Hui-Yan Wang and Da-Qing Shi*

Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, People's Republic of China
*E-mail: dqshi@suda.edu.cn
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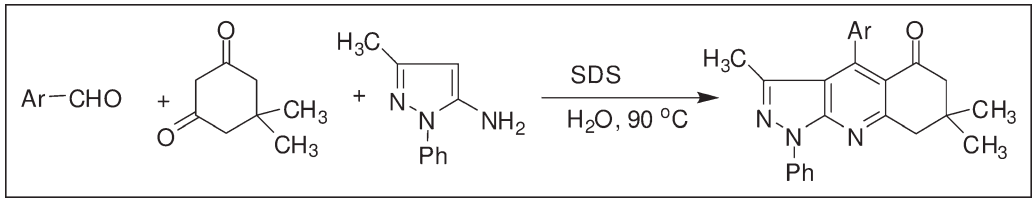

A series of 4-aryl-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1*H*-pyrazolo[3,4-*b*]quinolin- 5(6*H*)-ones were synthesized by the three-component reaction of aromatic aldehydes, 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, and 5,5-dimethyl-1,3-cyclohexandione in the presence of sodium 1-dodecanesulfonate in aqueous medium. Compared to the previous methods, this new protocol has the advantages of convenient operation, higher yields, lower cost, and environmentally benign procedure.

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INTRODUCTION

The need to reduce the amount of toxic waste and by-products arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods [1]. One of the most promising approaches uses water as the reaction medium [2]. Rideout and Breslow, who showed that hydrophobic effects could strongly enhance the rate of several organic reactions, rediscovered the use of water as a solvent in organic reactions in 1980s [3]. In recent years, there has been increasing recognition that water is an attractive medium for many organic reactions [4]. The aqueous medium with respect to organic solvent is less expensive, less dangerous, and environment friendly. Generally, the low solubility of most reagents in water is not an obstacle to the reactivity, which on the contrary, is reduced with the use of cosolvents.

Multicomponent reactions (MCRs), in which multiple reactions are combined into one synthetic operation, have been used extensively to form carbon-carbon bonds in the synthetic chemistry [5]. Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding the complicated purification operations and allowing savings of both solvents and reagents. In the past decade, there have been tremendous developments in three- and four-component reactions and grant efforts continue to be made to develop new MCRs [6].

Pyrazole derivatives exhibit pharmacological activities such as hypotensive, antibacterical, anti-inflammatory, and antitumor properties. In particular, fused pyrazole are known for various biological activities, *e.g.*, pyrazolo[3,4-*b*]quinolines as potential antiviral [7], antimalarial [8], and lowering of serum cholesterol. A number of methods are available for the synthesis of pyrazolo [3,4-*b*]quinolines [9]; the most efficient and commonly used method involves the reaction of aromatic aldehyde, 1,3-dicarbonyl compound, and aminopyrazole in organic solvent such as EtOH [10]. Each of the above methods has its own merits; however, these methods are also plagued by limitation of poor yields, difficult work-up, and effluent pollution. As part of our current studies on the developments of new routes to heterocyclic system in aqueous media [11], we herein described a clean synthesis of pyrazolo[3,4-*b*]quinoline-5(6*H*)-one derivatives by the three-component reaction of aromatic aldehyde, 5,5-dimethyl-1,3-cyclohexanedione, and 3-methyl-1-phenyl-1*H*- pyrazol-5-amine using water as reaction medium (Scheme 1).

RESULTS AND DISCUSSION

Choosing an appropriate solvent is of crucial importance for the successful organic synthesis. To search for the optimum reaction solvent, the reaction of 4-hydroxybenzaldehyde (**1a**), 5,5-dimethyl-1,3-cyclohexanedione (**2**), and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**3**) was examined using H_2O, acetone, 95% ethanol, DMF and

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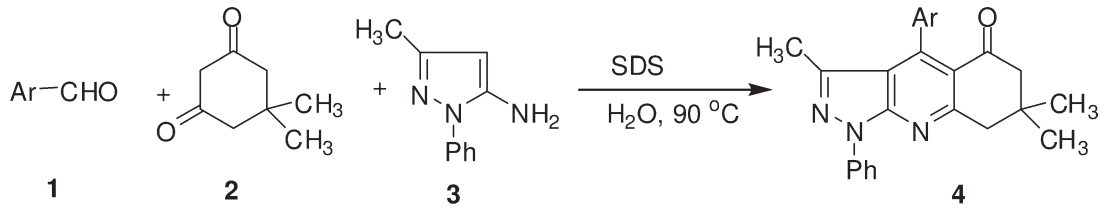
Scheme 1.



