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SYNTHESIS OF 1,8-DIOXODECAHYDROACRIDINES USING ZN(L-PROLINE)$_2$ AS AN ORGANOMETALLIC CATALYST UNDER SOLVENT-FREE CONDITIONS

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Abstract: Anefficient, greener approach was adopted for the synthesis of 1,8-dioxodecahydroacridines using Zn(L-proline)$_2$ as aLewis acid, recyclable organometallic catalyst in solvent-free conditionsemploying aromatic aldehydes, dimedone and ammonium acetate. Short reaction times, good to excellent yields, non-toxicity, easy separation and reusability of the catalyst and easy work-up are the main advantages of this method.

Keywords:1,8-dioxodecahydroacridines, Zn(L-proline)$_2$, recyclable catalyst, solvent-free, multicomponent reactions.

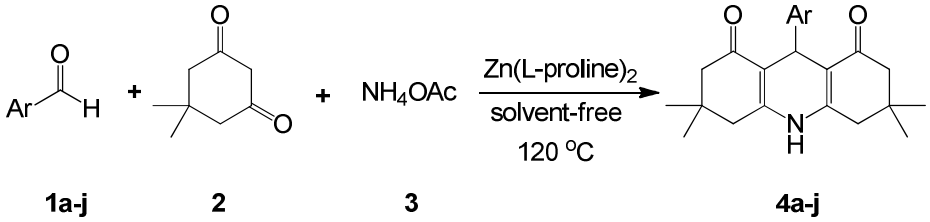
Introduction

Nowadays, one-pot multi-component reactions (MCRs) are more demand due to the benefit of their convergence, efficiency, facile performance and high yield.[I]There has been an enormous development in MCRs, particularly the Ugi,[II]Passerini,[III]Biginelli,[IV]Mannich[V]and Hantzsch[VI] reactions. Great effort is needed to find new MCRs and/or to modify the previously known reported procedures.

One such reaction is the synthesis of 1,8-dioxodecahydroacridines. Throughout the recent years, great attention has been paid to the synthesis of 1,8-dioxodecahydroacridines because of their highly complete physiological and biological activities for example antimalarial,[VII]anticancer,[VIII]cytotoxic,[IX]antimicrobial[X] and widely prescribed as calcium blockers.[XI]Also, 1,8-dioxodecahydroacridines were created to act as laser dyes[XII]and used as photo initiators.[XIII]These compounds have been commonly synthesized in a three-component one-pot Hantzschreaction of 1,3-diketone, aldehydes and ammonium acetate using several catalysts for example ionic liquids,[XIV]saccharose,[XV]ammonium chloride,[XVI]boron trifluoride,[XVII]Fe-ZrO_2,[XVIII]nanocrystalline TiO_2,[XIX]*p*-dodecylbenzenesulfonic acid (DBSA)[XX]and carbon based solid acid.[XXI]Most of these methods suffer from disadvantages such as harshcondition, low yield, very high reaction temperature, expensive reagent etc.

Recently, proline and zinc complexes have been shown to act as efficient catalysts for the reactions.[XXII-XXIV]Zn(L-proline)$_2$ is an efficient, inexpensive, non-toxic, stable and reusable catalyst which is not dissociated under reaction conditions. Also, many advantages such as

higher solubility in water, insolubilty in organic solvents, eco-friendly nature and convenient work-up make Zn(L-proline)$_2$ a green catalyst in organic synthesis.[XXV]
Due to our interest in the synthesis of heterocyclic compounds and in continuation of our previous works on the applications of reusable catalysts in organic reactions,[XXVI-XXXV] herein we report the new efficiently and green method for synthesis of 1,8-dioxodecahydroacridinesusing Zn(L-proline)$_2$as a catalyst (Scheme 1). To the best of our knowledge, this is the first report of synthesis of dioxodecahydroacridines using organometallic catalyst specially Zn(L-proline)$_2$under solvent-free conditions.



