# α-AMINO KETONE SYNTHESIS FROM ALDEHYDES AND *N*-(α-DIALKYLAMINOALKYL)BENZOTRIAZOLES§

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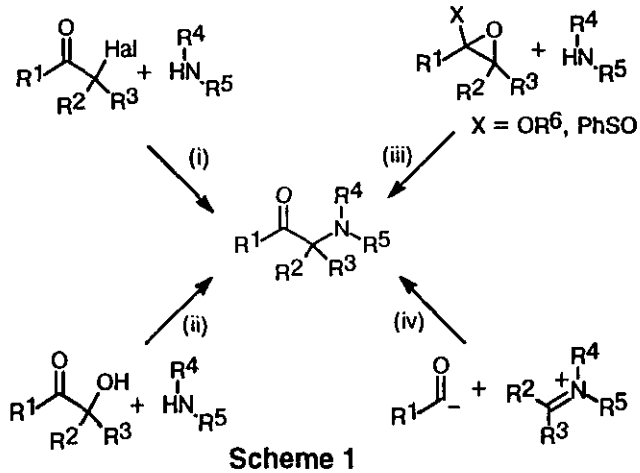
**Abstract**-Thiazolium salt-catalyzed reactions of aldehydes with morpholino-(alkylbenzotriazoles) allow the synthesis of a variety of α-amino ketones. The relationship between reaction conditions and selectivity is discussed.

α-Amino ketones are important and versatile compounds in organic synthesis particularly as useful building blocks in the synthesis of certain heterocycles.[1] Additionally, 2-aminocycloalkanones have been shown to be drug intermediates[2] while α-aminoisobutyrophenones have been used in the treatment of central nervous system depression.[3]

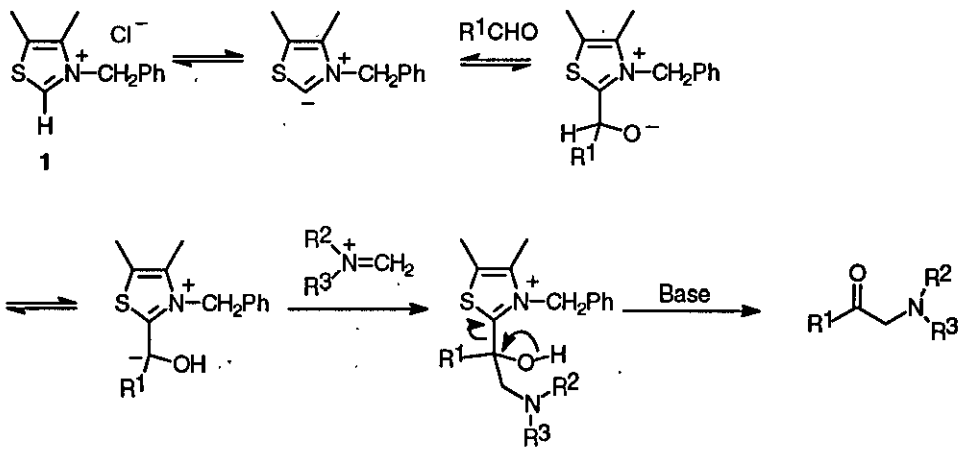



**Scheme 1**

§ Submitted in memory of the renowned Japanese chemist Yoshio Ban.

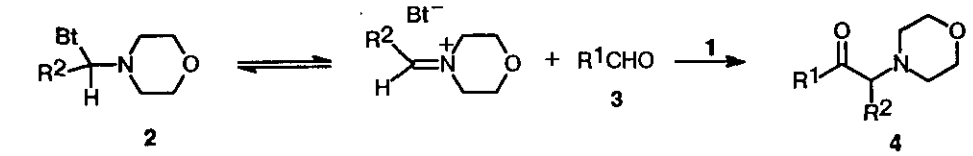
α-Amino ketones are most commonly prepared (for a review see Fisher and Muchowski[4]) by (i) amination of α-halo ketones[1] or (ii) α-hydroxy ketones[5] or by (iii) ring opening of phenylsulfinyl-[6] or alkoxy-epoxides[7] with amines. All of these methods have their disadvantages. For example, while α-amino ketones with various substituents have been prepared by method (i), side reactions such as dehalogenation followed by Michael addition,[1] Favorskii type rearrangement[8] and Voigt-Amadori rearrangement[1] (Scheme 5) may compete when certain combinations of substrates and amines are used. When method (ii) is applied, the α-carbon must be primary or secondary. If $R^1$ and $R^2$ are different, crossover products may result.[5] Examination of method (iii) shows that only α,α-disubstituted α-aminoalkylaryl ketones ($R^1$ = aryl; $R^2$, $R^3$ = alkyl) have been prepared through the amination of alkoxy epoxides[7] and that α-aminoalkyl ketones ($R^1$ = alkyl or alkylaryl) and α-amino aldehydes were synthesized through amination of phenylsulfinyl epoxides.[6]

