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ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 7640–7646

Remarkable synergism in methylimidazole-promoted decarboxylation of substituted cinnamic acid derivatives in basic water medium under microwave irradiation: a clean synthesis of hydroxylated (*E*)-stilbenes☆

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Received 11 December 2006; revised 28 April 2007; accepted 10 May 2007
Available online 17 May 2007

Abstract—A metal-free protocol for decarboxylation of substituted α-phenylcinnamic acid derivatives in aqueous media is developed, wherein a remarkable synergism between methylimidazole and aq $NaHCO_3$ in polyethylene glycol under microwave furnished the corresponding *para*/*ortho* hydroxylated (*E*)-stilbenes in a mild and efficient manner. The critical role of water in facilitating the decarboxylation imparts an interesting facet to the synthetic utility of water mediated organic transformations. The developed protocol provides a clean alternative to the hitherto indispensable multistep approaches involving toxic quinoline and a copper salt combination as the common decarboxylating agent.

1. Introduction

Hydroxylated (*E*)-stilbenes are natural polyphenols widely present in fruits like grapes, raspberries, peanuts and several medicinal plants. These compounds have been of considerable interest in recent times owing to their biological activities,[1] putative potential as nutraceuticals,[2] and their application in molecular photonics and optoelectronics.[3] For instance, resveratrol (3,4′,5-trihydroxy-(*E*)-stilbene), a major component of red wine, has been implicated as a potent cardio protective agent thus lending credence to the conjecture that red wine consumption retards cardiovascular mortality.[4] In addition, several epidemiological and immunological studies have identified resveratrol as a potent therapeutical agent for Alzheimer's disease.[5] Similarly, pterostilbene (3,5-dimethoxy-4′-hydroxy-(*E*)-stilbene) has been recognized to possess remarkable antitumour and antidiabetic activities.[6] Subsequent intensive pursuit of many other stilbenes has also revealed their wide spectrum of applications.[7]

Amongst the prevalent synthetic methodologies[8] for these bioactive stilbenes, decarboxylation of the corresponding α-phenylcinnamic acids obtained via the Perkin condensation between benzaldehydes and phenylacetic acids occupies a prominent position.[9] Since the pioneering investigations of Shepard et al., the use of quinoline/copper salts[10] with strong heating has been the method of choice for carrying out these decarboxylations[11] with periodic improvements in the form of alternative organic bases[12] and energy sources like microwave.[13] However, in addition to its toxicity, the quinoline/copper salt mediated decarboxylation protocol often provides poor yields of the product,[14] thus rendering the above protocols to be undesirable in view of concerns regarding overall synthetic efficiency and environmental impact. In our pursuit of developing a mild synthetic methodology for stilbenes, we were thus confronted with the task of devising a benign and efficient decarboxylation protocol.

Water, besides being nature's preferred solvent, is useful due to its versatile solvent properties,[15] safety and abundance. In addition to its ecofriendly and economical nature, there has also been a growing realization of the ability of water to facilitate organic transformations.[16] Though there have been some seminal attempts[17] to undertake decarboxylation of cinnamic acids with mineral acids or bases, but these investigations were mainly mechanistic in nature and the corresponding method was found to be comparatively ineffective for decarboxylation of α-phenylcinnamic acids into stilbenes. In view of this, we sought to ask the specific question, can a suitable decarboxylation protocol for

☆ IHBT Communication No. 0644.
Keywords: α-Phenylcinnamic acids; (*E*)-Stilbenes; Decarboxylation; Methylimidazole; Water chemistry.
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0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.05.046

α-phenylcinnamic acids be developed in basic aqueous conditions? Herein, we report the realization of this expectation with a remarkable synergism in methylimidazole-promoted decarboxylation of substituted cinnamic acids in basic aqueous medium under microwave irradiation.

