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A simple one-pot entry to cyclic ethers of varied ring sizes from diols via phosphonium ion induced iodination and base catalyzed Williamson etherification

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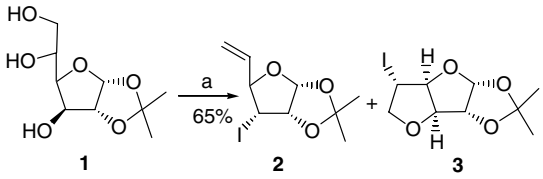
Abstract—A novel and an efficient one-pot cyclization method using triphenylphosphine, iodine and a nitrogenous base has been established for the synthesis of cyclic ethers of various ring sizes. This appears to follow a two-step procedure, which includes preferential substitution of one hydroxyl group by an iodide generated in situ followed by an intramolecular ring closure through the attack of a free hydroxyl group or the more nucleophilic oxide ion.

Cyclic ethers are the common backbone of a large number of natural products,[1] nucleosides[2] and antibiotics,[3] and their synthesis remains a compelling task for synthetic organic chemists. A number of attempts involving Lewis acid or transition metal catalyzed opening of epoxy,[4,5] cyclic sulfate[6] or cyclic orthoester[7] rings by hydroxy groups, metal catalyzed cyclization of olefin-alcohols,[8] and Mitsunobu cyclization[9] of diols have been made in this regard, resulting in a number of new methods for cycloetherification.[10] The Mitsunobu cyclization appears particularly attractive, but is restricted to diols having at least one phenolic, benzylic, allylic or anomeric hydroxy group. Most of the methods are also multistep, low yielding or intolerant to acid labile groups, and their applications are usually restricted to the formation of five- and six-membered cyclic ethers. However, the formation of cyclic ethers by cyclization involving two unactivated hydroxyl groups is not well known. During the work on a project directed towards



Scheme 1. Conversion of triol **1** to iodoolefin **2** and iodoether **3**. Reagents and conditions: (a) PPh_3 (3.75 equiv), imidazole (3.75 equiv), iodine (2.0 equiv), toluene, reflux.

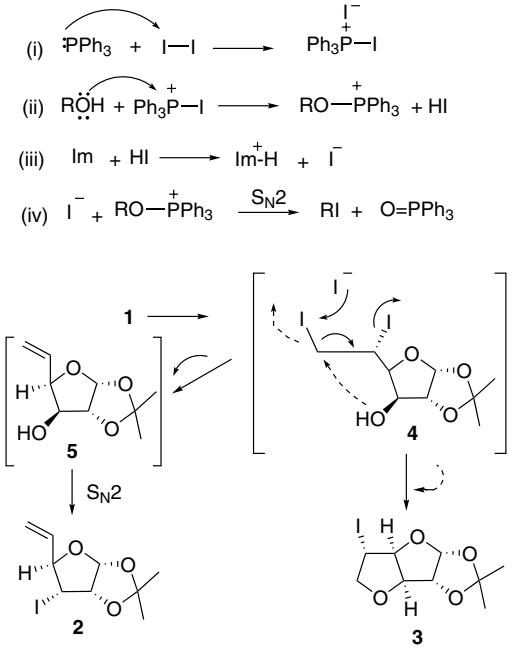


Figure 1. Probable mechanism of formation of **2** and **3** from **1**.

Keywords: One-pot; Synthesis; Cyclic ethers; Diols; Iodination; Etherification.
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the synthesis of carbohydrate derived molecules, we treated **1** with triphenylphosphine-imidazole-iodine in refluxing toluene to introduce an olefin moiety between vicinal hydroxy groups.[11] The reaction mixture yielded (Scheme 1) two novel compounds,[12] **2**, a hitherto unknown C-3 α-iodo substitution product, and **3**, a five-membered fused oxacycle, in the ratio of 2:3. The formation of products **2** and **3** suggested that the intermediate diiodide **4** (formed in situ, Fig. 1) underwent parallel reactions. Deiodination resulted in the formation of the expected olefin **5**, which then underwent a S_N2 attack (after activation by PPh_3) by an iodide ion at C-3 to afford **2**. On the other hand, an intramolecular S_N2 attack of the C-3 hydroxyl group in **4** on the terminal iodide led to the five-membered iodo-substituted cyclized product **3**.