A further potential method (Scheme 1, iv) is the addition of aldehydes, masked in the form of an acyl synthon, to an iminium cation. Castells *et al.*[9] indeed has reported that 3-benzyl-4,5-dimethylthiazolium chloride (**1**) catalyzes the addition of aldehydes to methyliminium salts and has suggested the mechanism of Scheme 2. This transformation can be considered a combination of the classical Mannich and benzoin reactions, both of which acting individually are the origin of byproducts of the main process. We have now modified and extended this synthetic route by using *N*-(α-morpholinoalkyl)benzotriazoles as iminium salt generators (cf ref.[10]), thus overcoming the limitation that aldehydes other than formaldehyde do not readily react with amines to form alkyliminium salts which participate in Mannich type additions (Scheme 3).




**Scheme 2**

Castells *et al.* reported[9] that isobutyraldehyde, formaldehyde and morpholine in the presence of **1** and a small amount of base gave a compound, bp 77-78 °C/ 2 mm Hg, which they postulated was 3-methyl-1-(*N*-morpholino)butan-2-one (**4f**). In our hands, when either *N*-(morpholino)methylbenzotriazole (**2a**) or the starting materials employed by Castells *et al.* were used as the iminium salt substrate, this method produced the same compound of bp 55 °C/ 0.5 mm Hg which was, however, shown by spectral analysis to be 2,2-dimethyl-3-(*N*-morpholino)propionaldehyde (**5**), the product of a simple Mannich reaction.



**2**

Bt = 1-benzotriazolyl or 2-benzotriazolyl

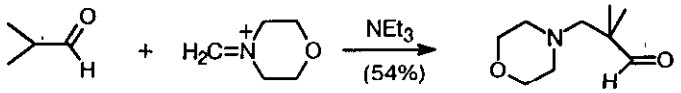
**2a:** $R^2$ = H
**2b:** $R^2$ = Ph
**2c:** $R^2$ = *p*-$MeC_6H_4$
**2d:** $R^2$ = *p*-$ClC_6H_4$
**2e:** $R^2$ = *p*-$MeOC_6H_4$

**3a:** $R^1$ = *i*-Pr
**3b:** $R^1$ = Ph
**3c:** $R^1$ = *p*-$MeC_6H_4$
**3d:** $R^1$ = *p*-$ClC_6H_4$
**3e:** $R^1$ = *p*-$CNC_6H_4$

**4a:** $R^1$ = Ph, $R^2$ = H (58%)
**4b:** $R^1$ = Ph, $R^2$ = Ph (44%)
**4c:** $R^1$ = *p*-$MeC_6H_4$, $R^2$ = *p*-$MeC_6H_4$ (30%)
**4d:** $R^1$ = *p*-$ClC_6H_4$, $R^2$ = *p*-$ClC_6H_4$ (55%)
**4e:** $R^1$ = *p*-$CNC_6H_4$, $R^2$ = *p*-$MeOC_6H_4$ (42%)
**4f:** $R^1$ = *i*-Pr, $R^2$ = H (28%)

**Scheme 3**

Evidence for this conclusion was gained from $^1$H nmr as follows i) the two methyl groups appear as a singlet, and ii) upon treatment with $D_2O$, all peaks remained unchanged (eliminating the possibility of an enolate form). Castells *et al.* reported[9] essentially the same $^1$H nmr spectrum. As expected, compound (**5**) was also obtained in the absence of thiazolium salt (**1**) (Scheme 4).



