$Ag_3PW_{12}O_{40}$: A Novel and Recyclable Heteropoly Acid for the Synthesis of 1,5-Benzodiazepines under Solvent-Free Conditions

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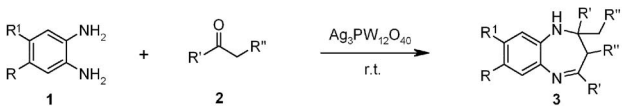
Abstract: *o*-Phenylenediamines undergo smooth condensation with ketones having hydrogens at α-position on the surface of heteropoly acid ($Ag_3PW_{12}O_{40}$) under extremely mild conditions to afford the corresponding 1,5-benzodiazepines in excellent yields with high selectivity. The catalyst can be recovered by simple filteration and can be reused in subsequent reactions.

Keywords: heteropoly acids, *o*-phenylenediamines, ketones, benzodiazepines

Benzodiazepines have received great importance because of their medicinal and therapeutic properties.[1] Many functionalized benzodiazepines are widely used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive, and hypnotic agents.[2] Benzodiazepines also find commercial use as dyes for acrylic fibers[3] and as anti-inflammatory agents.[4] In addition, 1,5-benzodiazepines are key intermediates for the synthesis of various fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, or furanobenzodiazepines.[5] Due to their wide range of biological, industrial, and synthetic applications, these compounds have recently received a great deal of attention. The simplest and the most straightforward procedure for the synthesis of 1,5-benzodiazepines involves the acid catalyzed condensation of *o*-phenylenediamines with ketones.[6] A variety of catalysts such as $BF_3{\cdot}OEt_2$, $NaBH_4$, polyphosphoric acid–SiO_2, MgO–$POCl_3$, $Yb(OTf)_3$, Al_2O_3–P_2O_5, HOAc–microwave, SO_4^{2-}–ZrO_2, and 1-butyl-3-methylimidazolium bromide ([bmim]Br) have been employed to effect this transformation.[6,7] Since 1,5-benzodiazepines have become increasingly useful and important in the fields of drugs and pharmaceuticals, the development of clean, high-yielding and environmentally friendly approaches are desirable.

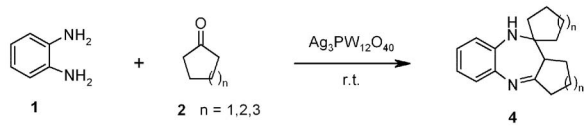
In recent years, the use of solid acids as heterogeneous catalysts has received considerable interest in different areas of organic synthesis.[8] Heterogeneous solid acids are advantageous over conventional homogeneous acid catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be reused after activation or without activation, thereby making the process economically viable. In many cases, heterogeneous catalysts can be recovered with only minor change in activity and selectivity so that they can be conveniently used in continuous flow reactions. Among various heterogeneous catalysts, heteropoly acids are most attractive, because of their reusability, flexibility in modifying the acid strength, ease of handling, environmental compatibility, non-toxicity and experimental simplicity.[9] However, there are no examples of the use of the silver salt of heteropoly acid for the preparation of 1,5-benzodiazepines. The use of heteropoly acid as a recyclable catalyst makes the reaction process more convenient, economic and environmentally benign.

In view of the emerging importance of the use of heterogeneous solid acids as reusable catalysts in organic synthesis, herein we wish to disclose a mild and efficient protocol for the synthesis of 1,5-benzodiazepines using a silver salt of heteropoly acid ($Ag_3PW_{12}O_{40}$)[10] as a novel heterogeneous catalyst (Scheme 1).



Scheme 1

Accordingly, treatment of *o*-phenylenediamine with acetone in the presence of silver salt of 12-tungustophosphoric acid ($Ag_3PW_{12}O_{40}$) at room temperature afforded 2,4,4-trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine in 92% yield (Table 1, entry **3a**). Similarly, various ketones such as acetone, acetophenone, 2-butanone, and isobutyl methylketone underwent smooth condensation with *o*-phenylenediamines in solvent-free conditions[11] to give the corresponding 1,5-benzodiazepines in 80–95% yields (Table 1, entries **3a**–**3m**). The reactions were clean and the products were obtained in high yields in short reaction times. The crude products were purified either by recrystallization from a mixture of Et_2O–*n*-hexane or by silica gel column chromatography. The reaction of cyclic ketones such as cyclohexanone, cyclopentanone, and cycloheptanone with *o*-phenylenediamine in the presence of



Scheme 2

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$Ag_3PW_{12}O_{40}$ afforded fused ring 1,5-benzodiazepines in good yields (Table 1, entries **4n**, **4o**, **4p**; Scheme 2).