Scheme 1. Synthesis of 1,8-dioxodecahydroacridines in the presence of Zn(L-proline)$_2$

Results and Discussion

Catalytic activity for synthesis of 1,8-dioxodecahydroacridines

The one-pot synthesis of 1,8-dioxodecahydroacridineswas carried out by the three-component condensation of aromatic aldehydes,dimedone and ammonium acetatein the presence of Zn(L-proline)$_2$ as a recyclable catalyst (Scheme 1). Initially, 4-chlorobenzaldehyde (1 mmol), dimedone (2 mmol) and ammonium acetate (1 mmol) were selected as representative substrates to investigate the reaction conditions (Table 1). The catalyst plays an important role in the formation of 3,3,6,6-tetramethyl-1,8-dioxo-9-(4-chlorophenyl)-decahydroacridine (**4a)**.No product was obtained in the absence of the catalyst after 90 min (entry 1).Thus, we focused our attention on using Zn(L-proline)$_2$ catalyst, that might help to reduce the reaction time and improve the yields of the target compound. Our studies show that increasing the amount of the catalyst increased the yield of the product (entries 2-10). The optimum amount of Zn(L-proline)$_2$was 0.05 g (entry 10) under solvent-free conditions; increasing the amount of the catalyst beyond this value did not increase the yield noticeably (entries 11, 12).Furthermore, we observed that, temperature could improve yield of the reaction and the reaction was carried out in three different temperature under solvent-free conditions(entries 2-10).The best result was obtained at 120 ºC for 15 minusing 0.05 g of the catalyst (entry 10).Finally, we used the various solvents in this reaction (entries 13-17).We found that yield of the reaction with using the different solvents is lower than solvent-free conditions. Therefore,all reactions were carried out at 120 ºCin the presence of 0.05 g Zn(L-proline)$_2$under solvent-free conditions.

Table 1. Screening of the reaction conditions for the synthesis of **4a**[a]

Entry	Catalyst (gr)	Conditions	Time (min)	Temperature (°C)	Yield (%)[b]
1	None	Solvent-free	90	120	---
2	0.01	Solvent-free	30	90	54
3	0.01	Solvent-free	20	110	76
4	0.01	Solvent-free	15	120	89
5	0.03	Solvent-free	30	90	59
6	0.03	Solvent-free	20	110	82
7	0.03	Solvent-free	15	120	82

8	0.05	Solvent-free	30	90	63
9	0.05	Solvent-free	20	110	78
10	0.05	Solvent-free	15	120	91
11	0.07	Solvent-free	15	120	85
12	0.08	Solvent-free	15	120	90
13	0.05	H_2O	270	reflux	48
14	0.05	EtOH	270	reflux	75
15	0.05	MeOH	270	reflux	70
16	0.05	$CHCl_3$	270	reflux	62
17	0.05	n-Hexan	270	reflux	53

[a] Reaction conditions: dimedone (2 mmol), 4-chlorobenzaldehyde (1 mmol), and ammonium acetate (1 mmol).
[b] Isolated yields

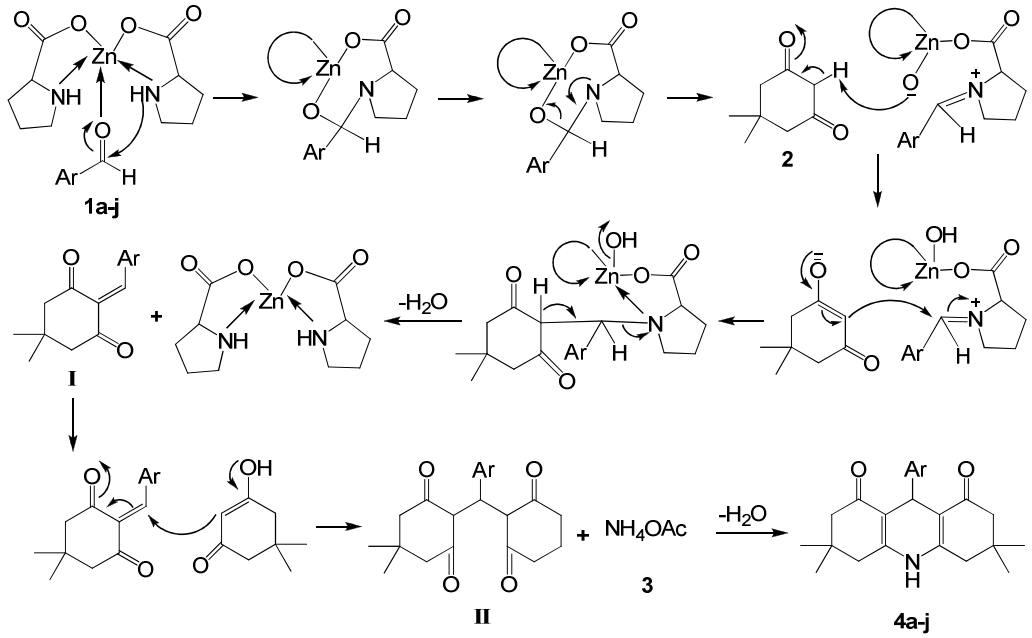
After optimization of the reaction conditions, the catalyticactivitiy of Zn(L-proline)$_2$was tested by different aromatic aldehydes, dimedone and ammonium acetate. The corresponding compounds (**4a–j**) were synthesized by the reaction of aromatic aldehydes, dimedone and ammonium acetate using 0.05 g Zn(L-proline)$_2$at 120 ºC under solvent-free conditions. As shown in Table 2, it was found that this method works well with a wide variety of substrates and the yields of the reactions in the presence of the catalyst weregood to excellent(entries 1-10).

