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Iodine as a mild and versatile reagent for the synthesis of 1,3-dioxane derivatives via the Prins reaction

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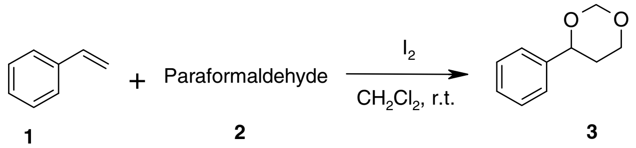
ABSTRACT

Iodine is found to be an effective reagent for the cross-coupling of olefins with aldehydes under mild conditions to produce 4-substituted 1,3-dioxane derivatives in excellent yields and in short reaction times with high selectivity. The use of iodine makes this procedure simple, convenient, cost-effective and practical. This method works not only with formaldehyde but also with acetaldehyde, propionaldehyde and cyclohexanecarboxaldehyde.

The dioxane moiety is a common structural motif in several bioactive molecules such as (+)-dactylolide (a cytotoxic agent), derivatives of 2-substituted-1,3-dioxanes (antimuscarinic agents) and (+)-SCH 351448 (a novel activator of the lipoprotein receptor).[1–3] Recently, 1,3-dioxanes have also been evaluated as effective modulators for multi-drug resistance.[4] The acid-catalyzed condensation of olefins with aldehydes, the Prins reaction, is generally used for the preparation of 1,3-dioxanes.[5] The major products of the classical Prins reaction are normally 1,3-glycols, 1,3-dioxanes or unsaturated alcohols depending on the reaction conditions.[6] Generally, Lewis acids as well as Brønsted acids are employed in both catalytic and stoichiometric amounts to promote this transformation.[7–10] However, many of these acids are highly corrosive and involve tedious separation procedures and also require prolonged reaction times and high temperatures resulting in low to moderate selectivity of products due to the polymerization of the starting materials. Therefore, the development of a simple, convenient and efficient protocol using inexpensive and readily available reagents would extend the scope of the Prins reaction in natural product synthesis. Recently, molecular iodine has received considerable attention as an inexpensive, non-toxic, readily available catalyst for various organic transformations; affording the corresponding products with high selectivity in excellent yields.[11] The mild Lewis acidity associated with iodine has enhanced its use in organic synthesis for several organic transformations using stoichiometric to catalytic amounts. Owing to advantages associated with this eco-friendly catalyst, molecular iodine has been explored as a powerful reagent for various organic transformations.[12]

In continuation of our interest on the use of molecular iodine for various transformations,[13] we herein report the first direct and metal catalyst-free Prins reaction for the synthesis of 4-substituted 1,3-dioxane derivatives from olefins and aldehydes using molecular iodine under neutral conditions. Accordingly, treatment of styrene (**1**) with paraformaldehyde (**2**) in the presence of molecular iodine at ambient temperature for 45 min gave the corresponding 4-phenyl-1,3-dioxane **3a** in 92% yield (Scheme 1).

Similarly, 1-[(*E*)-1-propenyl]benzene, 1-isopropenyl-benzene, 1,2-dihydronaphthalene, indene, 2-vinylnaphthalene, *trans*-stilbene and 1-dodecene underwent smooth coupling with paraformaldehyde under the influence of molecular iodine to give the respective 1,3-dioxanes in excellent yields (Table 1, entries **b**–**h**). Since there have been no reports on the use of aliphatic aldehydes, except formaldehyde, we attempted the coupling of alkenes with aliphatic aldehydes such as acetaldehyde, propionaldehyde and cyclohexanecarboxaldehyde. Interestingly, these substrates reacted well with alkenes to produce the corresponding 2,4,6-trisubstituted 1,3-dioxane derivatives under similar reaction conditions (Table 1, entries **i**–**o**, Scheme 2).



Scheme 1. Preparation of 4-phenyl-1,3-dioxane **3a**.