2. Results and discussion

As part of our ongoing interest in microwave induced synthesis of important bioactive compounds[18] including the one pot two-step synthesis of hydroxystyrenes[19] under microwave, we were interested in devising an environmentally friendly and efficient synthetic methodology for bioactive stilbenes. To this end, we employed the Perkin condensation between vanillin (4-hydroxy-3-methoxybenzaldehyde) and phenylacetic acid in the presence of triethylamine and acetic anhydride to obtain the corresponding acetoxylated α-phenylcinnamic acid.[9] We thought to perform the subsequent decarboxylation of acetoxylated α-phenylcinnamic acid under basic aqueous conditions due to several inherent advantages. Water is rapidly heated by microwave irradiation to high reaction temperatures, which enables it to behave as a pseudo-organic solvent.[15] In addition, water has been known to significantly enhance the equilibrium constant for the formation of charged intermediates through intermolecular charge-dipole as well as hydrogen bonding interactions.[20] In this light, we hypothesized that water might also help stabilize the transition state/intermediate(s) in the base induced decarboxylation of α-phenylcinnamic acids.

In order to test this hypothesis, a mixture of α-phenyl-4-acetoxy-3-methoxycinnamic acid (**1a**) and 10% aq $NaHCO_3$ solution was irradiated under microwave (150 W, 110 °C) for 20 min. It was indeed a delight to observe the corresponding (*E*)-stilbene **1b** albeit in 18% yield along with the deacetylated α-phenyl-4-hydroxy-3-methoxycinnamic acid. This partial success inspired us to further refine our protocol. We realized that the low yield of stilbene might in part be attributed to the inability of low boiling aqueous solution to attain temperatures appropriate for decarboxylation. Thereafter, a number of high boiling solvents (DMF, DMSO, EG, PEG) were screened for the above reaction under microwave (200 W, 180 °C; Table 1) and 10% aq $NaHCO_3$ in PEG was found to augment the yield of **1b** by up to 39%. Our attempts to further optimize the reaction conditions proved futile in improving the performance of the reaction. For instance, the replacement of $NaHCO_3$ with NaOH[17] or KOH did provide **1b** in comparative yield but it led to the formation of some side products due to the enhanced basicity.[21] In view of the ineptness of a single base to bring about the desired transformation, we subsequently focused our attention towards the synergistic application of two bases. A number of literature precedents have reported the efficacy of such a combination.[22] Consequently, various base combinations were explored towards the decarboxylation of cinnamic acid into stilbenes. To our fascination, an increased yield of **1b** was obtained in almost all instances (Table 2). For instance, the combination of $NaHCO_3$ with catalytic amount of organic bases such as triethylamine, pyridine or piperidine had almost a similar effect as the yield of **1b** was increased by up to 45–52% in these cases. Nonetheless, it was the aq $NaHCO_3$-imidazole (cat.) combination

Table 1. Effect of different solvents and bases on the yield of **1b** under microwave irradiation[a]

Sr. no.	Solvent	Aq base	Yield (%)
1	—	$NaHCO_3$	18
2	*N*,*N*-Dimethylformamide	$NaHCO_3$	24
3	Dimethyl sulfoxide	$NaHCO_3$	22
4	Ethylene glycol	$NaHCO_3$	34
5	Polyethylene glycol	$NaHCO_3$	39
6	Polyethylene glycol	NaOH	36
7	Polyethylene glycol	KOH	35
8	Polyethylene glycol	Na_2CO_3	38
9	Polyethylene glycol	K_2CO_3	38

[a] CEM monomode microwave; for 1 (150 W, 110 °C); for others (200 W, 180 °C); conditions **1a** (0.0037 mol), base (10% aq soln 6–7 mL), solvent (10–12 mL) for 20 min.

(Table 2, entry 4), which delivered **1b** in a highest 65% yield. In our desire to further augment the yield of **1b**, we explored the dependence of yield on structural changes in the imidazole moiety. Interestingly, while methylimidazole (Table 2, entry 5) provided **1b** in an enhanced yield of 87%, histidine (Table 2, entry 6) and 1-butyl-3-methylimidazolium chloride (Table 2, entry 7) gave **1b** in only 38% and 42% yield, respectively. To reinforce our premise of synergistic action, cinnamic acid **1a** was treated with aq methylimidazole in PEG, i.e., without $NaHCO_3$, but the stilbene could be obtained in only 28% yield even after prolonged reaction times of 60 min. It may be mentioned that the above reaction was also conducted by treating **1a** and aq methylimidazole in PEG by replacing $NaHCO_3$ with an ionic salt like NaCl, however, the reaction provided **1b** in only 32% yield. The foregoing observation ruled out the role of $NaHCO_3$ as a simple ionic conduit and thus indicated a synergistic interaction between methylimidazole and aq $NaHCO_3$.