Table 2. Preparation of 1,8-dioxodecahydroacridines using Zn(L-proline)$_2$ as catalyst[a]

Entry	Ar	Product[b]	Time (min)	Yields (%)[c]	Mp ºC	
					Found	Reported
1	4-ClC_6H_4	**4a**	15	91	>300	300-302[XXI]
2	4-BrC_6H_4	**4b**	15	91	240-241	239-242[XXI]
3	2-$MeOC_6H_4$	**4c**	15	85	298-300	294-296 [XXXVI]
4	C_6H_5	**4d**	15	92	190-192	192-195[XXI]
5	4-MeC_6H_4	**4e**	15	86	275-276	269-271[XXI]
6	2-HOC_6H_4	**4f**	15	82	312-315	>300[XXXVI]
7	3-$O_2NC_6H_4$	**4g**	15	86	290-292	288-290[XXI]
8	4-$O_2NC_6H_4$	**4h**	15	91	285-286	286-289[XXI]
9	Pyridin-3-yl	**4i**	15	89	300-302	298-300[XXXVI]
10	Thiophen-2-yl	**4j**	15	88	307-310	>300[XXXVII]

[a] Reaction conditions: dimedone (2 mmol), aromatic aldehyde (1 mmol), and ammonium acetate (1 mmol) at 120 ºC under solvent-free conditions.
[b] All the products were characterized by IR spectral data and comparison of their melting points with those of authentic samples. Also the structures of some products were confirmed by ^{1}H NMR spectral data.
[c] Isolated yields.

Based on the proposed mechanism in the literature,[XXXVIII,XXXIX]it is reasonable to assume that, at first, intermediate**I** is formed from the Knoevenagel condensation ofaromatic aldehyde **1a-j** with dimedone**2** in which the carbonylgroup of aldehyde is activated with Znin Zn(L-proline)$_2$anddimedone is deprotonated with assistant of the catalyst. Next,another dimedonethat is activated with catalyst,react with intermediate **I**to produce intermediate **II** through a Michael addition reaction. Finally,from the nucleophilic attack of ammonium acetate to carbonyl part of intermediate **II**, 1,8-dioxodecahydroacridine**4a-j**is produced (Scheme 2).



Scheme 2. Proposed mechanism

In order to examine the efficiency of the present methodfor the synthesis of 1,8-dioxodecahydroacridines,compound **4d**wascompared with some of those reported in the literature(Tables 3). As one can see, our results show a very goodcomparability with previously reported data when all termsincluding yield, reaction time, and reaction conditions aretaken into account.

Table 3. Comparison of catalytic activity of Zn(L-proline)$_2$ with other catalysts

Entry	Catalyst	Conditions	Time (min)	Yield (%)	Ref
1	Zn(L-proline)$_2$	Solvent free, 120 ºC	15	92	This study
2	CTAB	H_2O, reflux	90	80	XL
3	SPNP	H_2O, reflux	120	91	XLI
4	PVPP-BF_3	CH_3CN, reflux	180	92	XVII
5	Brønsted acid (IL)	H_2O, reflux	240	85	XXXIX
6	FSG-Hf(NPf$_2$)$_4$	C_2H_5OH, reflux	240	82	XLII
7	Amberlyst-15	CH_3CN, reflux	300	81	XLIII

Conclusion

In summary, we have developed a green and efficient method for the synthesis of 1,8-dioxodecahydroacridines usingZn(L-proline)$_2$ as an organometallic high-loaded of Lewis acid, which is stable, easy to prepare and handle and retains effective activity after several time using. In addition, this catalyst is suitable both for preparative and industrial usage because of its low cost, non-toxic and recyclability.