1 2 3 4

chloroform as solvent, respectively. The results were summarized in Table 1.

From Table 1, it can be seen that this reaction using water as solvent exhibited the most excellent yield. Therefore, water was chosen as the solvent for this reaction. To examine the efficiency and the applicability of this three-component reaction, a series of different aromatic aldehydes were tested in aqueous media. As shown in Table 2, this protocol could be applied to the aromatic aldehydes with either electron-withdrawing groups (such as halide groups) or electron-donating groups (such as alkyl and alkoxyl groups). The products were different from those literature reported [10].

Apart from the mild conditions of the process and its excellent results, the simplicity of product isolation and the possibility to recycle the reaction solution offer a significant advantage. Because SDS is soluble in water and the desired product is less soluble in water, the products can be directly separated by cooling to room temperature and filtering after the reaction is completed. The remaining reaction solution can be recycled. Studies using **1a**, **2,** and **3** as model substrates showed that the recovered reaction solution could be successively recycled in subsequent reaction without any decrease of yield (Table 3).

The structures of the products were established on the spectroscopic data. The structure of compound **4k** was further confirmed by X-ray diffraction analysis. The molecular structure of the product **4k** is shown in Figure 1. The crystallographic data of compound **4k** is summarized in Table 4.

Although the detailed mechanism of this reaction has not been clarified yet, the formation of **4** can be explained by the possible mechanism presented in Scheme 2. The reaction occurs *via* an initial formation of the α,β-unsaturated ketone, from the condensation of aldehyde and 5,5-dimethyl-1,3-cyclohexanedione as shown in Scheme 2, which suffers nucleophilic attack to give the Michael adduct [A]. The intermediate [A] then isomerizates, cyclizes, dehydrates, and subsequently losses a hydrogen molecule to afford the fully aromatized compound. This type of hydrogen loss is well documented [12].

In summary, we developed an efficient three-component reaction of aromatic aldehydes, 5,5-dimethyl-1,3-cyclohexanedione, and 3-methyl-1-phenyl-1H-pyrazol-5-amine for the synthesis of pyrazolo[3,4-*b*]quinolne-5-one derivatives using water as reaction medium. Compared to the previous methods, this new protocol has the advantages of convenient operation, higher yields, low cost, and environmentally benign procedure.

EXPERIMENTAL

Melting points are uncorrected. IR Spectra were recorded on a FT-IR Temsor 27 spectrometer in KBr with absorptions in cm^{-1}. ^{1}H-NMR spectra were determined on a Bruker DPX-400 MHz spectrometer using DMSO-d_6 solutions. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. High resolution mass spectra were obtained using TOF-MS instrument.

General procedure for the synthesis of 4-aryl-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1*H*-pyrazolo [3,4-*b*]quinolin-5(6*H*)-ones 4. A mixture of aromatic aldehyde **1** (2 mmol), 5,5-dimethyl-1,3-cyclohexanedione **2** (2 mmol), 3-methyle-1-phenyl-1H-pyrazol-5-amine **3** (2 mmol), and SDS (0.2 g) in

Table 1

Solvent optimization for the synthesis of **4a**.

Entry	Solvent	Reaction temperature (°C)	Time (h)	Isolated yield (%)
1	H_2O/SDS	90	11	98
2	CH_3COCH_3	Reflux	11	0
3	EtOH	Reflux	11	35
4	DMF	90	11	18
5	$CHCl_3$	Reflux	11	12

Table 2

The synthesis of **4** in aqueous medium.

Entry	Product	Ar	Time (h)	Isolated yield (%)
1	**4a**	4-HOC_6H_4	10	96
2	**4b**	2-ClC_6H_4	16	86
3	**4c**	4-FC_6H_4	10	93
4	**4d**	3-ClC_6H_4	12	95
5	**4e**	4-ClC_6H_4	9	95
6	**4f**	4-$CH_3C_6H_4$	15	97
7	**4g**	4-BrC_6H_4	12	98
8	**4h**	4-$(CH_3)_2NC_6H_4$	17	98
9	**4i**	3,4-$Cl_2C_6H_3$	6	84
10	**4j**	3,4-$OCH_2OC_6H_3$	11	98
11	**4k**	4-$CH_3OC_6H_4$	12	97

Table 3

Studies on the reuse of reaction solution in the preparation of **4a**.