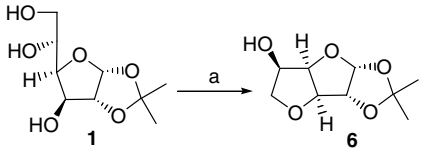
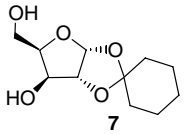
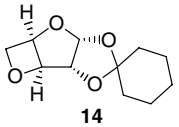
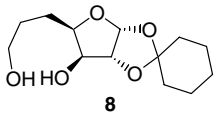
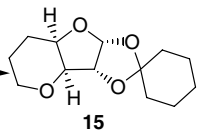
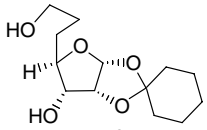
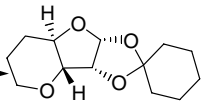
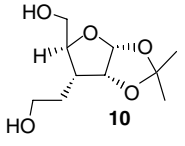
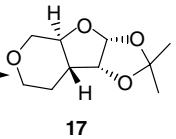
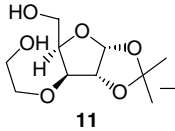
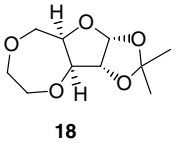
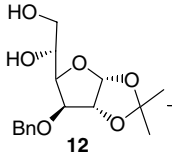
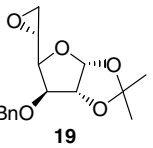
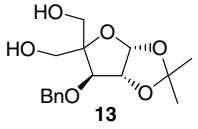
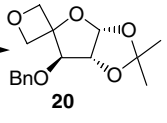
These results led us to speculate that the use of less reagent to iodinate only the primary hydroxyl group should furnish the cyclic ether after nucleophilic attack by the second hydroxyl group. This was indeed realized, allowing us to achieve a versatile, cost effective and rapid one-pot synthesis of cyclic ethers directly from 1,*n*-diols.

Initially, when we carried out the reaction on **1** with PPh_3 (1.1 equiv), iodine (1 equiv) and imidazole (2.5 equiv), only the five-membered cyclic ether **6**[13] was formed in 45% yield. In order to establish this reaction as a potential method for the preparation of cyclic ethers of different ring sizes from unactivated diols,[14] we applied this method to substrates **7**–**13** to obtain products **14**–**20**[15] (Table 1). However, the reaction appeared to be sluggish and required the addition of NaH for a quicker cyclization.

Thus, the treatment of **7**[16] with the reagent followed by the addition of NaH (1 equiv) in the same reaction pot at room temperature resulted in the formation of the four-membered cyclic ether **14** (60%) in less than an hour. During the formation of the six-membered cis-fused cyclic ether **15** (70%), two newly generated spots were detected by TLC after 45 min. The subsequent addition of NaH (1 equiv) at room temperature converted one of the spots to the other, that is, full conversion to a six-membered cyclic ether was achieved in 5 min. Thus, addition of NaH appears to speed up the reaction by facilitating S_N2 attack by the more nucleophilic oxide ion. Similarly, the trans-fused bicyclic ethers **16** and **17** were prepared from their respective starting materials **9** and **10**[17] in good yields. The dioxacycloheptane derivative **18** was derived from the carbohydrate precursor **11** using this method, though the yield was unsatisfactory.[18] Further, if the C-3 hydroxy group is blocked by benzylation (**12**[19]), the reaction furnishes the expected three-membered cyclic ether (**19**, 62%). Therefore, the change in proportions of PPh_3 and iodine led to an epoxide formation instead of a double bond generation as is typical for vicinal dihydroxy compounds. The reaction was also successfully applied to the formation of the spirocyclic product **20**[20] from **13**.[21]