Experimental

General

All chemicals were available commercially and used without additional purification.Melting points were recorded on a Stuart SMP3 melting point apparatus. The IR spectra were obtained using a 4300 Shimadzu spectrophotometer as KBr disks. The ^{1}H NMR (400 and 500 MHz) spectra were recorded with Bruker DRX400and 500 spectrometers.

General experimental procedure for synthesis of 1,8-dioxodecahydroacridines 4a-j

A mixture of aromatic aldehyde **1a-j** (1 mmol),dimedone**2** (2 mmol), ammonium acetate**3**(1 mmol) and Zn(L-proline)$_2$ (0.05 g) was heated in the oil bath at 120 °C for 15min. During the procedure, the reaction was monitored by TLC. Upon completion, hot ethanol was added to reaction mixture. The catalyst was insoluble in ethanol and could be separated from the product by filtration.The product was collected after evaporated the solvent and then recrystallized from ethanol to give compounds **4a-j** in high yields.

Selected ^{1}H NMR and FT-IR Data

3,3,6,6-Tetramethyl-1,8-dioxo-9-(4-chlorophenyl)-decahydroacridine(**4a**) (500 MHz, DMSO-d$_6$)δ0.86 (s, 6H, CH$_3$), 1.0 (s, 6H, CH$_3$), 1.99 (d, 2H, *J*= 16.1 Hz, CH$_2$), 2.16 (d, 2H, *J*= 16.1 Hz, CH$_2$), 2.32 (d, 2H, *J*=17.1 Hz, CH$_2$), 2.45 (d, 2H,*J*= 17.1 Hz, CH$_2$), 4.79 (s, 1H, CH), 7.16 (d, 2H, *J*= 8.4 Hz, arom-H), 7.22 (d, 2H, *J*= 8.4 Hz,arom-H), 9.33 (s br., 1H, NH).IR (KBr Disc) cm^{-1}= 3278 (NH), 1650 (C=O).

3,3,6,6-Tetramethyl-1,8-dioxo-9-(2-hydroxyphenyl)-decahydroacridine(**4f**): (400 MHz,DMSO-d$_6$) δ 0.91 (s, 6H, CH$_3$), 1.03 (s, 6H, CH$_3$), 2.07 (d, 2H, *J*= 16.4 Hz, CH$_2$), 2.28 (d, 2H, *J*= 16.4 Hz, CH$_2$), 2.38 (d, 2H, *J*=17.2 Hz, CH$_2$), 2.51 (d, 2H, *J*= 17.2 Hz, CH$_2$), 4.86 (s, 1H, CH), 6.68-6.75 (m, 2H, arom-H), 6.88-7.00 (m, 2H, arom-H), 9.48 (s br., 1H, NH), 9.66 (s, 1H, OH). IR (KBr Disc) cm^{-1}= 3300, 3202 (NH, OH), 1641 (C=O).

3,3,6,6-Tetramethyl-1,8-dioxo-9-(pyridin-3-yl)-decahydroacridine(**4i**) (400 MHz, DMSO-d$_6$) δ 0.86 (s, 6H, CH$_3$), 1.02 (s, 6H, CH$_3$), 2.22 (d, 2H, *J*= 16.4 Hz, CH$_2$), 2.31 (d, 2H, *J*= 16.4 Hz, CH$_2$), 2.38 (d, 2H, *J*=17.2 Hz, CH$_2$), 2.51 (d, 2H, *J*= 17.2 Hz, CH$_2$), 4.80 (s, 1H, CH), 7.20-7.25 (m, 1H, arom-H), 7.48-7.55 (m, 1H, arom-H), 8.25-8.45 (m, 2H, arom-H), 9.42 (s br., 1H, NH). IR (KBr Disc) cm^{-1}= 3172 (NH), 1636 (C=O).