In all cases, the reactions proceeded efficiently at room temperature under solvent-free conditions. All of the products were characterized by ^1H, ^{13}C NMR, IR, and mass spectral analysis and also by comparison with authentic samples.[6,7] Both cyclic and acyclic ketones worked well under similar reaction conditions. This method is effective for the preparation of benzodiazepines from both electron-rich as well as electron-deficient *o*-phenylenediamines. However, in the absence of heteropoly acid, the reaction did not proceed at room temperature even after long reaction times (8–12 h). The efficacy of other solid acids such as K10 clay, SiO_2, and H-ZSM-5 was studied for this reaction. Among these catalysts, silver salt of 12-tungustophosphoric acid ($Ag_3PW_{12}O_{40}$) was found to be superior in terms of conversion and reaction rates. The catalyst was easily separated by simple filtration and reused after drying with gradual decrease in activity. For instance, the reaction of *o*-phenylenediamine and acetone afforded 2,3-dihydro-1,5-benzodiazepine in 95%, 89%, 85%, and 80% yields over four cycles. Thus, this procedure provides an easy access to the preparation of substituted 1,5-benzodiazepines with a wide range of substitution patterns.

In summary, we describe a mild, convenient and efficient protocol for the synthesis of 2,3-dihydro-1*H*-1,5-benzodiazepines via the condensation of *o*-phenylenediamines with ketones using heteropolyacid as a recyclable heterogeneous catalyst. The simple experimental procedure combined with ease of recovery and reuse of this novel catalyst makes this procedure quite simple, more convenient and environmentally benign.

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^1H NMR and ^{13}C spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. All commercially available reagent grade chemicals were purchased from Aldrich Chemical Company and used as received without further purification unless otherwise stated. All the solvents were distilled, dried and stored under nitrogen prior to use.

Synthesis 2,3-dihydro-1,5-benzodiazepines; General Procedure

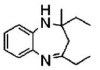
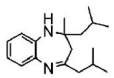
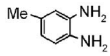
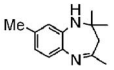
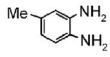
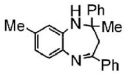
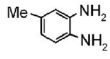
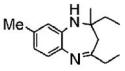
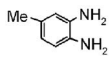
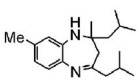
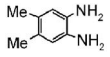
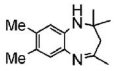
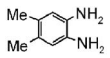
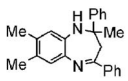
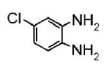
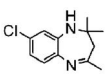
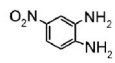
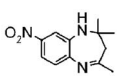
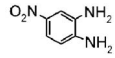
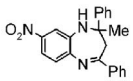
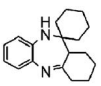
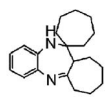
A mixture of *o*-phenylenediamine (1 mmol), ketone (2.5 mmol), and $Ag_3PW_{12}O_{40}$ (0.3 mmoL) was stirred at ambient temperature for an appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was filtered and washed with EtOAc (2 × 10 mL). The combined organic extracts were concentrated in vacuo and the resulting product was directly charged on small silica gel column and eluted with a mixture of EtOAc–*n*-hexane (2:8) to afford pure diazepine. The recovered catalyst was washed with MeOH and activated at 120 °C for 3–4 h prior to reuse.[7,8]

2,4,4-Trimethyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3a)

Light yellow solid; mp 136–138 °C.

IR (KBr): 3340, 1650, 1600 cm^{-1}.

Table 1 $Ag_3PW_{12}O_{40}$-Catalyzed Synthesis of 1,5-Benzodiazepines under Solvent-Free Conditions

Entry	Diamine	Ketone	Product[a]	Reaction Time (h)	Yield (%)
a		CH_3COCH_3		3.0	92
b		$PhCOCH_3$		5.0	86
c		$CH_3COCH_2CH_3$		3.5	85[c]
d				4.0	82
e		CH_3COCH_3		2.5	93
f		$PhCOCH_3$		5.5	85
g		$CH_3COCH_2CH_3$		4.0	83[c]
h				4.5	80
i		CH_3COCH_3		3.0	95
j		$PhCOCH_3$		4.5	84
k		CH_3COCH_3		3.5	92
l		CH_3COCH_3		5.0	86
m		$PhCOCH_3$		6.5	82
n				5.5	79
o				6.0	85
p				7.0	72

[a] All products were characterized by ^1H NMR, IR, and mass spectroscopy.