Round	1	2	3	4	5
Yield (%)	96	95	94	92	92

H_2O (10 mL) was stirred for 6–17 h at 90°C, then cooled to room temperature. The crystalline powder formed was collected by filtration, washed with water. The crude products were purified by recrystallization from DMF to give **4**.

4-(4-Hydroxyphenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4a). M.p.: 281–283°C (ref. 13; M.p.: 277–279°C); IR (potassium bromide): 3304, 3058, 1666, 1613, 1593, 1512, 1456, 1437, 1385, 1264, 1172, 1026, 849, 758 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.07 (6H, s, 2 × CH_3), 1.88 (3H, s, CH_3), 2.51 (2H, s, CH_2), 3.19 (2H, s, CH_2), 6.84 (2H, d, J = 8.4 Hz, ArH), 7.07 (2H, d, J = 8.4 Hz, ArH), 7.35 (1H, t, J = 8.0 Hz, ArH), 7.57 (2H, t, J = 8.0 Hz, ArH), 8.24 (2H, d, J = 8.0 Hz, ArH), 9.60 (1H, s, OH).

4-(2-Chlorophenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4b). M.p.: 156–158°C; IR (potassium bromide): 3056, 1682, 1593, 1569, 1498, 1479, 1384, 1268, 1125, 853, 753 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.06 (3H, s, CH_3), 1.11 (3H, s, CH_3), 1.81 (3H, s, CH_3), 2.58 (2H, s, CH_2), 3.29 (2H, s, CH_2), 7.34–7.40 (2H, m, ArH), 7.44–7.53 (2H, m, ArH), 7.57–7.61 (3H, m, ArH), 8.25 (2H, d, J = 7.6 Hz, ArH); HRMS [Found: m/z: 415.1457 (M^+); Calcd for $C_{25}H_{22}^{35}ClN_3O$: M 415.1451].

4-(4-Fluorophenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4c). M.p.: 170–172°C (ref. 13; M.p.: 172–174°C); IR (potassium bromide): 3062, 1678, 1596, 1561, 1509, 1470, 1455, 1382, 1260, 1158, 1093, 848, 753 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.08 (6H, s, 2 × CH_3), 1.84 (3H, s, CH_3), 2.51 (2H, s, CH_2), 3.22 (2H, s, CH_2), 7.28–7.39 (5H, m, ArH), 7.59 (2H, t, J = 8.0 Hz, ArH), 8.24 (2H, d, J = 8.0 Hz, ArH).

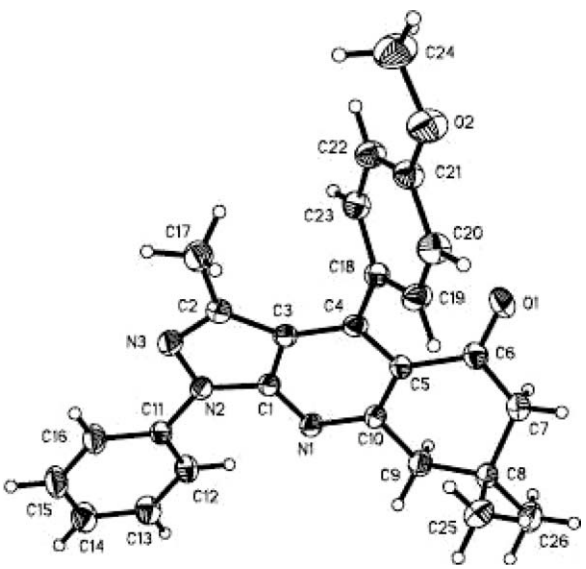


Figure 1. The X-ray crystal structure of compound **4k**.

Table 4

Crystallographic data of compound **4k**.

