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Note

One pot synthesis of some novel 2,4-diaryl-6-(5-methyl-1-*p*-tolyl-1*H*- 1,2,3-triazol-4-yl)pyridine derivatives

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New 2,4-diaryl-6-(5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazol-4- yl)-pyridine derivatives have been prepared *via* the Kröhnke reaction of 1-[2-(5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl)-2-oxoethyl]-pyridinium bromide and a series of α,β-unsaturated ketones. One pot reaction is used in synthesis procedure. All new compounds are investigated by ^{1}H NMR, MS, IR spectral data and elemental analyses.

Keywords: 1,2,3-Triazoles, pyridine, Kröhnke reaction, α,β-unsaturated ketones, synthesis, One pot reaction

Pyridine derivatives are both potential and proven source of pharmaceuticals and agrochemicals, for the treatment of alzheimer's disease[1], agonists at 5-HT1a receptors[2], mycobacterium tuberculosis H37Rv[3], calcium channel agonist-antagonist modulation activities[4], inhibitors of caspase-3 (Ref. 5), mGlu5 receptor antagonist[6], sodium channel inhibitors[7], neuronal nicotinic acetylcholine receptors[8], C-Jun NH_2 terminal kinases inhibitors[9], and so on. While 1,2,3-triazole derivatives have been reported to inhibit tumor proliferation, invasion and metastasis[10,11]. So synthesis of pyridine derivatives with 1,2,3-triazole nucleus is of great importance.

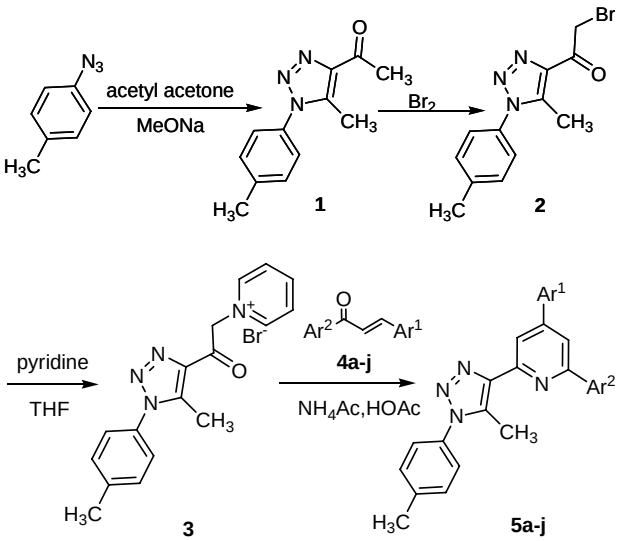
Kröhnke reaction is a major efficient way of synthesis of 2,4,6-trisubstituted pyridine derivatives[12-14]. We have reported that synthesis of 3-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-6-substituted-*s*- triazolo[3,4-*b*]-1,3,4-thiadiazoles[11], 3,6-bis(1,2,3-tri- azolyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole derivatives[15]. As an extension to this work, the synthesis of a series of 2,4-diaryl-6-(5-methyl-1-*p*- tolyl-1*H*-1,2,3-triazol-4-yl)pyridine derivatives by Kröhnke reaction is studied. Synthetic route of the titled compounds is showed in **Scheme I**.

5a Ar^1= Ph, Ar^2= Ph; **5b** Ar^1= 4-$CH_3OC_6H_4$-, Ar^2=Ph; **5c** Ar^1= 3-ClC_6H_4-, Ar^2= ph; **5d** Ar^1= 2-furanyl, Ar^2=Ph; **5e** Ar^1= 4-$(CH_3)_2NC_6H_4$-, Ar^2= Ph; **5f** Ar^1= Ph, Ar^2= 4-$CH_3C_6H_4$-; **5g** Ar^1= 4-$CH_3OC_6H_4$-, Ar^2= 4-$CH_3C_6H_4$-; **5h** Ar^1= 3-ClC_6H_4-, Ar^2= 4-$CH_3C_6H_4$-; **5i** Ar^1= 2-furanyl, Ar^2= 4-$CH_3C_6H_4$-; **5j** Ar^1= 4-$(CH_3)_2NC_6H_4$-, Ar^2= 4-$CH_3C_6H_4$-

Results and Discussion

In this work the classic Kröhnke reaction was applied, some novel 2,4-diaryl-substituted-6-(5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl)pyridine derivatives were synthesized by one pot reaction of 2-bromo-1-(5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl) ethanone, in pyridine, and added subsequently dropwise, a solution of a 1,3-diaryl-2-propen-1-ones **4a-j** (1 mmole) in 3 mL gl. acetic acid. Because 1 eq of pyridine reacts with hydrobromide, 2 eq of pyridines is required for the one pot reaction, to give good yield. All new compounds were investigated by ^{1}H NMR, MS, IR spectral data and elemental analyses (see **Tables I** and **II**).