**5**

**Scheme 4**

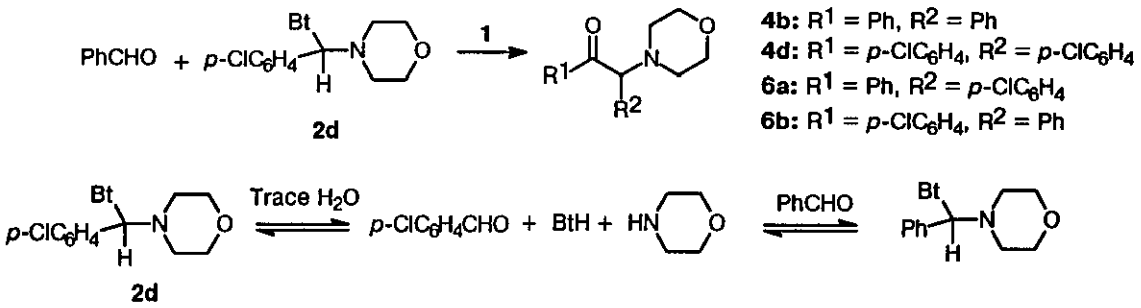
However, when we modified the originally reported conditions by changing the reaction solvent to acetonitrile and omitting base we obtained authentic α-amino ketone (**4f**) in 20% yield, which was improved to 28% by the use of iminium salt (**2a**). The $^1$H nmr spectrum of **4f** showed the methyl groups as a doublet and possessed the other peaks expected (see experimental) with different chemical shifts to those observed in the $^1$H nmr spectrum of **5**.

Castells *et al.*[9] reported that the use of benzaldehyde as the aldehydic substrate under the conditions employing formaldehyde, morpholine, thiazolium salt (**1**) and a base, resulted in the formation of α-(*N*-

morpholino)acetophenone (**4a**) in 33% yield. In our hands, gcms showed that this method indeed produced **4a** together with significant amounts of benzoin. In this case, no Mannich reaction can occur because there is no α-hydrogen in the aldehydic substrate. Benzoin is believed to be formed *via* attack of the benzaldehyde-thiazolium salt complex (Scheme 2) by another molecule of benzaldehyde. It was found that when the reaction conditions were modified by changing the solvent to acetonitrile and not adding base, that benzoin formation could be minimized. The desired α-amino ketone (**4a**) was thus obtained in 52% yield. When the iminium salt substrate (**2a**) was used, instead of morpholine and formaldehyde, the yield of **4a** was further improved to 58%. The $^1$H nmr spectrum obtained for **4a** was in agreement with that obtained by Castells *et al.*[9] and is in accord with the proposed structure (see experimental).

Thus, modification of the method of Castells and coworkers[9] to omit base from the reaction mixture has favored the formation of α-amino ketones by suppressing benzoin and Mannich reaction side products. This result may be rationalized as follows. Firstly, when base is not added, the thiazolium salt is deprotonated (Scheme 2) by the iminium salt counter-ion. This leads to faster generation of the iminium salt and a greater probability that the α-amino ketone, and not the benzoin product, will be formed. Secondly, since the classical Mannich reaction is base-catalyzed, it is expected that it may be suppressed under the less basic conditions.

Application of the method using acetonitrile as solvent with no addition of base to the reactions of *N*-α-(morpholinobenzyl)benzotriazoles (**2b-2d**) with the benzaldehydes (**3b-3d**)(each containing the same *para* substituent as **2b-2d**) led to the formation of symmetrically substituted α-amino ketones (**4b-4d**) in 30%-55% yields (Scheme 3). For example, when α-(*p*-methylphenyl)-*N*-α-morpholinobenzotriazole (**2c**) was reacted with *p*-methylbenzaldehyde (**3c**), the symmetrically substituted α-amino ketone (**4c**) was formed in 30% yield. However, the methoxy derivative (**2e**) failed to react with *p*-anisaldehyde.




