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Tandem Bis-aldol Reaction of Ketones: A Facile One-Pot Synthesis of 1,3-Dioxanes in Aqueous Medium

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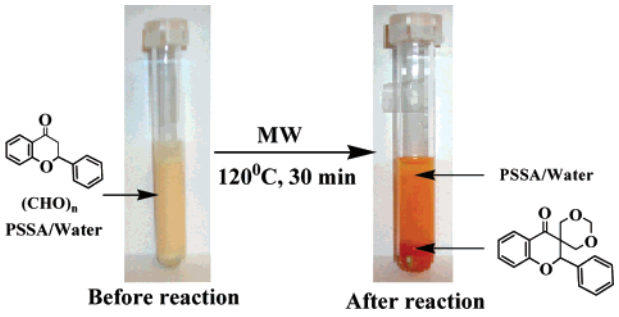
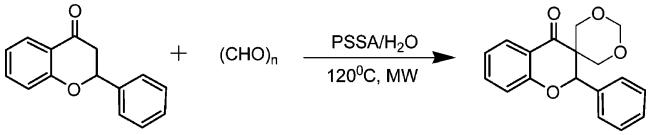


A novel tandem bis-aldol reaction of ketone with paraformaldehyde catalyzed by polystyrenesulfonic acid in aqueous medium delivers 1,3-dioxanes in high yield. This one-pot, operationally simple microwave-assisted synthetic protocol proceeds efficiently in water in the absence of organic solvent, with excellent yield.

Dioxane rings are common structural motifs in numerous bioactive molecules such as (+)-Dactylolide (a cytotoxic agent),[1] derivatives of 2-substituted-1,3-dioxanes (antimuscarinic agents),[2] and (+)-SCH 351448 (a novel activator of low-density lipoprotein receptor promoters).[3] A variety of biologically active molecules have been identified from libraries of diverse, natural product-like 1,3-dioxanes.[4] Recently 1,3-dioxane derivatives have been found to be effective modulators for multidrug resistance.[5] Over the years, there has been a plethora of elegant methodologies developed independently for the synthesis of these molecules. The acid-catalyzed condensation of olefins with aldehyde known as Prins reaction is generally used for these dioxane syntheses.[6] The major product of this reaction consists of tetrahydropyran, 1,3-dioxane, 1,3-glycol, or an unsaturated alcohol depending on the reaction conditions.[7] In fact, several groups have taken advantage of this transformation as an efficient approach to natural product targets.[8]

While dioxanes have great potential as a drug candidate, the synthetic protocol of this important molecule has been largely untapped. In view of our ongoing research effort devoted to the development of greener synthetic pathways for a range of bioactive molecules,[9] herein, we report a novel tandem bis-aldol reaction of ketones with paraformaldehyde catalyzed by polymer-supported polystyrenesulfonic acid (PSSA) under microwave (MW) irradiation in aqueous media to yield 1,3-dioxanes (Scheme 1).

SCHEME 1. Bis-aldol Reaction of Flavanone in Water



We initially investigated the reaction of acetophenone with paraformaldehyde to establish the feasibility of our strategy to 1,3-dioxane systems and to optimize the reaction conditions (Table 1).

TABLE 1. Optimization of Reaction Conditions with Use of MW Irradiation

entry	catalyst	solvent	temp (°C)	reaction time (min)	yield (%)
1		MeOH	100	60	NR
2	clay	MeOH	120	45	NR
3	Nafion	MeOH	120	45	NR
4	AcOH		120	45	25
5	TFA		120	45	81
6	PSSA	water	120	30	83
7	PSSA	water	sonication	24 h	NR

First the reaction was conducted without any catalyst by using MW and no reaction (NR) was observed. Then montmorillonite-K10 (clay) and Nafion-H catalysts in methanol (MeOH) were tested and in both these conditions, little dehydrated product and no bis-aldol products were obtained. Acetic acid (AcOH) did catalyze the reaction, but the yield was very poor. However, trifluroacetic acid (TFA) and PSSA did efficiently catalyze this reaction and afforded high yields of the desired product.

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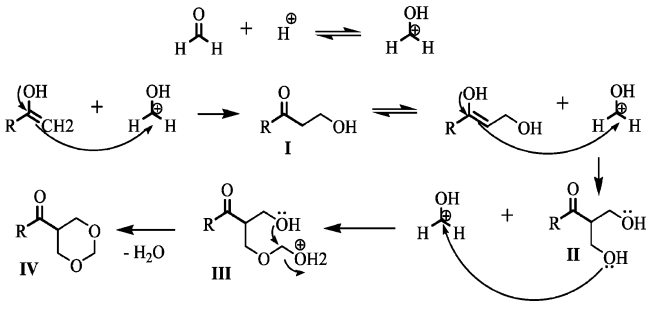
In view of the emerging MW chemistry interest in aqueous reaction medium,[10] and in keeping with our emphasis on exploration of cleaner pathways,[9] we tried to develop greener reaction conditions and observed that PSSA efficiently catalyzed this reaction in water. Thus, we have developed an aqueous one-pot protocol for the tandem bis-aldol reaction of ketone with paraformaldehyde. To further define the scope of this reaction, a wide variety of ketones were evaluated for this cyclization reaction and the results are summarized in Table 2.