As the use of imidazole as a base led to the generation of a heterogeneous reaction mixture, we had to perform

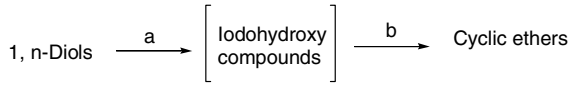
Table 1. Cyclization of triol/diols to the cyclic ethers **6** and **14**–**20**

Entry	Substrate	Reagents/conditions[a]	Product	Yield (%)
1		a		45
2		a, b		60
3		a, b		70
4		a, b		65
5		a, b		60
6		a, b		23
7		a, b		62
8		a, b		72

[a] (a) PPh_3 (1.1 equiv), imidazole (2.5 equiv), iodine (1 equiv), toluene, reflux, 120 min (for **1**), 40–45 min (for **7**–**13**); (b) NaH (1 equiv), rt, 5–10 min.

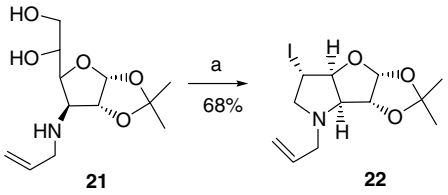
the reaction at higher temperatures to make it homogeneous. A better alternative involved the use of bases such as Et_3N and pyridine, which yielded homogeneous mixtures at room temperature and led to an increase in the yields (Table 2). To study the effect of solvent polarity we carried out some of the reactions in DCM and found no increase in the yield. It was noticed that iodination followed by a base-catalyzed cyclization at room temperature using pyridine yielded the best results. However, triol **1** was insoluble in toluene at room temperature, and required refluxing for iodination, though the cyclization proceeded without the addition of NaH. The cyclization of the monoiodinated products,

Table 2. Cyclization study using pyridine/triethyl amine



Entry	Diol	Reagents/conditions[a]	Product	Isolated yield (%) Py/Et_3N
1	**7**	a, b	**14**	82/70
2	**8**	a, b	**15**	90/78
3	**9**	a, b	**16**	86/75
4	**10**	a, b	**17**	80/75
5	**11**	a, b	**18**	30/25
6	**12**	a, b	**19**	85/73
7	**13**	a, b	**20**	78/78

[a] (a) Ph_3P (1.1 equiv), I_2 (1 equiv), Py/Et_3N (2.5 equiv), toluene, rt, 70–120 min; (b) NaH, rt, 5–10 min.



Scheme 2. Cyclization of amino alcohol **21** to amine **22**. Reagents and conditions: (a) PPh_3 (3.75 equiv), imidazole (3.75 equiv), iodine (2.0 equiv), toluene, reflux, 45 min.

derived easily from diols **8**–**12** with triphenylphosphine-imidazole-iodine at room temperature, to afford the corresponding ethers **15**–**19** necessitated the addition of NaH. On the other hand, iodination of one of the hydroxyl groups of **13** in toluene (being attached to the quaternary carbon of the furanose moiety) was slow and required a longer time (120 min) because of steric hindrance. However, the cyclization occurred easily at room temperature upon addition of sodium hydride.

We also decided to extend the methodology for the synthesis of cyclic amines from amino alcohols. Indeed **21**,[22] the C-3 amino analogue of **1**, underwent the reaction smoothly, affording the cyclized product **22** in good yield (Scheme 2). In this case addition of sodium hydride was not required. The nucleophilic attack by nitrogen at the terminal iodide appears to be faster than olefin formation from the diiodide.

In conclusion, a one-pot method has been developed for the synthesis of cyclic ethers of varied ring sizes from unactivated diols using easily available precursors and cheap reagents. Considering the paucity of effective methods for cyclic ethers, the present approach appears to be the useful method for the synthesis of such molecules. It is also shown to work with amino alcohols to produce cyclic amines. Future work is aimed at the generation of a variety of chiral heterocycles as well as modified bicyclic nucleosides of biological importance.