The observed synergism might result from the tendency of methylimidazole (pK_a=7) to participate in proton exchange with water, which effectively reduces the number of neutral methylimidazole molecules capable of acting as a base[23] (Fig. 1). The presence of $NaHCO_3$ in the reaction mixture might then lead to a suppression of this proton exchange, thus increasing the effective molarity of free methylimidazole

Table 2. Effect of different organic bases with aq $NaHCO_3$ in PEG on the yield of **1b** under microwave irradiation[a]

Sr. no.	Base	Yield (%)
1	Triethylamine	45
2	Pyridine	48
3	Piperidine	52
4	Imidazole	65
5	Methylimidazole	87
6	Histidine	38
7	1-Butyl-3-methylimidazolium chloride	42
8	Quinoline	54

[a] CEM monomode microwave (200 W, 180 °C); conditions **1a** (0.0037 mol), $NaHCO_3$ (10% aq soln 6–7 mL), organic base (0.0018 mol), solvent (10–12 mL) for 20 min.

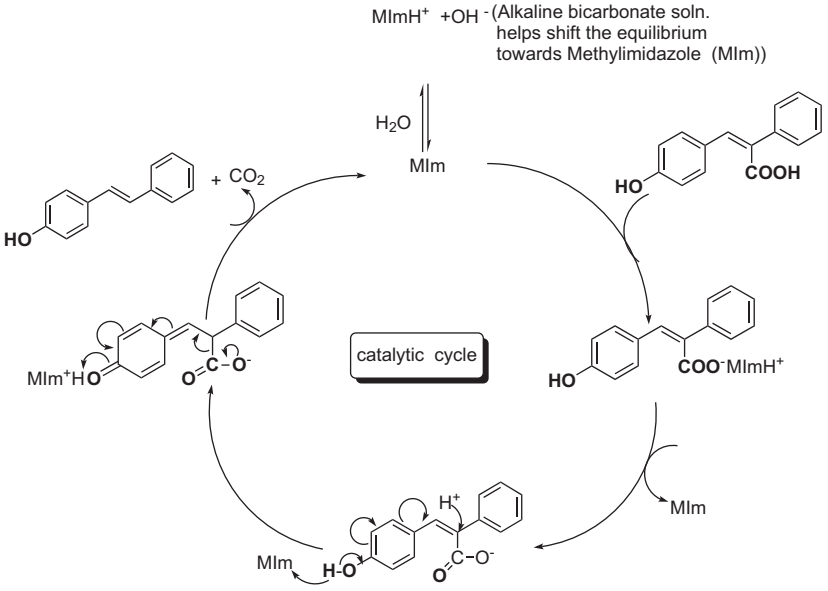
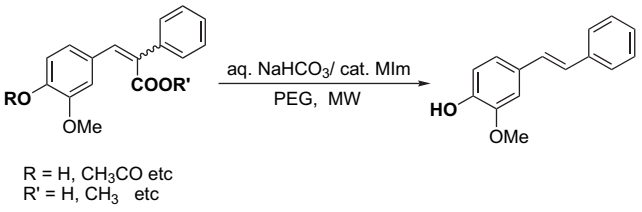


Figure 1.

molecules, which subsequently get implicated in the decarboxylative pathway.

In order to discern the significance of aqueous medium in bringing about the transformation of **1a** to **1b**, the above reaction was conducted with $NaHCO_3$ and methylimidazole in PEG under anhydrous conditions. Interestingly, the product **1b** was obtained in only 64% yield, thus unequivocally demonstrating the critical role of water in bringing about the decarboxylation of **1a**.

