMR δ 3.26 (s, 3H), 3.27

(12) Shaefer, F. C. *J. Org. Chem.* **1962**, *27*, 3608.

(13) Vollenbroek, F. A.; Nijssen, W. P. M.; Geomini, M. J. H. Eur. Pat. Appl. EP 244,019, 04 Nov 1987; *Chem. Abstr.* **1987**, *109*, P83459z.

(s, 3H), 7.34 (dd, J = 2.2, 8.4 Hz, 1H), 7.51 (d, J = 2.2 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 8.66 (s, 1H); MS (IS) m/e 269, 271 (MH^+).

2-(2,4-Dichlorophenyl)-4-(dimethylamino)-6-methyl-1,3,5-triazine (7l): white solid, mp 70 °C; ^{1}H NMR δ 2.50 (s, 3H), 3.25 (s, 6H), 7.32 (dd, J = 2.0, 8.4 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H); IR (cm^{-1}) 2920, 2851, 1581, 1549, 1502, 1407, 1242; MS (IS) m/e 283, 285 (MH^+).

2-[*N*-(Cyclopropylmethyl)-*N*-propylamino]-4-(2,4-dichlorophenyl)-1,3,5-triazine (7m): colorless oil; 1:1 isomers; ^{1}H NMR δ 0.32 (m, 2H), 0.54 (m, 2H), 0.93 (t, J = 7.5 Hz, 0.5 × 3H), 0.96 (t, J = 7.5 Hz, 0.5 × 3H), 1.12 (m, 1H), 1.70 (m, 2H), 3.56 (t, J = 6.3 Hz, 2H), 3.65 (m, 2H), 7.34 (dd, J = 2.1, 8.4 Hz, 1H), 7.49 (d, J = 2.1 Hz, 0.5 × 1H), 7.51 (d, J = 2.1 Hz, 0.5 × 1H), 7.80 (d, J = 8,4 Hz, 0.5 × 1H), 7.84 (d, J = 8.4 Hz, 0.5 × 1H), 8.63 (s, 0.5 × 1H), 8.65 (s, 0.5 × 1H); MS (IS) m/e 337, 339 (MH^+); HR FAB MS calcd for $C_{16}H_{19}Cl_2N_4$ (M + H) 337.0987, found 337.0987.

2-(*N*-Benzyl-*N*-butylamino)-4-methyl-6-(2,4-dichlorophenyl)-1,3,5-triazine (7n): colorless oil; 1:1 isomers; 1H NMR d 0.90 (t, J = 6.9 Hz, 0.5 × 3H), 0.95 (t, J = 6.9 Hz, 0.5 × 3H), 1.33 (m, 2H), 1.62 (m, 2H), 2.50 (s, 0.5 × 3H), 2.53 (s, 0.5 × 3H), 3.60 (m, 2H), 4.93 (s, 0.5 × 2H), 4.95 (s, 0.5 × 2H), 7.25–7.50 (m, 7H), 7.72 (d, J = 8.4 Hz, 0.5 × 1H), 7.80 (d, J = 8.4 Hz, 0.5 × 1H); MS (IS) m/e 401, 403 (MH^+); HR FAB MS calcd for $C_{21}H_{22}Cl_2N_4$ (M + H) 401.1300, found 401.1285.

Supporting Information Available: Copies of ^{1}H NMR spectra of **7a–n** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO951193P

Additions and Corrections

Vol. 59, 1994

Ulrike Salzner and Paul von Ragué Schleyer*. Ab Initio Examination of Anomeric Effects in Tetrahydropyrans, 1,3-Dioxanes, and Glucose.

We regret the following errors and oversights in Table 1:

Page 2141, Table 1. Corrected values are given below for entries 2, 4 and 10:

entry	compd.	level	E_e	E_a	ΔE_{a-e}
2	**14**	HF/6-31+G*			
4	**14**			-333.13181	0.04
10	**15**				3.02

Page 2143, Table 5. The last entry for compound **9** and the first entry for compound **10** (entries 21 and 22) were misrepresented as one line. The corrected entries for compounds **9** and **10** are as follows:

entry		conformn	E_{tot}	E_{rel}	Θ C6-O1-C2-O7	Θ O1-C2-O7-R
18	**9**	a_1	-419.73115	0.0	-67.0	-65.0
19		e_3	-419.72954	1.0	-179.5	61.0
20		e_1	-419.72659	2.9	176.9	64.4
21		a_3	-419.71661	9.1	-103.2	66.1
22	**10**	e_3	-289.23034	0.0	-178.9	-63.3/-178.4
23		e_1	-289.23003	0.2	-178.5	-59.1/58.8
24		a_3	-289.22923	0.7	-67.3	-55.0/173.9
25		a_1	-289.22704	2.1	-71.1	-59.4/59.2

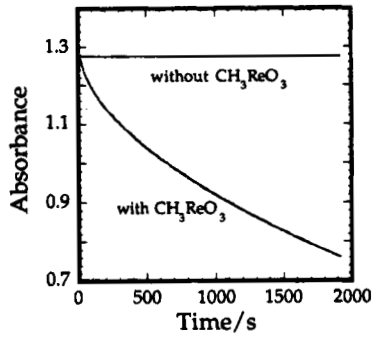
JO954026Y

Vol. 60, 1995

Zuolin Zhu and James H. Espenson*. Kinetics and Mechanism of Oxidation of Anilines by Hydrogen Peroxide As Catalyzed by Methylrhenium Trioxide.

Page 1330. Figure 4 correctly deals with $PhNH_2$; the caption should read as follows: Typical absorbance–time kinetic trace at 320 nm for the oxidation of $PhNH_2$ in methanol by hydrogen peroxide with and without CH_3ReO_3. The concentrations were 0.15 mM CH_3ReO_3, 1.96 mM H_2O_2, and 1.32 mM $PhNH_2$.

The figure that matches the caption in the published Figure 4 is the following:



JO954013K