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12. Data for **2**: ^1H NMR ($CDCl_3$, 300 MHz): $[\alpha]_D^{30}$ +29.4 (*c* 0.22, $CHCl_3$); δ 1.38 (s, 3H), 1.57 (s, 3H), 3.58 (dd, $J = 4.3$,

10.3 Hz, 1H), 4.50 (dd, $J = 6.9$, 10.0 Hz, 1H), 4.64 (t, $J = 9.3$ Hz, 1H), 5.36 (d, $J = 10.3$ Hz, 1H), 5.49 (d, $J = 17.1$ Hz, 1H), 5.70–5.82 (m, 1H), 5.86 (d, $J = 3.5$ Hz, 1H); FABMS, m/z: 297 $(M+H)^+$. Anal. Calcd for $C_9H_{13}IO_3$: C, 36.51; H, 4.43. Found: C, 36.32; H, 4.37. For **3**: $[\alpha]_D^{30}$ +65.5 (c 1.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.33 (s, 3H), 1.50 (s, 3H), 4.18 (dd-like, $J = 3.7$, 9.5 Hz, 1H), 4.31–4.35 (m, 2H), 4.63 (d, $J = 3.5$ Hz, 1H), 4.88 (d, $J = 3.0$ Hz, 1H), 5.10 (d, $J = 3.0$ Hz, 1H), 5.88 (d, $J = 3.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.7 (CH), 26.6 (CH_3), 27.3 (CH_3), 76.6 (CH_2), 83.7 (CH), 85.0 (CH), 90.2 (CH), 107.0 (CH), 112.5 (C); FABMS, m/z: 313 $(M+H)^+$. Anal. Calcd for $C_9H_{13}IO_4$: C, 34.63; H, 4.20. Found: C, 34.60; H, 4.13.