The substrate scope of the developed method (Scheme 1) was gauged by extending the reaction to other optionally substituted α-phenylcinnamic acids (Table 3). It is apparent from Table 3 that 2- or 4-hydroxy substitution at the aryl ring of cinnamic acid moiety is necessary for the decarboxylation of α-phenylcinnamic acids under the given conditions. Presumably, the acetoxylated α-phenylcinnamic acids underwent deacetylation before being incorporated in the decarboxylation pathway. Surprisingly, a very rapid transformation was observed with the substrate possessing 4-acetoxy substitution at both aromatic rings (Table 3, entry 9), however, the stilbene was formed in only 56% yield along with several side products. It is also evident from Table 3 that the methoxylated substrate gave the expected product only in traces (Table 3, entry 14). Further, the reaction with α-phenyl-2′-acetoxy-3′-methoxycinnamic acid (Table 3, entry 10) provided the corresponding stilbene in 64% yield along with the formation of some side products including coumarin.[24] Interestingly, a simultaneous hydrolysis–decarboxylation was observed in case of α-phenylcinnamic ester (Table 3, entry 16) and the product was obtained in 78% yield. Surprisingly, the decarboxylation product was obtained in traces when the hydroxy substituent was present at *para* position of α-phenyl ring (Table 3, entry 13) instead of the aromatic ring of cinnamic acid moiety. Later on, the method was also extended towards the decarboxylation of hydroxylated cinnamic acid (Table 3, entries 18 and 19) into the corresponding styrenes, but the product could be obtained in low yield due to formation of polymeric side products. Following the success with cinnamic acid derivatives, the above method was explored towards decarboxylation of aromatic acids. However, aromatic acids such as 4-hydroxy substituted phenylpropanoic acid (entry 20), phenylacetic acid (entry 21) and benzoic acid (entry 22) did not undergo the above reaction, thus indicating a probable selectivity towards cinnamic acid derivatives as compared to aromatic acids. It is worth mentioning that the prevalent decarboxylation protocol involving quinoline/copper salt does not allow the selective decarboxylation of cinnamic acid moiety[9–11] in comparison to aromatic acids.[13b] In this context, the pronounced selectivity observed with MIm/$NaHCO_3$ (Scheme 1) can be a useful synthetic tool for chemoselective decarboxylation in total synthesis of complex organic compounds including natural products.

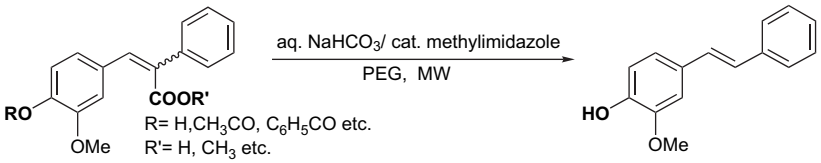


Scheme 1.

Thus, the developed protocol allowed us to synthesize the immensely important (*E*)-stilbenes in a mild and stereoselective manner. It is pertinent to mention that a secondary nonetheless useful advantage of the method lies in the one pot deacetylation–decarboxylation or debenzoylation–decarboxylation of acetoxylated/benzoylated α-phenylcinnamic acids, which could considerably simplify the synthetic strategy and subsequent workup procedures for the synthesis of stilbenes.[25]

In order to ascertain the efficacy of microwaves, **1a** was refluxed with aq $NaHCO_3$/methylimidazole (cat.) in PEG

Table 3. Decarboxylation of cinnamic acid derivatives (**1a–19a**) under microwave irradiation[a]