**Scheme 5**

Attempts to prepare unsymmetrically substituted α-amino ketones in acceptable yield by reaction of compounds of type **2** with benzaldehydes containing different substituents failed due to crossover reactions. For example, when benzaldehyde was reacted with α-(*p*-chlorophenyl)-*N*-α-morpholinobenzotriazole (**2d**), gcms and nmr suggested that four products (**4b**, **4d**, **6a** and **6b**) were formed in comparable amounts (Scheme 5). The $^1$H nmr spectrum showed four peaks of similar areas at around the chemical shift expected for the α-hydrogen of an α-amino ketone (4.5-5.0 ppm) and gcms showed four equally abundant compounds with the expected molecular ions and characteristic ms patterns. The *p*-chloro derivative (**2d**) is evidently in equilibrium with its aldehydic component (*p*-chlorobenzaldehyde) and undergoes exchange with the unsubstituted benzaldehyde in the reaction mixture. However, *p*-cyanobenzaldehyde reacted with methoxy derivative (**2e**) to form **4e** without appreciable formation of crossover products. It is presumed that this reaction to form the α-amino ketone (**4e**) proceeds more quickly than the aldehydic crossover.

In conclusion, this method for preparing α-amino ketones of type **4** overcomes some of the problems associated with the other methods mentioned earlier. Any products due to side reactions (such as benzoins) are easily removed in the workup procedure. Additionally, the starting materials required for this process are more conveniently accessed than, for example, for the methods requiring the use of epoxides.[6,7] Since a wide range of *N*-(α-dialkylamino)alkylbenzotriazoles are readily available,[10] synthesis of other α-amino ketones (aside from α-morpholino ketones) should also be possible through use of this method. In summary, this preparation allows the convenient generation of α-unsubstituted α-amino ketones (such as **4a** and **4f**) and symmetrically substituted α-aryl α-aminoaryl ketones (e.g. **4b-4d**) from readily available starting materials.

## EXPERIMENTAL SECTION

### General

Melting points are uncorrected. All nmr spectra were obtained using a Varian VXR 300 spectrometer operating at 300 MHz in deuteriochloroform unless otherwise stated. The catalyst 3-benzyl-4,5-dimethylthiazolium chloride (**1**) was prepared by standard methods from commercially available 4,5-dimethylthiazole. The preparations of *N*-morpholinomethylbenzotriazole (**2a**),[11] α-phenyl-(*N*-morpholino)methylbenzotriazole (**2b**),[12] α-(*p*-methoxyphenyl)-(*N*-morpholino)methylbenzotriazole (**2e**)[11] have been reported previously. Compounds (**2c**) and (**2d**) were prepared as outlined below. All other starting materials are commercially available.

*General Procedure for the Preparation of N-Morpholino(alkylbenzotriazoles) (2c-2d). Typical Procedure for the Preparation of p-Methylphenyl-(N-morpholino)methylbenzotriazole* (**2c**): A mixture of benzotriazole (2.38 g, 20 mmol), morpholine (1.74 g, 20 mmol) and *p*-methylbenzaldehyde (2.40 g, 20 mmol) was refluxed in benzene (100 ml) with a Dean-Stark trap until the calculated amount of water had been collected. The solvent was evaporated and the residue taken up into $CH_2Cl_2$, washed with 10% $Na_2CO_3$ (2 × 40 ml) and water (2 × 40 ml). The organic phase was dried ($MgSO_4$) and evaporated to dryness to give **2c** as a mixture of benzotriazol-1-yl and benzotriazol-2-yl isomers (4.92 g, 80%), mp 113-114 °C. Anal. Calcd for $C_{18}H_{20}N_4O$: C, 70.13; H, 6.49; N, 18.18. Found: C, 69.80; H, 6.52; N, 18.31.

*p-Chlorophenyl-(N-morpholino)methylbenzotriazole* (**2d**): The title compound was prepared as above from *p*-chlorobenzaldehyde as an oil (81%). Anal. Calcd for $C_{17}H_{17}N_4OCl$: C, 62.10; H, 5.18; N, 17.05. Found: C, 62.36; H, 5.25; N, 17.08.