Various ketones reacted efficiently with paraformaldehyde to afford the desired 1,3-dioxanes in good yield (entries 1−7). This approach establishes a convenient and flexible method to attach functional arms to indanone and flavanone (entries 8 and 9) for further elaboration in synthetic design. The aliphatic ketones, however, afforded low yields (entries 10−12), which may be due to their unavoidable self-condensation. 1-Methyl-2-pyrrolidinone (entry 11) gave no product indicating the nonreactivity of amide carbonyl toward this reaction. The reaction is completed under conventional heating in an oil bath at the same temperature to afford comparable yields but requires an extended period of time, 4−5 h.

It is noteworthy to mention that these reactions are working well in an aqueous medium without using any phase-transfer catalyst (PTC). This may be due to selective absorption of microwaves by reactants, intermediates, and polar aqueous medium,[10] which accelerate the reaction even in the absence of PTC. In most of the experiments, we observed that after completion of reactions, the phase separation of the desired product from the aqueous media occurs under hot condition, which facilitates isolation of the crude product by simple decantation instead of tedious extraction processes, thus reducing the use of volatile organic solvents for extraction. As exemplified by the reaction of flavanone with paraformaldehyde in PSSA/water, a distinct phase separation was exhibited (as shown in the graphical abstract).

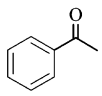
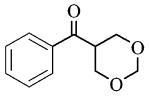
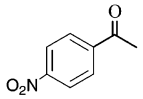
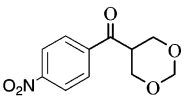
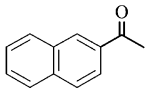
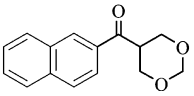
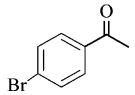
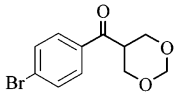
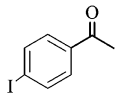
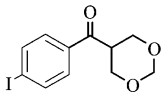
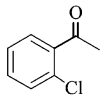
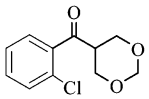
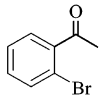
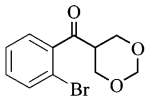
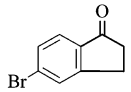
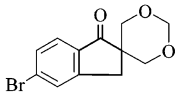
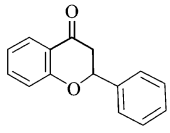
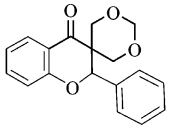
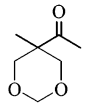
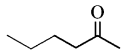
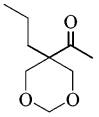
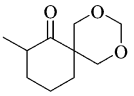
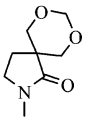
The mechanism of the similar cyclization reaction has been studied by Ross et al. in the synthesis of 1,3-dioxanes from alkene and aldehyde,[6] stereoaspects of which were then explored by Portoghese et al.[11] We postulate the following mechanism for the PSSA-catalyzed tandem bis-aldol reaction of ketone with paraformaldehyde in water (Scheme 2).

SCHEME 2. Mechanism of the Bis-aldol Reaction



The reaction involved the addition of a protonated formaldehyde (generated by microwave exposure of paraformaldehyde with PSSA/water) molecule to ketone (enol) to form β-hydroxy ketone **I**. This was followed by the addition of another protonated formaldehyde molecule to **I** to yield diol **II**, that in turn attacks the third formaldehyde molecule to give adduct **III**, which after dehydration yields the final product 1,3-dioxane **IV**.

TABLE 2. Tandem Bis-aldol Reaction of Ketones with Paraformaldehyde Catalyzed by PSSA in Water

entry	ketone	product	time (min)	yield (%)[a]
1			30	83 (78)
2			30	79 (77)
3			20	85 (79)
4			30	83 (80)
5			30	80 (78)
6			30	79 (75)
7			30	81 (75)
8			25	89 (84)
9			35	87 (85)
10			30	35 (30)
11			30	45 (40)
12			30	50 (48)
13			60	NR

[a] GC yields (isolated yield). All compounds were characterized by MS, ^{1}H NMR, and ^{13}C NMR.

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In conclusion, we have demonstrated a new and efficient approach to attach 1,3-dioxane functional arms to ketones. This reaction will be very useful in drug discovery for the synthesis of bioactive molecules bearing a 1,3-dioxane moiety. Also the use of polymer-supported commercially available, and inexpensive PSSA as a catalyst and water as a reaction medium are additional eco-friendly attributes of this synthetic protocol.

Experimental Section

All starting ketones and paraformaldehyde were used as obtained. TLC (silica gel; 20% EtOAc:hexane) and GC-MS was used to monitor the reactions. The crude products were identified by GC/MS qualitative analysis, using a GC system with a mass selective detector. The identities were further confirmed by ^{1}H and ^{13}C NMR spectra that were recorded in chloroform-*d* ($CDCl_3$) with TMS as internal reference, using a 300 MHz NMR spectrometer.