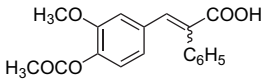
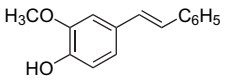
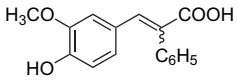
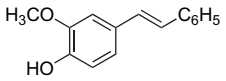
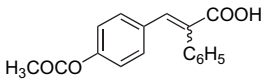
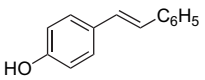
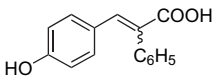
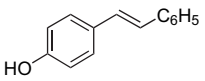
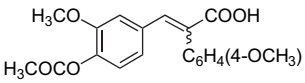
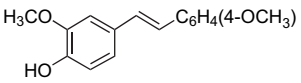
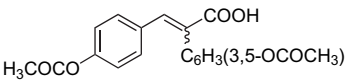
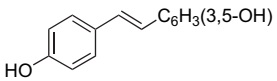
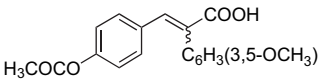
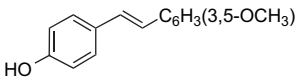
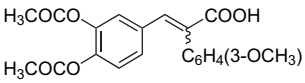
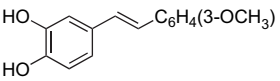
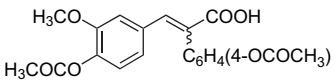
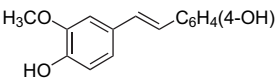
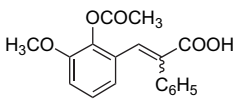
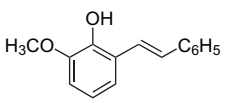
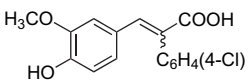
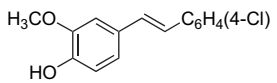
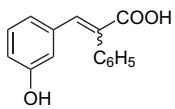
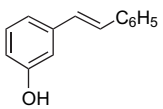
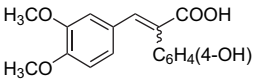
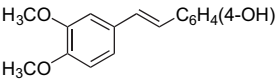
Sr. no.	Substrate (**a**)	Reaction time in min	Product (**b**)	Yield (%)	References
1		20		87	28b,f
2		20		91	28b,f
3		20		83	28b,f
4		20		86	28b,f
5		20		81[b]	—
6		20		84	28e
7		20		84	6
8		20		82	28d
9		8		56	28i
10		25		64	28c
11		20		78[b]	—
12		20		ND[c]	1c
13		40		Traces	28i

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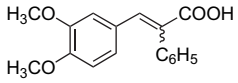
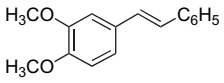
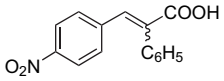
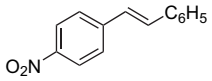
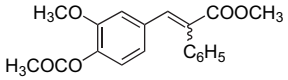
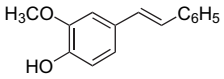
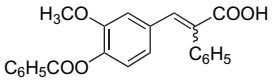
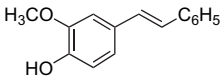
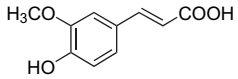
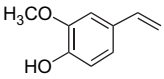
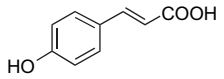
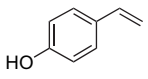
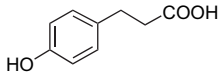
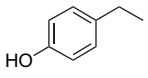
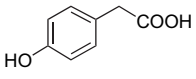
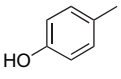
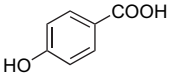
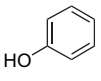
Table 3. (*continued*)

Sr. no.	Substrate (**a**)	Reaction time in min	Product (**b**)	Yield (%)	References
14		40		ND[c]	28h
15		40		ND[c]	28a
16		20		78	28b,f
17		20		76	28b,f
18		20		38	18d,19,28g
19		20		34	18,19,28g
20		40		ND[c]	
21		40		ND[c]	
22		40		ND[c]	

[a] CEM monomode microwave, (200 W, 180 °C).
[b] Spectral data of the new compounds is given in Section 4.
[c] Not detected, general conditions: substrate **1a**–**22a** (0.0037 mol), $NaHCO_3$ (10% aq soln 6–7 mL), methylimidazole (0.0018 mol) and PEG (10–12 mL).

under conventional method for 16 h or heated in a sealed tube for 5 h, but the expected stilbene could be obtained in only 62% and 64% yield, respectively. The foregoing evidently emphasizes the significance of microwave in effectively bringing about the transformation of **1a** to **1b**.

Mechanistically, the above reactions are believed to proceed via the base catalyzed formation of a quinomethine intermediate, which subsequently gets decarboxylated.[26] The same process was presumably occurring in our case (Fig. 1). In addition, methylimidazole might also help promote the reaction due to the formation of polar methylimidazole carboxylate salts, which can efficiently absorb microwave energy.[27] It is evident from Figure 1 that all the intermediates in the proposed mechanistic pathway are more polar than the substrate itself, hence the reaction proceeds smoothly under the coupling of aqueous conditions with microwave irradiation. Further studies regarding elucidation of the precise mechanism are currently under progress.