In the **Table II**, it can be seen that chemical shift of the two hydrogens on pyridine ring are at the range of δ7.689-7.976 and 8.431-8.507, but there are little coupling and coupling constant are at 0.9-1.8 Hz. The possible reason for the nitrogen atom on pyridine ring is a stronger electronegative atom than that of carbon have some influence upon them.



Scheme I — Synthetic route of the titled compounds.

Table I — Physical and IR spectral data of compounds **5a-j**

No	m.p. (°C)	Yield (%)	Found/(Calcd)(%) C	H	N	IR (cm^{-1}) (KBr disc)
5a	180-81	72	79.68 (80.57	5.45 5.51	14.64 13.92)	3081 (pyridine-H), 3035 (Ar-H), 2919 (CH_3-H), 1607 (C=N), 1549, 1515, 1494 (Ar), 973 (N-N=N)
5b	159-60	68	78.21 (77.75	5.65 5.59	11.55 12.95)	3037 (Ar-H), 2924 (CH_3-H), 1604 (C=N), 1545, 1514, 1457 (Ar), 974 (N-N=N)
5c	184-85	77.8	74.71 (74.22	4.63 4.84	12.25 12.82)	3043 (Ar-H), 2923 (CH_3-H), 1608 (C=N), 1546, 1515, 1473 (Ar), 975 (N-N=N)
5d	167-68	73.4	75.85 (76.51	5.02 5.14	13.77 14.28)	3140, 3111, 3066 (pyridine-H), 3039 (Ar-H), 2920 (CH_3-H), 1735 (C-O), 1610 (C=N), 1546, 1515, 1485 (Ar), 977 (N-N=N)
5e	190-91	60.8	78.01 (78.17	5.94 6.11	15.95 15.72)	3038 (Ar-H), 2916 (CH_3-H), 1597 (C=N), 1562, 1523, 1493 (Ar), 975 (N-N=N)
5f	150-51	77.6	77.85 (80.74	5.84 5.81	12.67 13.45)	3086 (pyridine-H), 3029 (Ar-H), 2916 (CH_3-H), 1605 (C=N), 1548, 1514, 1450 (Ar), 973 (N-N=N)
5g	77-78	70	78.21 (78.00	6.33 5.87	11.94 12.55)	3035 (Ar-H), 2921 (CH_3-H), 1604 (C=N), 1545, 1513 (Ar), 973 (N-N=N)
5h	137-38	75	74.33 (74.57	5.10 5.14	11.44 12.42)	3085, 3064 (pyridine-H), 3034 (Ar-H), 2920 (CH_3-H), 1606 (C=N), 1547, 1512, 1475 (Ar), 974 (N-N=N)
5i	140-41	67	77.56 (76.83	5.73 5.46	12.80 13.78)	3103, 3068 (pyridine-H), 3025 (Ar-H), 2918 (CH_3-H), 1737 (C-O), 1609 (C=N), 1547, 1514, 1487 (Ar), 980 (N-N=N)
5j	218-19	62	78.56 (78.40	6.73 6.36	14.10 15.24)	3029 (Ar-H), 2915 (CH_3-H), 1598 (C=N), 1532, 1517, 1442 (Ar), 975 (N-N=N)

In the **Table II**, it is known that the titled compounds have strong molecule ion peak and M-28. In compounds **5a, 5d, 5e** and **5i**, due to easy lose of N_2, the abundance of M-28 peak is up to 100%. In the infra-red absorption spectroscopy (**Table I**), the vibration bands of C=N of pyridine ring is in the region of 1598-1610 cm^{-1}.

Experimental Section

All melting points were uncorrected and determined on a XT4-100X microscopic melting point apparatus. IR spectra were obtained in KBr discs on a Nicolet 170SX FT-IR spectrometer. ^{1}H NMR spectroscopy was recorded on a Varian Mercury Pius 300 MHz instrument with TMS as an internal standard. MS were performed on a HP-5988A spectrometer (EI at 70 eV). Elemental analyses were carried out on a Yanaco CHN Corder MT-3 analyzer.

The starting 1,3-diaryl-2-propen-1-ones **4a-j** have been synthesized according to literature methods[16].