Empirical formula	$C_{26}H_{25}N_3O_2$
Formula weight	411.49
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	Pn
Unit cell dimensions	a = 14.101(9) Å α = 90°
	b = 7.584(5) Å β = 122.73(3)°
	c = 23.376(11) Å γ = 90°
Volume	2103(2) $Å^3$
Z	4
Density (calculated)	1.300 Mg/m^3
Absorption coefficient	0.083 mm^{-1}
F(000)	872
Crystal size	0.29 × 0.18 × 0.11 mm^3
Theta range for data collection	1.84° to 25.01°
Limiting indices	$-16 \le h \le 16$, $-8 \le k \le 9$, $-19 \le l \le 27$
Reflections collected	10637
Independent reflections	3687 [R(int) = 0.0712]
Data/restraints/paramenters	3687/0/281
Goodness-of-fit on F^2	1.004
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0524, wR_2 =0.1056
R indices (all data)	R_1 = 0.1316, wR_2 = 0.1365
Largest diff. peak and hole	0.192 and −0.210 e·$Å^{-3}$

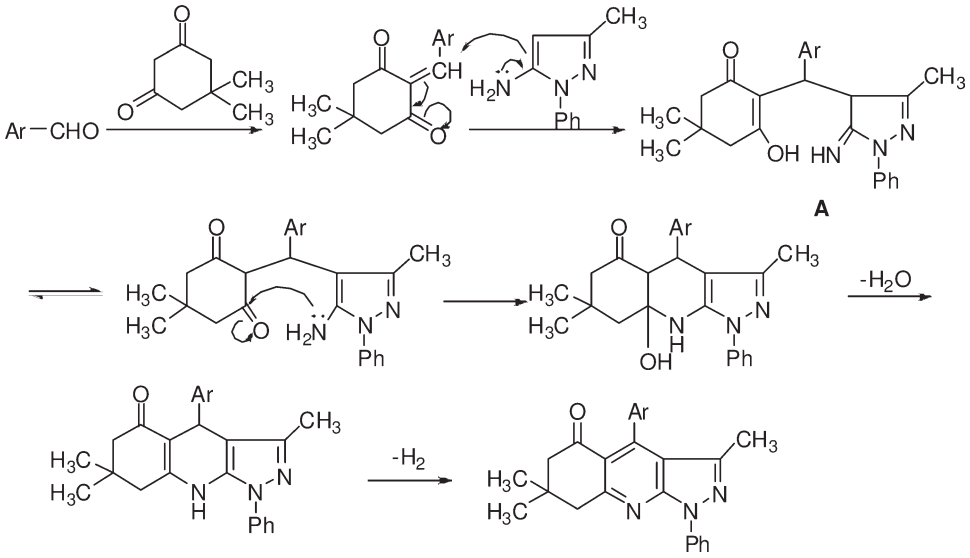
4-(3-Chlorophenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4d). M.p.: 163–165°C; IR (potassium bromide): 3063, 1685, 1599, 1509, 1483, 1382, 1265, 1128, 985, 758, 736 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.09 (6H, s, 2 × CH_3), 1.83 (3H, s, CH_3), 2.53 (2H, s, CH_2), 3.22 (2H, s, CH_2), 7.27 (1H, d, J = 7.2 Hz, ArH), 7.37 (1H, t, J = 7.2 Hz, ArH), 7.43 (1H, s, ArH), 7.48–7.65 (4H, m, ArH), 8.24 (2H, d, J = 8.0 Hz, ArH); HRMS [Found: m/z: 415.1445 (M^+); Calcd for $C_{25}H_{22}^{35}ClN_3O$: M 415.1451].

4-(4-Chlorophenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4e). M.p.: 181–183°C (ref. 13; M.p.: 180–183°C); IR (potassium bromide): 3060, 1680, 1595, 1489, 1455, 1386, 1264, 1126, 844, 752 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.08 (6H, s, 2 × CH_3), 1.84 (3H, s, CH_3), 2.51 (2H, s, CH_2), 3.21 (2H, s, CH_2), 7.32–7.38 (3H, m, ArH), 7.53 (2H, d, J = 8.4 Hz, ArH), 7.58 (2H, t, J = 8.0 Hz, ArH), 8.24 (2H, d, J = 8.0 Hz, ArH).

4-(4-Methylphenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4f). M.p.: 182–184°C (ref. 13; M.p.: 184–186°C); IR (potassium bromide): 3021, 1677, 1591, 1560, 1499, 1455, 1386, 1263, 1126, 803, 752 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.08 (6H, s, 2 × CH_3), 1.81 (3H, s, CH_3), 2.42 (3H, s, CH_3), 2.51 (2H, s, CH_2), 3.21 (2H, s, CH_2), 7.16 (2H, d, J = 8.0 Hz, ArH), 7.27 (2H, d, J = 8.0 Hz, ArH), 7.36 (1H, t, J = 8.0 Hz, ArH), 7.58 (2H, t, J = 8.0 Hz, ArH), 8.24 (2H, d, J = 8.0 Hz, ArH).