3. Conclusion

In conclusion, we disclose a methylimidazole-promoted, metal-free decarboxylation protocol for substituted cinnamic acids in basic water medium under microwave irradiation. The striking synergism between catalytic methylimidazole and aq $NaHCO_3$ gives a facile access to biologically important stilbenes. The critical role of water in facilitating the reaction imparts an interesting facet to the synthetic utility of water mediated organic transformations. The developed method provides an efficient and ecofriendly alternative to the prevalent multistep protocols involving quinoline/metal salt, a toxic decarboxylating agent for the synthesis of stilbenes. In addition, the one pot deacetylation–decarboxylation of acetoxylated α-phenylcinnamic acids could considerably help simplify the associated workup procedures. Further investigations to improve the scope of the developed method are currently underway.

4. Experimental section

4.1. General procedure

The cinnamic acid derivatives were obtained as a mixture of cis and trans isomers through the Perkin reaction.[9] ^{1}H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded on a Bruker Avance-300 spectrometer. A CEM Discover© focused microwave (2450 MHz, 300 W) was used wherever mentioned. HREIMS spectra were determined using micromass Q-TOF ultima spectrometer.

4.2. Synthesis of stilbenes under focused microwave irradiation

A mixture of cinnamic acid derivatives (**1a**–**19a**) (0.0037 mol), $NaHCO_3$ (aq 10%, 6–7 mL), methylimidazole (0.0018 mol) and PEG (10–12 mL) were mixed in a 100 mL round bottom flask. The flask was shaken well and irradiated under focused monomode microwave system fitted with reflux condenser for 20–40 min (200 W, 180 °C). After the completion of reaction, the reaction mixture was cooled and water (20 mL) was added to it, which resulted in the precipitation of the product. The precipitated product was filtered and recrystallized in most cases, to obtain pure (*E*)-stilbene or purified further by Si-gel (60–120 mesh size) column with a 1:5 mixture of ethylacetate and hexane. Spectral data and melting point of obtained products agreed well with the reported values.[1c,6,18,19,28]

4.3. Spectral data of novel compounds

4.3.1. Compound 5, Table 3: 4′-hydroxy-3,4′-dimethoxystilbene. White crystalline solid (mp 163–166 °C); ^{1}H NMR ($CDCl_3$) δ 7.36 (2H, d, J=8.5 Hz), 6.94 (2H, m), 6.83 (5H, m), 5.59 (1H, s), 3.86 (3H, s), 3.75 (3H, s); ^{13}C NMR ($CDCl_3$) δ 159.0, 146.7, 145.2, 130.3, 127.4, 126.6, 126.1, 120.1, 114.5, 114.1, 108.0, 55.9, and 55.3. HREIMS data: m/z $[M+H]^+$ for $C_{16}H_{17}O_3$, calculated 257.3103; observed 257.3107.

4.3.2. Compound 11, Table 3: 4-chloro-4′-hydroxy-3′-methoxystilbene. White solid (mp 121–124 °C); ^{1}H NMR ($CDCl_3$) δ 7.35 (2H, d, J=8.5 Hz), 7.25 (2H, d, J=8.1 Hz), 6.96 (3H, m), 6.87 (2H, d, J=8.07 Hz), 5.72 (1H, s), 3.87 (3H, s); ^{13}C NMR ($CDCl_3$) δ 146.8, 145.8, 136.1, 132.7, 129.6, 129.2, 128.8, 127.4, 125.1, 120.6, 114.6, 108.3 and 55.9. HREIMS data: m/z $[M+H]^+$ for $C_{15}H_{14}O_2Cl$, calculated 261.7229; observed 261.7228.

Acknowledgements

Two of us (V.K. and Anuj Sharma) are indebted to UGC and CSIR Delhi, respectively, for the award of SRF. The authors gratefully acknowledge the Director of I.H.B.T., Palampur for his kind cooperation and encouragement.

Supplementary data

Spectral data of synthesized products. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.05.046.

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