The preparation of 1-(5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl)ethanone 1

The mixture of 1-azido-4-methylbenzene (0.1mole) and acetyl acetone (0.1mole) in methanol (50 mL) was cooled to 0°C. Sodium methoxide (0.1mole) in methanol (50 mL) was added dropwise to the mixture under inert atmosphere and stirred at 50°C for 8 hr. Progress of the reaction was monitored by TLC (ethyl acetate/ petroleum ether, 1:4, v/v). After completion of the reaction, the mixture was cooled and some precipitate was obtained. The crude product was recrystallized from ethanol to give the pure compound **1** (9.9 g, 46% yield), m.p. 106-107°C, ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 2.76 (s, 3H, CH_3), 7.31-7.34 (d, 2H, J = 8.1Hz, Ar), 7.35-7.38 (d, 2H, J = 8.1Hz, Ar).

The preparation of 2-bromo-1-(5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl)ethanone 2

Bromine (0.01mole) was added dropwise to a solution of 1-(5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl) ethanone **1** (0.01mole) in 10 mL absolute methanol at 40°C and the mixture was stirred for 4 hr. After cooling, the mixture was poured into ice-water and stirred for 30 min. The solid was filtered to give quantitative yield. ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 4.76 (s, 2H, CH_2), 7.30-7.41 (m, 4H, Ar); MS: 293 (5.05), 295 (4.70), 264 (0.28), 250 (0.28), 236 (1.24), 222 (1.51), 200 (0.84), 186 (12.54), 172 (34.90), 158 (17.81), 144 (45.34), 132 (30.09), 91 (100); IR (KBr): 3066 (Ar-H), 2954, 2922 (C-H), 1706 (C=O), 1590 (C=N), 969 (N-N=N).