*General Procedure for the Preparation of α-Amino Ketones. Typical Procedure for the Preparation of α-(N-Morpholino)acetophenone* (**4a**): A solution of benzotriazolyl compound (**2a**, 0.55 g, 2.5 mmol), thiazolium salt (**1**, 0.06 g, 0.25 mmol) and benzaldehyde (0.53 g, 5 mmol) in 20 ml of acetonitrile was refluxed under nitrogen for 8 h. The solvent was evaporated, the residue taken up into $CH_2Cl_2$ and washed with 10% $Na_2CO_3$ (3 × 30 ml). The mixture was extracted with 10 M HCl (3 × 30 ml), neutralized with 30% $NH_4Cl$ and extracted with $CH_2Cl_2$ (2 × 60 ml). Evaporation yielded a residue which was subjected to flash chromatography (dichloromethane/acetone 10:1) followed by distillation to give **4a** (0.30 g, 58%), bp 124 °C/1 mm Hg, mp [HCl salt] 216-218 °C (lit.,[13] mp [HCl salt] 222-223 °C). Anal. Calcd for $C_{12}H_{12}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.89; H, 7.30; N, 6.98. $^1$H Nmr (δ, ppm): 2.64 (t, 4H, $J$ = 4.7 Hz), 3.78 (t, 4H, $J$ = 4.7 Hz, $OCH_2$), 3.84 (s, 2H), 7.45 (m, 2H), 7.57 (m, 1H), 8.00 (d, 2H, $J$ = 6.9 Hz). $^{13}$C Nmr (δ, ppm): 53.8, 64.7, 66.8, 128.0, 128.5, 133.2, 136.0, 196.1.

*α-(N-Morpholino)-α-phenylacetophenone* (**4b**): The title compound was prepared as above from benzotriazolyl compound (**2b**, 2.94 g, 10 mmol), thiazolium salt (**1**, 0.24 g, 1 mmol) and benzaldehyde (2.12 g, 20 mmol) except that the reaction was refluxed for 20 h. Flash chromatography (dichloromethane/acetone 20:1) followed by trituration with ether gave **4b** (1.24 g, 44%), mp 79-81 °C (lit.,[14] mp 78 °C). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.52; H, 6.79; N, 5.00. $^1$H Nmr (δ, ppm): 2.52 (m, 4H), 3.76 (m, 4H), 4.94 (s, 1H), 7.28-7.46 (m, 8H), 8.01 (d, 2H, $J$ = 7.0 Hz). $^{13}$C Nmr (δ, ppm): 52.2, 66.9, 76.5, 128.4, 128.7, 128.8, 129.7, 133.1, 134.7, 136.5, 197.3.

*α-(p-Methylphenyl)-α-(N-morpholino)-p-methylacetophenone* (**4c**): The title compound was prepared as above

from benzotriazolyl compound (**2c**, 1.84 g, 6.0 mmol), thiazolium salt (**1**, 0.71 g, 3.0 mmol) and *p*-methylbenzaldehyde (1.43 g, 11.9 mmol) except that the reaction was refluxed for 24 h. Flash chromatography (dichloromethane/acetone 20:1) gave **4c** as an oil (0.58 g, 30%). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.67; H, 7.44; N, 4.53. Found: C, 77.51; H, 7.63; N, 4.85. $^1$H Nmr (δ, ppm): 2.28 (s, 3H), 2.34 (s, 3H), 2.50 (m, 4H), 3.75 (m, 4H), 4.86 (s, 1H), 7.10 (d, 2H, $J$ = 8.0 Hz), 7.17 (d, 2H, $J$ = 8.2 Hz), 7.31 (d, 2H, $J$ = 8.0 Hz), 7.92 (d, 2H, $J$ = 8.2 Hz). $^{13}$C Nmr (δ, ppm): 21.0, 21.5, 52.2, 66.9, 76.1, 127.2, 128.8, 129.1, 129.1, 129.5, 138.1, 143.8, 196.8.