4-(4-Bromophenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4g). M.p.: 184–186°C (ref. 13; M.p.: 188–189°C); IR (potassium bromide): 3069, 1679, 1592, 1569, 1558, 1498, 1455, 1416, 1386, 1264, 1174, 1099, 909, 843, 752 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.06 (6H, s, 2 × CH_3), 1.88 (3H, s, CH_3), 2.51 (2H, s, CH_2), 3.21 (2H, s, CH_2),

Scheme 2. The possible mechanism for the synthesis of compound **4**.



7.27 (2H, d, J = 8.4 Hz, ArH), 7.37 (1H, t, J = 7.6 Hz, ArH), 7.58 (2H, t, J = 7.6 Hz, ArH), 7.67 (2H, t, J = 8.4 Hz, ArH), 8.24 (2H, d, J = 8.0 Hz, ArH).

4-(4-Dimethylaminophenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4h). M.p.: 195–197°C (ref. 13; M.p.: 194–196°C); IR (potassium bromide): 3066, 1687, 1612, 1567, 1506, 1473, 1419, 1385, 1283, 1260, 1201, 1130, 983, 816, 790, 766 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.07 (6H, s, 2 × CH_3), 1.92 (3H, s, CH_3), 2.51 (2H, s, CH_2), 2.99 (6H, s, $(CH_3)_2N$), 3.19 (2H, s, CH_2), 6.78 (2H, d, J = 8.4 Hz, ArH), 7.09 (2H, d, J = 8.8 Hz, ArH), 7.35 (1H, t, J = 7.6 Hz, ArH), 7.57 (2H, t, J = 8.0 Hz, ArH), 8.25 (2H, d, J = 7.6 Hz, ArH).

4-(3,4-Dichorophenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4i). M.p.: 176–178°C (ref. 13; M.p.: 179–181°C); IR (potassium bromide): 3062, 1683, 1598, 1568, 1509, 1482, 1439, 1419, 1385, 1309, 1291, 1264, 1130, 985, 812, 755 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.17 (6H, s, 2 × CH_3), 2.00 (3H, s, CH_3), 2.60 (2H, s, CH_2), 3.26 (2H, s, CH_2), 7.14 (1H, dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, ArH), 7.34 (1H, d, J = 7.2 Hz, ArH), 7.38 (1H, d, J = 2.0 Hz, ArH), 7.53–7.59 (3H, m, ArH), 8.28 (2H, d, J = 7.6 Hz, ArH).

4-(3,4-Methylenedioxyphenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4j). M.p.: 178–180°C (ref. 13; M.p.: 175–177°C); IR (potassium bromide): 3055, 1672, 1598, 1557, 1507, 1491, 1473, 1456, 1381, 1351, 1291, 1255, 1176, 1037, 934, 810, 752 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.08 (6H, s, 2 × CH_3), 1.93 (3H, s, CH_3), 2.51 (2H, s, CH_2), 3.20 (2H, s, CH_2), 6.12 (2H, s, OCH_2O), 6.72 (1H, d, J = 7.6 Hz, ArH), 6.89 (1H, s, ArH), 7.00 (1H, d, J = 7.6 Hz, ArH), 7.36 (1H, t, J = 7.6 Hz, ArH), 7.58 (2H, t, J = 7.6 Hz, ArH), 8.24 (2H, d, J = 8.0 Hz, ArH).

4-(4-Methoxyphenyl)-3,7,7-trimethyl-1-phenyl-7,8-dihydro-1H-pyrazolo[3,4-b]quinolin-5(6H)-one (4k). M.p.: 139–141°C (ref. 13; M.p.: 138–140°C); IR (potassium bromide): 3017, 2956, 2868, 2834, 1676, 1608, 1581, 1556, 1514, 1467, 1439, 1410, 0382, 1305, 1292, 1244, 1175, 906, 842, 808, 751, 687 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.07 (6H, s, 2 × CH_3), 1.85 (3H, s, CH_3), 2.51 (2H, s, CH_2), 3.20 (2H, s, CH_2), 3.84 (s, 3H, CH_3O), 7.02 (2H, d, J = 8.4 Hz, ArH), 7.20 (2H, d, J = 8.4 Hz, ArH), 7.36 (1H, t, J = 7.6 Hz, ArH), 7.58 (2H, t, J = 8.0 Hz, ArH), 8.24 (2H, d, J = 8.0 Hz, ArH).

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