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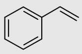
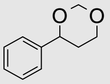
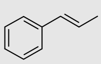
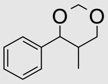
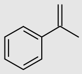
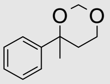
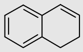
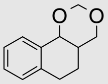
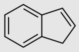
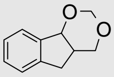
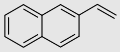
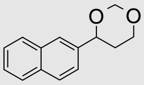
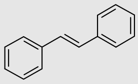
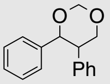
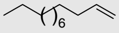
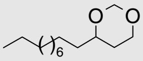
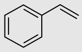
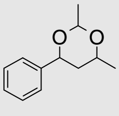
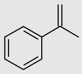
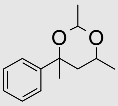
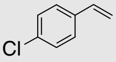
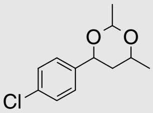
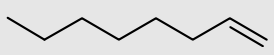
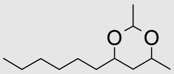
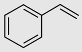
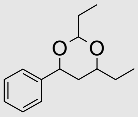
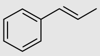
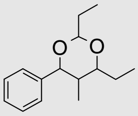
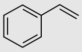
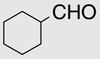
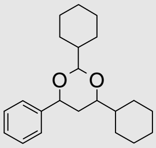
Table 1
Iodine promoted Prins reaction of olefins with aldehydes

Entry	Olefin	Aldehyde	Product[a]	Time (min)	Yield[b] (%)
a		$(CH_2O)_n$		45	92
b		$(CH_2O)_n$		40	90
c		$(CH_2O)_n$		50	89
d		$(CH_2O)_n$		45	86
e		$(CH_2O)_n$		45	85
f		$(CH_2O)_n$		55	82
g		$(CH_2O)_n$		60	92
h		$(CH_2O)_n$		90	84
i		CH_3CHO		50	92
j		CH_3CHO		40	90
k		CH_3CHO		55	88
l		CH_3CHO		90	82
m		CH_3CH_2CHO		70	84
n		CH_3CH_2CHO		75	88
o				90	86

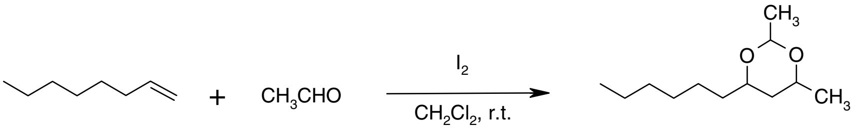
[a] All the products were characterized by ^1H NMR, ^{13}C NMR, IR and mass spectroscopy.

[b] Yield refers to pure products after chromatography.

The structure of 2,4-dimethyl-6-phenyl-1,3-dioxane **3i**, shown in Figure 1, was deduced from the NMR studies. The proton H4 has a large ($J = 11.2$ Hz) and a small ($J = 2.9$ Hz) coupling. The presence of the large coupling allows us to place H4 in an axial position, with large diaxial coupling with H3a. This implies that the aromatic group at C4 takes an equatorial orientation. Similarly H2 has a large diaxial coupling with H3a with $J = 12.6$ Hz, suggesting that it is also axial disposed. The equatorial orientation of the methyl substituent at C2 and C5 and the axial orientation of H2, H4 and H5 in the chair form of the six-membered ring are additionally supported by H2/H5, H4/H5 and H2/H4 correlations in the NOESY spectrum. This structure with three substituents placed in *cis* position to each other was further supported by NOE cross peaks, Ar/H3a, Ar/H3e, Me-1/ H3a and Me-1/H3e.

The structure of 2,4-diethyl-5-methyl-6-phenyl-1,3-dioxane **3n**, shown in Figure 2, was assigned from NOE experiments. The presence of correlations between H3, H5 and H7 in the NOESY experiments provides emphatic support for their diaxial orientation. This also implies that the bulky substituents at C3, C5 and C7 are equatorially placed. Small couplings of H4 with H5 and H3 ($J = 2.3$ Hz) support an equatorial disposition for H4. Equatorial position of the aromatic group was additionally confirmed from cross peak H-ortho/H4e in the NOESY spectrum. The structure was further confirmed by NOESY cross peaks for H2′/H4e. All the above observations, including cross NOE peak H2′/H4e, are consistent with the structure proposed in Figure 2, with the six-membered ring taking a chair conformation.