Acknowledgments

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References

I. Zhu, J.; Bienayme, H.; Eds.; Wiley-VCH: Weinheim, Germany, **2005**.
II. Moni, L.; Banfi, L.; Basso, A.; Carcone, L.; Rasparini, M.; Riva,R.*J. Org. Chem.* **2015**, *80*, 3411.
III. Moni, L.; Banfi,L.; Basso,A.; Martino,E.;Riva,R.*Org. Lett.***2016**, *18*, 1638.
IV. Puripat, M.;Ramozzi,R.;Hatanaka,M.;Parasuk, W.;Parasuk, V.; Morokuma,K.*J. Org. Chem.***2015**, *80*, 6959.
V. Jeffrey, J. L.;Petronijević, F. R.;MacMillan,D. W. C.*J. Am. Chem. Soc.***2015**, *137*, 8404.
VI. Rostamnia, S.;Xin,H.*Appl. Organometal. Chem*. **2014**, *28*, 359.
VII. Spalding,D. P.;Chapin,E. C.;Mosher,H. S.*J. Org. Chem.***1954**, *19*, 357.
VIII. Gamega,S. A.;Spicer,J. A.;Atwell,G. J.;Finlay,G. J.;Baguley,B. C.;Deny,W. A. *J. Med. Chem.***1999**, *42*, 2383.
IX. Antonini, I.;Polucci, P.;Kelland, L.R.;Menta, E.;Pescalli, N.;Martelli, S. *J. Med. Chem.***1999**, *42*, 2535.
X. Ngadi,L.;Galy,A. M.;Galy,J. P.;Barbe,J.;Chevalier,A. J.;Sharples,D. *Eur. J. Med. Chem.***1990**, *25*, 67.
XI. Berkan,O.;Sarac,B.;Simsek,R.;Yildirim,S.;Sariogli,Y.;Safak, C.*Eur. J. Med. Chem.***2002**, *37*, 519.

XII. Murugan,P.;Shanmugasundaram,P.;Ramakrishnan,V. T.;Venkatachalapathy,B.; Srividya,N.;Ramamurthy,P.;Gunasekaran,K.;Velmurugan,D.*J. Chem. Soc. Perkin. Trans* **1998**, *2*, 999.

XIII. Tu,S. J.;Miao,C.;Gao,Y.;Fang,F.;Zhuang,Q.;Feng,Y.;Shi, D. *Synlett.***2004**, 255.

XIV. Zolfigol, M. A.;Bahrami-Nejad, N.;Baghery, S.*J. Mol. Liquid.***2016**, *218*, 558.

XV. Maghsoodlou, M. T.;Lashkari, M.;Naghshbandi, B.;Rashidi, M.;Salahi, S.;Hazeri, N.;NejadShahrokhabadi, F.;Kazemi, M. S.;Mir, F.;Kangani, M.*Research.Chem. Int*. **2015**, *41*, 6985.