*α-(p-Chlorophenyl)-α-(N-morpholino)-p-chloroacetophenone* (**4d**): The title compound was prepared as above from benzotriazolyl compound (**2d**, 2.50 g, 7.6 mmol), thiazolium salt (**1**, 0.85 g, 3.6 mmol) and *p*-chlorobenzaldehyde (2.13 g, 15.2 mmol) except that the reaction was refluxed for 24 h. Flash chromatography (dichloromethane/acetone 20:1) and trituration with ether gave **4d** (1.45 g, 55%) as an oil. Anal. Calcd for $C_{18}H_{17}NO_2Cl_2$: C, 61.89; H, 4.87; N, 3.99. Found: C, 61.89; H, 4.90; N, 4.01. $^1$H Nmr (δ, ppm): 2.49 (m, 4H), 3.74 (m, 4H), 4.83 (s, 1H), 7.27-7.51 (m, 8H), 7.97 (d, 2H, $J$ = 8.7 Hz). $^{13}$C Nmr (δ, ppm): 52.0, 66.8, 76.0, 128.9,129.2, 130.1, 130.8, 133.0, 134.6, 134.5, 139.9, 195.8.

*α-(p-Methoxyphenyl)-α-(N-morpholino)-p-cyanoacetophenone* (**4e**): The title compound was prepared as above from benzotriazolyl compound (**2e**, 1.80 g, 5.6 mmol), thiazolium salt (**1**, 0.66 g, 2.8 mmol) and *p*-cyanobenzaldehyde (0.36 g, 2.8 mmol) except that the reaction was refluxed for 6 h. Flash chromatography (dichloromethane/acetone 20:1) gave **4e** as an oil (0.39 g, 42%). Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.43; H, 5.95; N, 8.33. Found: C, 71.29; H, 6.15; N, 8.28. $^1$H Nmr (δ, ppm): 2.50 (m, 4H), 3.75 (m, 4H), 3.76 (s, 3H), 4.81 (s, 1H), 6.84 (d, 2H, $J$ = 8.9 Hz), 7.27 (d, 2H, $J$ = 8.8 Hz) 7.68 (d, 2H, $J$ = 8.7 Hz), 8.07 (d, 2H, $J$ = 8.8 Hz). $^{13}$C Nmr (δ, ppm): 52.0, 55.2, 66.8, 114.6, 116.2, 117.8, 125.2, 129.0, 130.9, 132.3, 139.5, 159.9, 196.0.

*3-Methyl-1-(N-morpholino)-2-butanone* (**4f**): The title compound was prepared as above from benzotriazolyl compound (**2a**, 0.55 g, 2.5 mmol), thiazolium salt (**1**, 0.06 g, 0.25 mmol) and isobutyraldehyde (0.36 g, 5 mmol) except that the reaction was refluxed for 72 h. Distillation gave **4f** (0.71 g, 28%), bp 50 °C/0.5 mm Hg (lit., bp[15] 77-78 °C/2 mm Hg). Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.00; N, 8.18. Found: C, 62.88; H, 9.98; N, 8.18. $^1$H Nmr (δ, ppm):1.10 (d, 6H, $J$ = 6.9 Hz), 2.50 (t, 4H, $J$ = 4.5 Hz), 2.71 (septet, 1H, $J$ = 7.0 Hz), 3.27 (s, 2H), 3.76 (t, 4H, $J$ = 4.5 Hz). $^{13}$C Nmr (δ, ppm): 18.2, 38.5, 53.7, 65.8, 66.7, 211.5.

*2,2-Dimethyl-3-(N-morpholino)propionaldehyde* (**5**): A mixture of paraformaldehyde (0.60 g, 20 mmol) and morpholine (1.74 g, 20 mmol) in ethanol (20 ml) was refluxed until a clear solution was obtained. The mixture was cooled and isobutyraldehyde (2.88 g, 40 mmol) and triethylamine (0.40 g, 4 mmol) were added and the

solution refluxed for 8 h. The reaction was worked up as described above. The residue was subjected to column chromatography (dichloromethane/acetone 20:1) to give **5** (1.85 g, 54%), bp 55 °C/0.5 mm Hg (lit.,[16] bp 105-110 °C/10 mm Hg). Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.00; N, 8.18. Found: C, 62.75; H, 10.06; N, 8.24. $^1$H Nmr (δ, ppm): 1.08 (s, 6H), 2.46 (t, 4H, $J$ = 4.7 Hz), 2.48 (s, 2H), 3.27 (s, 2H), 3.64 (t, 4H, $J$ = 4.7 Hz), 9.56 (s, 1H). $^{13}$C Nmr (δ, ppm): 20.5, 47.4, 55.2, 65.5, 67.0, 206.2.

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