Though the reaction was successful with aliphatic aldehydes, no coupling of aromatic aldehydes with styrene was observed even under drastic conditions (in refluxing dichloroethane). Furthermore, the reaction did not proceed in the absence of iodine even after a long reaction time (12 h). As solvent, dichloromethane gave the best results. In all cases, the reactions proceeded rapidly at room temperature under mild conditions. The reactions were clean and no side products were detected under these conditions as determined from the NMR spectra of the crude products. The structures of the products were established from spectral data and also



3l

Scheme 2. Preparation of **3l**.

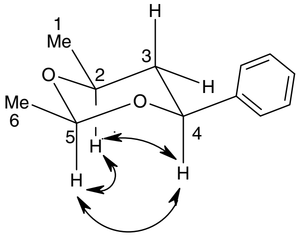


Figure 1. Characteristic NOE's of **3i**.

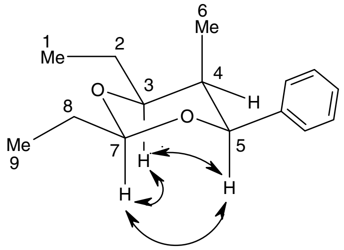
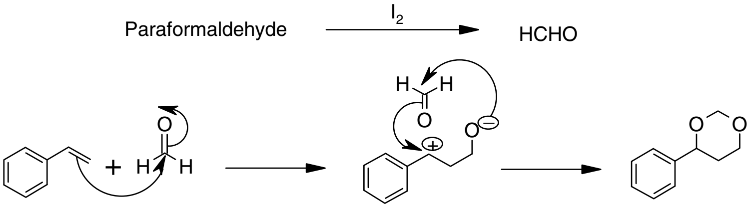


Figure 2. Characteristic NOE's of **3n**.



Scheme 3. A plausible reaction mechanism.

by comparison with authentic samples.[7] A plausible reaction mechanism is depicted in Scheme 3.

It should be noted that the reactions were faster with paraformaldehyde compared to aliphatic aldehydes. In addition, styrene derivatives gave higher yields of products when compared to aliphatic olefins. The reaction was sluggish when a catalytic amount of iodine was used and thus a stoichiometric amount of iodine to achieve high conversions. The scope and generality of this process is illustrated with respect to various aldehydes and alkenes, and the results are presented in Table 1.[14]

In summary, molecular iodine has proved to be a useful and novel reagent for the Prins reaction to produce 4-substituted 1,3-dioxanes in excellent yields and in short reaction times. The experimental procedure is simple, convenient and the reaction conditions are amenable to scale-up. This method provides an easy access to a wide range of 1,3-dioxanes with diverse chemical structures.