XVI. Banerjee, B.;Brahmachari, G. *J. Chem. Res.***2014**, *38*, 745.

XVII. Mokhtary, M.;Langroudi, S. A. M.*Monatsh.Chemie*. **2014**, *145*, 1489.

XVIII. Pradhana, S.;Mishra, B. G.*RSC Adv*.**2015**, *5*, 86179.

XIX. Eidi, E.;Kassaee, M. Z.;Nasresfahani,Z.*Appl. Organometal. Chem.* **2015**, *29*, 793.

XX. Jin,T. S.;Zhang,J. S.;Guo,T. T.;Wang,A. Q.;Li,T. S.*Synthesis***2004**, 2001.

XXI. Davoodnia, A.;Khojastehnezhad,A.;Tavakoli-Hoseini, N. *Bull. Korean Chem. Soc.* **2011**, *32*, 2243.

XXII. NageswaraRao, S.;Chandra Mohan, D.;Adimurthy, S. *Org. Lett.***2013**, *15*, 1496.

XXIII. Kong, Y.;Tan,R.;Zhaoa, L.;Yin, D. *Green Chem.***2013**,*15*, 2422.

XXIV. Kumar Bose, S.;Fucke, K.;Liu, L.;Steel, P. G.;Marder, T. B.*Angew. Chem. Int. Ed.* **2014**, *53*, 1799.

XXV. a) Kidwai, M.;Jain, A. *Appl. Organometal. Chem.***2012**, *26*, 528; b) Kidwai, M.;Jain, A.;Poddar, R. *J. Organometal.Chem.***2011**, *696*, 1939; c) Siddiqui, Z. N.;Musthafa, T. N. M.*Tetrahedron Lett*.**2011**, *52*, 4008; d) Heravi, M. M.;Ghods, A.;Bakhtiari, K.;Derikvand, F. *Synth.Commun*.**2010**, *40*, 1927; e) Winck, C. R.;Darbem,M. P.;Gomes, R. S.;Rinaldi, A. W.;Domingues, N. L. C.*Tetrahedron Lett.***2014**, *55*, 4123.

XXVI. Eshghi, H.;Khojastehnezhad, A.;Seyedi, S. M.;Moeinpour, F.;Bakavoli, M.; Abbasi, M. *RSC Adv*. **2014**,*4*, 39782

XXVII. Ghiaci, M.;Zarghani,M.; Moeinpour, F.;Khojastehnezhad, A. *Appl.Organometal. Chem.***2014**, *28*, 589.

XXVIII. Khojastehnezhad, A.;Rahimizadeh, M.;Eshghi, H.;Moeinpour, F.;Bakavoli, M. *Chin. J. Cat*.**2014**, *35*, 376.

XXIX. Ghiaci, M.;Zarghani, M.;Khojastehnezhad, A.;Moeinpour, F. *RSC Adv*.**2014**,*4*, 15496.

XXX. Maleki, B.;Chalaki, S. B.;Ashrafi, S. S.;RezaeeSeresht, E.;Moeinpour, F.; Khojastehnezhad, A.;Tayebee, R. *Appl.Organometal.Chem*.**2015**, *29*, 290.

XXXI. Rohaniyan, M.;Davoodnia, A.;Nakhaei, A.*Appl.Organometal. Chem.***2016**, *30*, 626.

XXXII. Khojastehnezhad, A.;Rahimizadeh, M.;Moeinpour, F.;Eshghi, H.;Bakavoli, M. *C. R. Chimie*.**2014**, *17*, 459.

XXXIII. Khojastehnezhad, A.; Moeinpour, F.;Shams, A. R. *Synth. React.Inorg. Met. Org. Chem*. **2012**, *42*, 273.

XXXIV. Khojastehnezhad, A.;Davoodnia, A.;Bakavoli, M.;Tavakoli-Hoseini, N.;Zeinali-Dastmalbaf, M. *Chin. J. Chem.***2011**, *29*, 297.

XXXV. Khojastehnezhad, A.; Moeinpour,F.;Davoodnia, A. *Chin. Chem. Lett.***2011**, *22*, 807.

XXXVI. Patil, D.;Mulik, A.;Kant, R.;Chandam, D.;Patil, P.;Gupta, V.;Jagadale, S.; Deshmukh, M. *Catal. Lett.***2014**, *144*, 949.

XXXVII. Hazeri, N.;Masoumnia, A.;Mghsoodlou, M. T.;Kangani, M.;Kiaee, S.;Salahi, S.; Kianpour, S.;Abonajmi, J.*Res. Chem. Intermed.***2015**, *41*, 4123.

XXXVIII. Alinezhad, H.;Tajbakhsh, M.;Ghobad, N.*Res. Chem. Int*. **2015**, *41*, 9979.

XXXIX. Maleki, B.; Babaee,S.;Tayebee, R.*Appl. Organometal. Chem*. **2015**, *29*, 408.
XL. Xia,J. J.; Zhang, K. H. *Molecules*. **2012**,*17*, 5339.
XLI. Javid, A.; Khojastehnezhad, A.; Heravi, M. M.; Bamoharram, F. F. *Synth. React. Inorg.Met-Org. Nano-Met.Chem.***2012**, *42*,14.
XLII. Hong, M.;Xiao,G. *J. Fluor. Chem*. **2012**,*144*, 7.
XLIII. Das, B.;Thirupathi, P.;Mahender, I.;Reddy, V. S.;Rao,Y. K.*J. Mol. Catal. A Chem.* **2006**, *247*, 233.

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