[b] Isolated and unoptimized yields

[c] 5–8% of other regioisomer was observed in ^1H NMR spectrum of crude product.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.35 (s, 6 H), 2.20 (s, 2 H), 2.35 (s, 3 H), 2.95 (br s, 1 H, NH), 6.65–7.30 (m, 4 H).

^{13}C NMR (^{1}H-decoupled, 50 MHz, $CDCl_3$): δ = 29.7, 30.4, 45.0, 67.8, 121.6, 122.0, 125.4, 126.7, 137.8, 140.6, 171.8.

EIMS: *m*/*z* (% relative intensity) = 188 (100) [M^+], 173 (52), 132 (15), 104 (15), 77 (32), 65 (20).

2-Methyl-2,4-diphenyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3b)
Yellow crystalline solid; mp 150–152 °C.

IR (KBr): = 3325, 1635, 1598 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.80 (s, 3 H), 2.95 (d, *J* = 12.8 Hz, 1 H), 3.15 (d, *J* = 12.8 Hz, 1 H) 3.45 (br s, 1 H, NH), 6.55–7.0 (m, 3 H), 7.15–7.35 (m, 7 H), 7.55–7.65 (m, 4 H).

^{13}C NMR (^{1}H-decoupled, $CDCl_3$): δ = 29.7, 42.9, 73.3, 121.2, 121.4, 125.2, 126.1, 126.8, 126.9, 127.8, 128.1, 128.5, 129.5, 137.9, 139.5, 139.9, 147.4, 167.3.

EIMS: *m*/*z* = 312 (10) [M^+], 295 (100), 235 (25), 194 (30), 103 (20), 77 (60), 40 (80).

2,4-Diethyl-2-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3c)
Yellow solid; mp 137–139 °C.

IR (KBr): 3329, 1637, 1605 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.99 (t, *J* = 6.9 Hz, 3 H), 1.25 (t, *J* = 7.0 Hz, 3 H),1.70 (q, *J* = 6.9 Hz, 2 H), 2.15 (m, 2 H), 2.35 (s, 3 H), 2.69 (q, *J* = 7.0 Hz, 2 H), 3.25 (br s, 1 H, NH), 6.78–7.35 (m, 4 H).

^{13}C NMR (^{1}H-decoupled, 50 MHz, $CDCl_3$): δ = 8.7, 10.8, 26.9, 35.5, 35.7, 42.1, 70.5, 121.8, 125.4, 126.2, 127.0, 137.9, 140.8, 175.6.

EIMS: *m*/*z* (%) = 216 (15) [M^+], 141(5), 108 (100), 80 (38), 40 (75).

2-Methyl-2,4-diisobutyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3d)
Light yellow solid; mp 118–120 °C.

IR (KBr): 3320, 1650, 1599 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95–1.05 (m, 12 H), 1.32 (s, 3 H), 1.49–1.52 (m, 2 H), 1.65–1.75 (m, 1 H), 2.05–2.25 (m, 3 H), 2.24 (d, *J* = 12.7 Hz, 2 H), 6.60–6.65 (m, 1 H), 6.85–6.95 (m, 2 H), 7.05–7.15 (m, 1 H).

^{13}C NMR (^{1}H-decoupled, 50 MHz, $CDCl_3$): δ = 22.5, 22.7, 24.2, 24.9, 25.0, 26.3, 28.1, 43.5, 51.7, 51.9, 70.8, 121.4, 121.5, 125.2, 127.2, 137.8, 140.4, 173.9.

EIMS: *m*/*z*(%) = 272 (10) [M^+], 157 (12), 141 (25), 105 (100), 80 (50), 53 (14).

2,2,4-Trimethyl-2,3-dihydro-8-methyl-1*H*-1,5-benzodiazepine (3e)
Solid; mp 127–129 °C.

IR (KBr): 3325, 1665, 1600 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30 (s, 6 H), 2.19 (s, 2 H), 2.23 (s, 3 H), 2.80 (s, 3 H), 6.65–6.75 (s, 1 H), 6.70–6.80 (1 H), 7.05–7.10 (m, 1 H).

^{13}C NMR (^{1}H-decoupled, 75 MHz, $CDCl_3$): δ = 20.9, 29.6, 30.4, 30.8, 45.8, 67.0, 122.6, 126.6, 127.0, 131.8, 136.7, 138.1, 174.3.

EIMS: *m*/*z* (%) = 202 (40) [M^+], 187 (100), 146 (70), 77(15), 41 (20).

2-Methyl-2,4-diphenyl-2,3-dihydro-8-methyl-1*H*-1,5-benzodiazepine (3f)
Yellow solid; mp 91–93 °C.