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References and notes

1. Aubele, D. L.; Wan, S.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3485–3488.
2. Marucci, G.; Piero, A.; Brasili, L.; Buccioni, M.; Giardina, D.; Gulini, U.; Piergentili, A.; Sagratini, G. *Med. Chem. Res.* **2005**, *14*, 274–296.
3. Chan, K.; Ling, Y. H.; Loh, T. *Chem. Commun.* **2007**, 939–941.
4. Schmidt, M.; Ungvari, J.; Glode, J.; Dobner, B.; Langner, A. *Bioorg. Med. Chem.* **2007**, *15*, 2283–2297.
5. Yang, N. C.; Yang, D. H.; Ross, C. B. *J. Am. Chem. Soc.* **1959**, *81*, 133–136.
6. (a) Fuson, R. C.; Ross, W. E.; McKeever, C. H. *J. Am. Chem. Soc.* **1938**, *60*, 2935–2936; (b) Lumma, W. C.; Ma, O. H. *J. Org. Chem.* **1970**, *35*, 2391–2393.
7. (a) Prins, H. J. *Chem. Weekbl.* **1919**, *16*, 1072; (b) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661–672; (c) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *51*, 505.
8. (a) Snider, B. B. The Prins and Carbonyl Ene Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, UK, 1991; Vol. 2, pp 527–561; (b) Delmas, M.; Gaset, A. *Synthesis* **1980**, 871; (c) Gharbi, R. E.; Delmas, M.; Gaset, A. *Synthesis* **1981**, 361.
9. (a) Kobzar, E. A.; Korchagina, D. V.; Salakhutdinov, N. F.; Ione, K. G.; Barkhash, V. A. *J. Org. Chem. USSR (Engl. Transl.)* **1992**, *28*, 1030; (b) Tateiwa, J.; Hashimoto, K.; Yamauchi, T.; Uemura, S. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2361; (c) Chandrasekhar, S.; Reddy, B. V. S. *Synlett* **1998**, 851.
10. (a) Bach, T.; Lobel, J. *Synthesis* **2002**, 2521; (b) Gu, Y.; Karam, A.; Jerome, F.; Barrault, J. *Org. Lett.* **2007**, *9*, 3145–3148 and references cited therein.
11. (a) Togo, H.; Iida, S. *Synlett* **2006**, 2159; (b) Lin, X.-F.; Cui, S.-L.; Wang, Y.-G. *Tetrahedron Lett.* **2006**, *47*, 4509; (c) Chen, W.-Y.; Lu, J. *Synlett* **2005**, 1337; (d) Royer, L.; De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2005**, *46*, 4595; (e) Banik, B. K.; Fernandez, M.; Alvarez, C. *Tetrahedron Lett.* **2005**, *46*, 2479; (f) Wang, S.-Y. *Synlett* **2004**, 2642; (g) Ko, S.; Sastry, M. N. V.; Lin, C.; Yao, C.-F. *Tetrahedron Lett.* **2005**, *46*, 5771.
12. (a) Yadav, J. S.; Reddy, B. V. S.; Hashim, S. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3025; (b) Yadav, J. S.; Reddy, B. V. S.; Premalatha, K.; Swamy, T. *Tetrahedron Lett.* **2005**, *46*, 2687; (c) Kumar, H. M. S.; Reddy, B. V. S.; Reddy, E. J.; Yadav, J. S. *Chem. Lett.* **1999**, 857; (d) Yadav, J. S.; Reddy, B. V. S.; Rao, C. V.; Chand, P. K.; Prasad, A. R. *Synlett* **2001**, 1638.
13. (a) Yadav, J. S.; Reddy, B. V. S.; Reddy, U. V. S.; Krishna, A. D. *Tetrahedron Lett.* **2007**, *48*, 5243; (b) Yadav, J. S.; Reddy, B. V. S.; Narayana Kumar, G. G. K. S.; Swamy, T. *Tetrahedron Lett.* **2007**, *48*, 2205; (c) Yadav, J. S.; Balanarsaiah, E.; Raghavendra, S.; Satyanarayana, M. *Tetrahedron Lett.* **2006**, *47*, 4921; (d) Yadav, J. S.; Satyanarayana, M.; Raghavendra, S.; Balanarsaiah, E. *Tetrahedron Lett.* **2005**, *46*, 8745.
14. *General procedure:* A mixture of olefin (1 mmol), aldehyde (2 mmol) and iodine (1 mmol) in dichloromethane (5 mL) was stirred at 23 °C for the specified amount of time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water and extracted with ether (2 × 10 mL). The combined organic layers were washed with aqueous sodium thiosulfate, brine and dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 0.5–9.5) gave the pure 4-iodotetrahydropyran. The products thus obtained were characterized by IR, NMR and mass spectroscopy. The spectral data were found to be consistent with authentic samples.[9,10] Compound **3d**: 4a,5,6,10b-tetrahydro-4*H*-naphtho[1,2-*d*][1,3]dioxane: Liquid, IR (KBr): ν 3434, 3320, 2926, 2860, 1645, 1543, 1446, 1375, 1078, 971, 759, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.66–1.78 (m, 2 H), 2.43 (m, 1H), 2.94 (ddd, 1H, J = 3.0, 6.0, 16.6 Hz), 3.90–4.04 (m, 2H), 4.61 (d, 1H, J = 3.0 Hz), 4.86 (d, 1H, J = 6.0 Hz), 4.99 (d, 1H, J = 6.0 Hz), 7.06–7.26 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.1, 35.1, 40.9, 77.2, 80.7, 99.7, 132.2, 134.4, 134.9, 136.5, 140.7, 143.4. LCMS: *m/z* (%): (M^++Na) 213. HRMS calcd for $C_{12}H_{14}O_2Na$: 213.0891. Found: 213.0897. Compound **3g**: 4,5-diphenyl-1,3-dioxane: Solid, mp 70–72 °C. IR (KBr): ν 3434, 3320, 2926, 2860, 1645, 1543, 1446, 1375, 1078, 971, 759, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.11 (dt, 1H, J = 4.5, 11.3 Hz), 3.90 (t, 1H, J = 11.3 Hz), 4.18 (dd, 1H, J = 4.5, 11.3 Hz), 4.64 (d, 1H, J = 9.8 Hz), 4.95 (d, 1H, J = 6.0 Hz), 5.26 (d, 1H, J = 6.0 Hz), 6.92–6.98 (m, 2H), 7.02–7.08 (m, 2H), 7.10–7.21 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 49.1, 71.8, 84.1, 94.0, 126.9, 127.1, 127.7, 127.9, 128.3, 128.4, 137.1, 139.0. LCMS: *m/z* (%): (M^++Na) 263. HRMS calcd for $C_{16}H_{16}O_2Na$: 263.1047. Found: 263.1054. Compound **3i**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.37(m, 2H, Ar), 7.34 (m, 2H, Ar), 7.27 (tt, J = 1.9, 6.3 Hz, 1H, para), 4.91 (q, J = 5.2 Hz, 1H, H5), 4.65 (dd, J = 2.6, 11.2 Hz, 1H, H4), 3.89 (ddq, J = 2.6, 12.6, 6.3 Hz, 1H, H2), 1.75 (dt, J = 13.3, 2.6 Hz, 1H, H3e), 1.57 (q$J \sim$ 12.4 Hz, 1H, H3a), 1.43 (d, J = 5.2 Hz, 1H, Me-6), 1.27 (d, J = 6.3 Hz, 1H, Me-1). Compound **3k**: 4-(4-chlorophenyl)-2,6-dimethyl-1,3-dioxane: Solid, mp 77–79 °C. IR (KBr): ν 3434, 3320, 2926, 2860, 1645, 1543, 1446, 1375, 1078, 971, 759, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.24 (d, 3H, J = 6.0 Hz), 1.38 (d, 3H, J = 5.2 Hz), 1.43–1.48 (m, 1H), 1.69 (td, 1H, J = 2.2, 13.6 Hz), 3.82 (m, 1H), 4.57 (dd, 1H, J = 3.0, 11.3 Hz), 4.83 (q, 1H, J = 5.3 Hz), 7.22–7.32 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 21.4, 40.3, 72.3, 77.5, 98.7, 127.1, 128.4, 133.2, 140.2. LCMS: *m/z* (%): (M^++Na) 249. HRMS calcd for $C_{12}H_{15}ClO_2Na$: 249.0658. Found: 249.0653. Compound **3o**: 2,4-dicyclohexyl-6-phenyl-1,3-dioxane: Solid, mp 94–96 °C. IR (KBr): ν 3434, 3320, 2926, 2860, 1645, 1543, 1446, 1375, 1078, 971, 759, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.82–2.02