Table II — ^{1}H NMR and mass spectral data for compounds **5a-j**

Compd	^{1}H NMR ($CDCl_3$) δ, ppm	Ms (*m/z*)
5a	2.479 (s, 3H, CH_3), 2.876 (s, 3H, CH_3), 7.369-7.567 (m, 10H, Ar^1 & Ar^2=Ph), 7.822-7.851 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.7), 7.913-7.918 (d, 1H, pyridine, *J*=1.5), 8.129-8.157 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.7), 8.502-8.507 (d, 1H, pyridine, *J*=1.5)	402 (25.5), 403 (5.6), 374 (100), 359 (9.1), 307 (5.2), 297 (5.8), 283 (12.5), 256 (67.8), 230 (15.0), 202 (21.6), 187 (16.4), 179 (12.5), 165 (8.5), 151 (15.3), 127 (14.4), 144 (49.8)
5b	2.478 (s, 3H, CH_3), 2.867 (s, 3H, CH_3), 3.893 (s, 3H, CH_3), 7.040-7.068 (d, 2H, *p*-$CH_3OC_6H_4$, *J*=8.7), 7.365-7.541 (m, 7H, *p*-$CH_3OC_6H_4$ & Ar^2=Ph), 7.782-7.811 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.7), 7.873-7.879 (d, 1H, pyridine, *J*=1.8), 8.146-8.125 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.7), 8.462-8.467 (d, 1H, pyridine, *J*=1.5)	432 (2.3), 433 (0.6), 404 (3.9), 389 (0.5), 337 (3.8), 313 (1.0), 286 (2.4), 268 (5.3), 239 (6.1), 224 (12.3), 209 (4.5), 191 (5.6), 163 (9.9), 149 (15.0), 125 (15.9), 44 (100)
5c	2.481 (s, 3H, CH_3), 2.872 (s, 3H, CH_3), 7.372-7.548 (m, 9H, *p*-$CH_3C_6H_4$, Ph, 3-ClC_6H_4), 7.691-7.716 (m, 1H, 3-ClC_6H_4), 7.808 (s, 1H, 3-ClC_6H_4), 7.862-7.866 (d, 1H, pyridine, *J*=1.2), 8.128-8.152 (d, 2H, *p*-$CH_3C_6H_4$, *J*=7.2), 8.464-8.468 (d, 1H, pyridine, *J*=1.2)	436 (10.8), 437 (2.5), 438 (2.6), 439 (0.6), 408 (59.8), 393 (5.8), 330 (1.0), 317 (3.5), 290 (16.7), 264 (4.6), 228 (8.5), 213 (3.6), 185 (2.3), 161 (3.6), 178 (5.0), 113 (9.0), 44 (100)
5d	2.477 (s, 3H, CH_3), 2.854 (s, 3H, CH_3), 6.579-6.591 (t, 1H, furanyl), 7.054-7.065 (d, 1H, furanyl, *J*=3.3), 7.364-7.535 (m, 7H, *p*-$CH_3C_6H_4$, Ph), 7.599 (s, 1H, furanyl), 7.973-7.976 (d, 1H, pyridine, *J*=0.9), 8.122-8.146 (d, 2H, *p*-$CH_3C_6H_4$, *J*=7.2), 8.470-8.474 (d, 1H, pyridine, *J*=1.2)	392 (14.2), 393 (10.9), 363 (100), 323 (4.7), 297 (4.0), 273 (12.8), 246 (20.4), 228 (5.6), 218 (7.1), 203 (10.9), 165 (18.7), 140 (22.6), 115 (16.4)
5e	2.477 (s, 3H, CH_3), 2.864 (s, 3H, CH_3), 3.057 (s, 6H, $2CH_3$), 6.873 (d, 2H, 4-$(CH_3)_2NC_6H_4$), 7.364-7.531 (m, 7H, *p*-$CH_3C_6H_4$, Ph), 7.774-7.803 (d, 2H, 4-$(CH_3)_2NC_6H_4$, *J*=8.7), 7.884-7.889 (d, 1H, pyridine, *J*=1.5), 8.121-8.150 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.7), 8.463-8.468 (d, 1H, pyridine, *J*=1.5)	445 (7.4), 446 (3.7), 422 (100), 417 (22.1), 403 (4.1), 388 (21.5), 331 (6.5), 243 (6.9), 228 (11.1), 203 (6.6), 178 (12.0), 164 (11.7), 149 (15.4)
5f	2.433 (s, 3H, CH_3), 2.478 (s, 3H, CH_3), 2.868 (s, 3H, CH_3), 7.306-7.331 (d, 2H, Ph, *J*=7.5), 7.366-7.394 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.4), 7.413-7.442 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.7), 7.466-7.556 (m, 3H, Ph), 7.804-7.833 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.7), 7.882 (s, 1H, pyridine, *J*=1.4), 8.029-8.057 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.4), 8.472 (s, 1H, pyridine, *J*=1.4)	416 (16.0), 417 (0.9), 388 (91.4), 335 (0.9), 297 (3.9), 270 (51.3), 244 (1.3), 228 (1.7), 202 (3.0), 186 (6.0), 165 (2.2), 144 (47.0), 115 (16.4)
5g	2.433 (s, 3H, CH_3), 2.479 (s, 3H, CH_3), 2.864 (s, 3H, CH_3), 3.896 (s, 3H, CH_3), 7.030-7.067 (dd, 2H, *p*-$CH_3OC_6H_4$, *J*=8.7, 2.4), 7.304-7.331 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.1), 7.366-7.444 (m, 4H, *p*-$CH_3C_6H_4$), 7.769-7.808 (dd, 2H, *p*-$CH_3OC_6H_4$, *J*=9, 2.4), 7.849-7.855 (d, 1H, pyridine, *J*=1.8), 8.019-8.046 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.1), 8.431-8.437 (d, 1H, pyridine, *J*=1.8)	446 (6.4), 447 (1.1), 418 (17.2), 403 (38.2), 327 (2.5), 300 (4.1), 281 (3.3), 253 (1.2), 248 (3.4), 223 (1.9), 215 (4.2), 177 (3.2), 163 (2.8), 149 (10.8), 44 (100)
5h	2.437 (s, 3H, CH_3), 2.479 (s, 3H, CH_3), 2.864 (s, 3H, CH_3), 7.310-7.337 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.1), 7.368-7.491 (m, 6H, *p*-$CH_3C_6H_4$, 3-ClC_6H_4), 7.689-7.706 (m, 1H, pyridine), 7.800-7.829 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.7), 8.023-8.050 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.1), 8.433 (s, 1H, pyridine)	450 (9.4), 451 (3.8), 452 (4.2), 453 (1.8), 422 (68.4), 407 (36.3), 351 (2.0), 282 (0.3), 256 (11.3), 240 (6.3), 223 (0.7), 205 (2.3), 177 (7.8), 163 (11.2), 138 (12.5), 44 (100)
5i	2.434 (s, 3H, CH_3), 2.479 (s, 3H, CH_3), 2.853 (s, 3H, CH_3), 6.577-6.594 (dd, 1H, furanyl, *J*=3.3, 1.2), 7.060-7.071 (d, 1H, furanyl, *J*=3.3), 7.307-7.335 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.4), 7.366-7.394 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.4), 7.413-7.441 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.4), 7.601-7.605 (d, 1H, furanyl, *J*=1.2), 7.951-7.956 (d, 1H, pyridine, *J*=1.2), 8.020-8.047 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.1), 8.438-8.443 (d, 1H, pyridine, *J*=1.5)	406 (28.1), 407 (6.6), 378 (100), 363 (9.2), 287 (12.6), 260 (69.2), 228 (2.4), 216 (4.8), 203 (16.0), 189 (14.5), 165 (12.6), 144 (42.6), 115 (22.1)
5j	2.431 (s, 3H, CH_3), 2.478 (s, 3H, CH_3), 2.859 (s, 3H, CH_3), 3.058 (s, 6H, $2CH_3$), 6.880 (m, 2H, 4-$(CH_3)_2NC_6H_4$), 7.296-7.325 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.7), 7.364-7.392 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.4), 7.413-7.442 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.7), 7.769-7.798 (d, 2H, 4-$(CH_3)_2NC_6H_4$, *J*=8.7), 7.855-7.859 (d, 1H, pyridine, *J*=1.2), 8.019-8.047 (d, 2H, *p*-$CH_3C_6H_4$, *J*=8.4), 8.433-8.437 (d, 1H, pyridine, *J*=1.2)	459 (3.1), 460 (0.8), 431 (4.4), 416 (3.7), 403 (0.9), 388 (4.5), 336 (0.8), 300 (1.2), 281 (2.5), 244 (1.6), 228 (2.2), 203 (3.2), 178 (8.9), 165 (11.5), 149 (20.4), 111 (15.9), 44 (100)