Typical Experimental Procedure: The ketone (5 mmol) and paraformaldehyde (20 mmol) were placed in a 10 mL crimp-sealed thick-walled glass tube equipped with a pressure sensor and a magnetic stirrer. The contents were dissolved in 20% PSSA solution in water (five times the weight of ketone) and the reaction tube was placed inside the cavity of a CEM Discover focused microwave synthesis system, operated at 120 ± 5 °C (temperature monitored by a built-in infrared sensor), power 40 to 140 W, and pressure 40−70 psi for 30 min (Table 2). After completion of the reaction, the phase separation of the desired product from the aqueous media occurs, facilitating the isolation of crude product by simple decantation, which was subjected to column chromatography to afford pure 1,3-dioxanes.

Entry 1: ^{1}H NMR ($CDCl_3$) δ 8 (d, 2H), 7.5 (m, 3H), 5.1 (d, 1H), 4.7 (d, 1H), 4.3 (d, 2H), 4 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 196, 135, 133, 128, 127, 93, 69, 43; MS 191 (M^+), 162, 145, 133, 120, 105, 77, 51.

Entry 2: ^{1}H NMR ($CDCl_3$) δ 8.3 (d, 2H), 8.1 (d, 2H), 5.1 (d, 1H), 4.7 (d, 1H), 4.3 (d, 2H), 3.9 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 198, 153, 140, 128, 124, 94, 68, 41; MS 236 (M^+), 207, 178, 150, 132, 104, 76, 55.

Entry 3: ^{1}H NMR ($CDCl_3$) δ 8.5 (s, 1H), 8 (m, 4H), 7.6 (m, 2H), 5.1 (d, 1H), 4.7 (d, 1H), 4.4 (d, 2H), 4 (d, 2H), 3.3 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 198, 135, 133, 132, 130, 129, 128, 127, 126, 124, 93, 69, 44; MS 242 (M^+), 212, 170, 155 (b), 127, 101, 77.

Entry 4: ^{1}H NMR ($CDCl_3$) δ 7.9 (d, 2H), 7.6 (m, 3H), 5.1 (d, 1H), 4.7 (d, 1H), 4.2 (d, 2H), 3.9 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 197, 138, 134, 130, 129, 93, 68, 43; MS 270 (M^+), 240, 227, 211, 198, 183, 155, 132, 104, 76, 55.

Entry 5: ^{1}H NMR ($CDCl_3$) δ 7.9 (d, 2H), 7.6 (m, 3H), 5.1 (d, 1H), 4.7 (d, 1H), 4.3 (d, 2H), 4 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 198, 139, 134, 131, 130, 94, 68, 44; MS 318 (M^+), 288, 246, 231, 203, 132, 104, 76, 55.

Entry 6: ^{1}H NMR ($CDCl_3$) δ 7.2−7.4 (m, 4H), 5 (d, 1H), 4.8 (d, 1H), 3.7−4.2 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 201, 138, 133, 131, 129, 127, 93, 68, 43; MS 225 (M^+), 196, 179, 167, 154, 139, 131, 111, 75, 55.

Entry 7: ^{1}H NMR ($CDCl_3$) δ 7.3−7.5 (m, 4H), 4.9 (d, 1H), 4.7 (d, 1H), 3.7−4.1 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 202, 139, 132, 130, 128, 126, 94, 68, 44; MS 270 (M^+), 242, 198, 183, 155, 132, 104, 76, 55.

Entry 8: ^{1}H NMR ($CDCl_3$) δ 7.5 (m, 3H), 5.2 (d, 1H), 4.8 (d, 1H), 4 (d, 2H), 3.8 (d, 2H), 3.4 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 201, 134, 131, 129, 126, 93, 72, 39; MS 282 (M^+), 264, 236, 223, 196, 144, 115 (b), 89, 63.

Entry 9: ^{1}H NMR ($CDCl_3$) δ 7.8 (d, 1H), 7.5 (t, 1H), 7.3 (m, 5H), 7.1 (m, 2H), 6.1 (s, 1H), 5.1 (d, 1H), 4.7 (d, 1H), 4.4 (m, 2H), 3.8 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 195, 160, 138, 136, 127, 126, 124, 121, 119, 93, 80, 70, 68; MS 296 (M^+), 266, 250, 235, 207, 175, 145, 121 (b), 92, 77.

Entry 10: ^{1}H NMR ($CDCl_3$) δ 4.9 (d, 1H), 4.7 (d, 1H), 4.3 (d, 2H), 3.5 (d, 2H), 2.3 (s, 3H), 1 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 210, 94, 72, 48, 26, 18; MS 144 (M^+), 126, 114 (b), 101, 84, 69, 57.

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Supporting Information Available: Experimental procedures, and NMR and MS data of compounds (entries 1−10). This material is available free of charge via the Internet at http://pubs.acs.org.

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