(m, 24H), 3.36 (m, 1H), 4.35 (d, 1H, *J* = 5.3 Hz), 4.53 (dd, 1H, *J* = 3.0, 11.3 Hz), 7.15–7.24 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.8, 26.6, 27.5, 27.8, 28.2, 28.8, 36.7, 42.5, 42.7, 78.1, 80.7, 104.8, 125.7, 127.3, 128.3, 142.6. LCMS: *m/z* (%): (M^++Na) 351. HRMS calcd for $C_{22}H_{32}O_2Na$: 351.2299. Found: 351.2293. Compound **3n**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37–7.22 (m, 4H, Ar), 7.22 (tt, *J* = 7.1, 1.9 Hz, 1H, para), 4.82 (d, *J* = 2.3 Hz, 1H, H5), 4.69 (t, *J* = 5.0 Hz, 1H, H7), 3.73 (ddd, *J* = 8.0, 6.0, 2.3 Hz, 1H, H3), 1.77 (m, 2H, H8), 1.75 (m, 1H, H4), 1.67 (ddq, *J* = 14.0, 8.0, 7.5 Hz, 1H, H2), 1.46 (ddq, *J* = 14.0, 6.0, 7.5 Hz, 1H, H2′), 1.02 (t, *J* = 7.5 Hz, 1H, Me-9), 0.96 (t, *J* = 7.5 Hz, 1H, Me-1), 0.64 (d, *J* = 6.9 Hz, 1H, Me-6).