General procedure for the preparation of 2,4-diaryl-substituted-6-(5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl)pyridine derivatives 5a-j

Method A: synthesis from compound 3

The mixture of 2-bromo-1-(5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl)ethanone **2** (0.002 mole) and pyridine (0.003 mole) in THF (20 mL) were heated under refulx for 2 hr. The solution was cooled to RT, and the white pyridinium salt **3** was separated by filtration. ^{1}H NMR(D_2O): δ 2.40 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 6.38 (s, 1H, CH), 7.37-7.41 (d, 2H, Ar, J = 8.7Hz), 7.43-7.47 (d, 2H, Ar, J = 8.3Hz), 8.12-8.19 (t, 2H, pyridine-H), 8.63-8.71 (t, 1H, pyridine-H), 8.79-8.82 (d, 2H, pyridine-H, J = 5.7Hz); IR (KBr): 3492, 3436 (CH-HBr), 3048 (Ar), 3019 (CH_3), 1698 (C=O), 1637 (C=N$^+$), 1558, 1514, 1492 (Ar), 978 (N-N=N).

The preparation of 2,4-diaryl-substituted-6-(5-methyl-1-*p*- tolyl-1*H*-1,2,3-triazol-4-yl)pyridine derivatives 5a-j

A solution of a 1,3-diaryl-2-propen-1-ones **4a-j** (1 mmole) in 3 mL gl. acetic acid to the solution of 1 mmole of 1-(2-(5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazol-4- yl)-2-oxoethyl)pyridinium bromide **3** in 3 mL gl. acetic acid containing ammonium acetate (1.0 g) and stirred. The whole mixture was changed to mass, heated at 120°C under reflux for 7-10 hr. The mixture was left overnight at RT and ice-cold water (20 mL) was added and the precipitate was separated. The solid was future purification by chromatographic column (silica gel, eluent ethyl acetate/petroleum ether=1:4) to give the pure title compounds **5a-j**.

Method B: one pot synthesis of 2,4-diaryl- substituted-6-(5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl)-pyridine derivatives 5a-j

The mixture of 2-bromo-1-(5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazol-4-yl)ethanone **2** (1 mmole) and pyridine (2 mmole) in THF (10 mL) were heated to reflux for 2 hr. After solvent was evaporated completely, 3 mL gl. acetic acid containing ammonium acetate (1.0 g) was added and stirred subsequently. A solution of 1,3-dialkyl/aryl-2-propen-1-ones **4a-j** (1 mmole) in 3 mL gl. acetic acid was added to the above mixture gradually. The whole mixture was changed to mass, heated at 120ºC under reflux conditions for 7-10 hr. The mixture was left overnight at RT and ice-cold water (20 mL) was added and the precipitate was separated. The solid was future purification by chromatographic column (silica gel, eluent ethyl acetate/petroleum ether=1:4) to give the pure title compounds **5a-j**. The results are given in **Table I**.

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