IR (KBr): = 3315,1657, 1600 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.80 (s, 3 H), 2.41 (s, 3 H), 2.98 (d, *J* = 12.7 Hz, 1 H), 3.15 (d, *J* = 12.7 Hz, 1 H), 3.50 (br s, 1 H, NH), 6.70–7.69 (m, 13 H).

^{13}C NMR (^{1}H-decoupled, 50 MHz, $CDCl_3$): δ = 20.6, 28.5, 45.8, 51.2, 113.5, 125.5, 126.4, 127.3, 128.1, 128.3, 128.6, 128.8, 129.1, 130.9, 131.2, 134.0, 136.8, 164.8.

EIMS: *m*/*z* (%) = 326 (10) [M^+], 261 (100), 246 (90), 206 (40), 145 (50), 102 (35), 76 (30).

2-Methyl-2,4-diethyl-8-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3g)
Light yellow solid; mp 116–118 °C.

IR (KBr): 3500, 3220, 1620 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.0 Hz, 3 H), 1.15–1.30 (m, 6 H), 1.50–1.70 (m, 2 H), 2.05–2.10 (d, *J* = 12.8 Hz, 1 H), 2.15–2.20 (d, *J* = 12.8 Hz, 1 H), 2.30 (s, 3 H), 2.50–2.65 (m, 2 H), 2.90 (brs, 1 H, NH), 6.55–7.00 (m, 3 H).

EIMS: *m*/*z* (%) = 230 (15) [M^+], 201 (20), 172 (40), 132 (100), 90 (50), 56 (25).

2-Methyl-2,4-diisobutyl-8-methyl-2,3-dihydro-1*H*-1,5-benzodiazepine (3h)
Pale yellow solid; mp 124–126 °C.

IR (KBr): 3550, 3253, 1670 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95–1.05 (m, 12 H), 1.30 (s, 3 H), 1.45–1.50 (m, 2 H), 1.70–1.80 (m, 1 H), 2.05–2.25 (m, 3 H), 2.28 (s, 3 H), 2.40–2.45 (m, 2 H), 3.0 (br s, 1 H, NH), 6.55–7.05 (m, 3 H).

EIMS: *m*/*z* (%) = 286 (15) [M^+], 271 (10), 229 (100), 228 (50), 187 (12), 146 (25), 41 (10).

2,2,4-Trimethyl-2,3-dihydro-7,8-dimethyl-1*H*-1,5-benzodiazepine (3i)
Yellow solid; mp 112–114 °C.

IR (KBr): 3290, 1635, 1597 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 6 H), 2.19 (s, 3 H), 2.20 (s, 3 H) 2.22 (s, 2 H), 2.34 (s, 3 H), 2.80 (br s, NH, 1 H), 6.52 (s, 1 H), 6.39 (s, 1 H).

^{13}C NMR (^{1}H-decoupled, 75 MHz, $CDCl_3$): δ = 18.9, 19.1, 29.8, 30.3, 30.4, 45.3, 67.7, 122.8, 127.8, 129.9, 133.6, 135.5, 138.4, 171.3.

EIMS: *m*/*z* (%) = 216 (20) [M^+], 201 (60), 161 (30), 145 (15), 97 (17), 71 (50), 43 (100).

2-Methyl-2,4-diphenyl-2,3-dihydro-7,8-dimethyl-1*H*-1,5-benzodiazepine (3j)
Solid; mp 115–116 °C.

IR (KBr): 3285, 1635, 1609 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.70 (s, 3 H), 2.25 (s, 6 H), 2.90 (d, *J* = 12.8 Hz, 1 H), 3.10 (d, *J* = 12.8 Hz, 1 H), 3.45 (br s, 1 H, NH), 6.60 (s, 1 H), 7.15 (s, 1 H), 7.30–7.18 (m, 6 H), 7.50–7.60 (m, 4 H).

^{13}C NMR (^{1}H-decoupled, $CDCl_3$): δ = 18.6, 19.3 29.7, 43,2, 73.0, 122.3, 125.4, 126.8, 126.9, 127.8, 128.2, 129.3, 129.4, 129.6, 134.8, 135.7, 137.6, 139.7, 147.8, 166.8.

EIMS: *m*/*z* (%) = 340 (20) [M^+], 195 (100), 103 (75), 77 (55), 65 (15).

2,2,4-Trimethyl-2,3-dihydro-8-chloro-1*H*-1,5-benzodiazepine (3k)
Pale yellow solid; mp 90–92 °C.

IR (KBr): 3283, 1649, 1597 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 6 H), 2.23 (s, 2 H), 2.26 (s, 3 H), 5.58–6.60 (s, 1 H), 6.86–6.90 (s, 1 H), 6.98–7.05 (s, 1 H).

^{13}C NMR (^1H-decoupled, 75 MHz, $CDCl_3$): δ = 29.2, 29.8, 30.0, 44.9, 67.0, 120.4, 120.8, 125.9, 127.8, 129.8, 139.1, 172.5.

EIMS: *m*/*z* (%) = 222 (10) [M^+], 207 (24), 167 (38), 142 (100), 114 (20), 80 (25), 41 (30).

2,2,4-Tri-methyl-2,3-dihydro-8-nitro-1*H*-1,5-benzodiazepine (3l)
Pale yellow solid; mp 113–114 °C.

IR (KBr): 3280, 1645, 1640 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.90 (s, 6 H), 2.95 (s, 3 H), 3.20 (s, 2 H), 4.0 (s, 1 H, NH), 7.15–7.20 (s, 1 H), 8.0–8.15 (m, 1 H), 8.75–8.80 (m, 1 H).

^{13}C NMR (^1H-decoupled, 75 MHz, $CDCl_3$): δ = 29.9, 30.0, 30.2, 45.6, 60.8, 118.3, 121.2, 126.2, 132.4, 137.9, 145.2, 170.7. EIMS: *m*/*z* (%) = 233 (30) [M^+], 218 (100), 177 (48), 172 (48), 131 (30), 90 (40), 63 (45).

2-Methyl-2,4-diphenyl-2,3-dihydro-8-nitro-1*H*-1,5-benzodiazepine (3m)
Yellow color solid; mp 136–138 °C.

IR (KBr): 3300, 1651 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.80 (s, 3 H), 3.05–3.15 (d, *J* = 12.6 Hz, 1 H), 3.35 (d, *J* = 12.6 Hz, 1 H), 4.40 (br s, 1 H, NH), 6.80–7.95 (m, 13 H).

EIMS: *m*/*z* (%) = 357 (20) [M^+], 345 (10), 282 (20), 241 (100), 194 (10), 130 (25), 119 (30), 78 (10), 57 (50).

10-Spirocyclopentan-1,2,3,9,10,10a-hexahydrobenzo [*b*]-cyclopenta[*e*][1,4] diazepine (4n)
Yellow solid; mp 137–138 °C.

IR (KBr): 3338, 1659, 1600 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.30–1.90 (m, 12 H), 2.30–2.60 (m, 3 H), 4.50 (br s, NH, 1 H), 6.70–7.39 (m, 4 H).

^{13}C NMR (^1H-decoupled, 50 MHz, $CDCl_3$): δ = 23.4, 24.1, 24.3, 28.7, 33.4, 38.5, 39.2, 54.4, 67.3, 118.6, 119.3, 126.9, 132.1, 139.2, 143.4, 178.0.

EIMS: *m*/*z* (%) = 240 (30) [M^+].

10-Spirocyclohexan-2,3,4,10,11,11a-hexahydro-1*H*-dibenzo[*b,e*][1,4]diazepine (4o)
Pale yellow solid; mp 136–137 °C.

IR (KBr): 3290, 1640, 1600 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.23–1.85 (m, 16 H), 2.30–2.70 (m, 3 H), 4.45 (br s, 1 H, NH), 6.65–7.35 (m, 4 H).

^{13}C NMR (^1H-decoupled, 50 MHz, $CDCl_3$): δ = 21.6, 21.7, 23.2, 24.5, 25.3, 33.2, 34.4, 39.3, 40.5, 52.4, 63.1, 121.3, 121.5, 126.3, 129.6, 138.1, 142.6, 178.9.

EIMS: *m*/*z* (%) = 268 (25) [M^+].

10-Spirocycloheptan-6,7,8,9,10,10a,11,12-octahydrobenzo[*b*]cyclohepta[*e*][1,4]diazepine (4p)
Pale yellow solid; mp 135–136 °C.

IR (KBr): 3320, 3275, 1630, 1600 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.90–1.95 (m, 20 H), 2.25–2.95 (m, 3 H), 3.60 (br s, NH, 1 H), 6.60–7.38 (m, 4 H).

^{13}C NMR (^1H-decoupled, 50 MHz, $CDCl_3$): δ = 22.5, 23.2, 26.5, 28.4, 28.9, 29.5, 29.7, 30.1, 38.2, 38.5, 40.9, 54.3, 72.5, 121.3, 121.6, 125.5, 127.6, 137.5, 139.8, 179.1.

EIMS: *m*/*z* (%) = 296 (15) [M^+].

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