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14. The substrate **8** was prepared from 5-aldo-1,2-*O*-cyclohexylidene-α-D-glucofuranose via Wittig reaction with $PPh_3{=}CHCO_2Et$ followed by $LiAlH_4$ reduction.[23] Similarly, **9** was synthesized from the corresponding C-3 epimer.[24] The substrate **11** was obtained from 3-*O*-methoxycarbonylmethyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[25] through selective opening of the 5,6-acetonide by HOAc, vicinal diol cleavage with $NaIO_4$ and reduction with $NaBH_4$.
15. *General procedure for the synthesis of the cyclic ethers* **14**–**20** *at room temperature*: To a solution of a dihydroxy compound (5 mmol) in dry toluene (25 mL) was added triphenyl-phosphine (5.5 mmol) and pyridine (12.5 mmol), and the mixture was stirred at rt for 5 min to afford a clear solution. Iodine granules (5 mmol) were added portionwise to the solution and stirring was continued at rt for 70–120 min (as in Table 2). Oil-free NaH (10 mmol) was added slowly and the mixture was stirred for 5–10 min at rt. Excess NaH was destroyed by slow addition of cold water to the reaction mixture. The solvent was washed with water (10 mL), saturated $Na_2S_2O_3$ solution (2×20 mL) and brine (2×10 mL), dried over Na_2SO_4 (anhydrous), and evaporated in vacuo to give a residue, which was purified by column chromatography to yield the cyclic ethers. In the case of **1**, the above procedure was followed with imidazole as base and with refluxing for 45 min to yield **6**.[13] Characterization data for **14**: $[\alpha]_D^{30}$ +31.2 (c 0.49, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.38 and 1.60 (br s, 10H), 4.25 (dd-like, $J = 1.8$, 7.6 Hz, 1H), 4.73–4.76 (m, 2H), 5.10 (d, $J = 2.0$ Hz, 1H), 5.21 (d, $J = 3.7$ Hz, 1H), 6.29 (d, $J = 3.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 23.6 (CH_2), 23.7 (CH_2), 24.7 (CH_2), 36.5 (CH_2), 37.4 (CH_2), 78.2 (CH), 78.3 (CH_2), 84.1 (CH), 87.5 (CH), 107.7 (CH), 114.4 (C); ESIMS, m/z: 235 $(M+Na)^+$. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.20; H, 7.55. For **15**: $[\alpha]_D^{30}$ +23.6 (c 0.49, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.33–1.89 (m, 13H), 2.13 (br d, $J = 14.0$ Hz, 1H), 3.34 (t-like, $J = 11.4$ Hz, 1H), 3.85–3.88 (m, 2H), 4.18 (s, 1H), 4.42 (d, $J = 3.5$ Hz, 1H), 5.91 (d, $J = 3.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.9 (CH_2), 23.5 (CH_2), 23.8 (CH_2), 24.0 (CH_2), 24.9 (CH_2), 35.5 (CH_2), 36.2 (CH_2), 66.4 (CH_2), 73.2 (CH), 78.8 (CH), 83.8 (CH), 104.7 (CH), 111.7 (C); ESIMS, m/z: 263 $(M+Na)^+$. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.80; H, 8.35. For **16**: $[\alpha]_D^{30}$ +9.8 (c 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 1.37 (m, 1H), 1.44 (m, 1H), 1.53–1.74 (m, 9H), 1.82 (t, $J = 6.6$ Hz, 2H), 2.27–2.30 (m, 1H), 2.95 (dd, $J = 3.6$, 9.0 Hz, 1H), 3.46–3.51 (m, 1H), 3.74–3.78 (m, 1H), 4.10 (d-like, $J = 9.0$ Hz, 1H), 4.63 (t, $J = 3.60$ Hz, 1H), 5.78 (d, $J = 3.60$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 23.5 (CH_2), 23.8 (CH_2), 24.1 (CH_2), 24.9 (CH_2), 28.8 (CH_2), 35.5 (CH_2), 35.6 (CH_2), 69.4 (CH_2), 72.7 (CH), 76.3 (CH), 82.2 (CH), 103.8 (CH), 113.9 (C); ESIMS, m/z: 263 $(M+Na)^+$. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.82; H, 8.20. For **17**: $[\alpha]_D^{30}$ +9.2 (c 0.49, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 1.34 (s, 3H), 1.41–1.45 (m, 1H), 1.53 (s, 3H), 1.83–1.86 (m, 2H), 3.27–3.32 (m, 2H), 3.69 (dt, $J = 4.8$, 10.2 Hz, 1H), 4.03–4.06 (m, 1H), 4.27 (t, $J = 4.2$, 9.6 Hz, 1H), 4.66 (t, $J = 3.6$ Hz, 1H), 5.83 (d, $J = 3.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 25.8 (CH_2), 26.0 (CH_3), 26.2 (CH_3), 48.2 (CH), 67.5 (CH_2), 70.7 (CH_2), 74.1 (CH), 79.9 (CH), 105.6 (CH), 112.2 (C); ESIMS, m/z: 223 $(M+Na)^+$. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.10; H, 7.95. For **18**: $[\alpha]_D^{30}$ −32.6 (c 0.46, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 3H), 1.49 (s, 3H), 3.56–3.69 (m, 3H), 3.87–3.98 (m, 2H), 4.15 (d, $J = 3.5$ Hz, 1H), 4.23 (dd, $J = 6.0$, 12.4 Hz, 1H), 4.53–4.57 (m, 2H), 5.96 (d, $J = 3.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 26.3 (CH_3), 26.9 (CH_3), 71.5 (CH_2), 73.6 (CH_2), 74.7 (CH_2), 80.9 (CH), 85.2 (CH), 87.6 (CH), 105.3 (CH), 111.5 (C); ESIMS, m/z: 239 $(M+Na)^+$. Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.38; H, 7.45. For **19**: $[\alpha]_D^{30}$ −44.3 (c 0.96, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.31 (s, 3H), 1.46 (s, 3H), 2.78 (dd, $J = 2.5$, 5.0 Hz, 1H), 2.93 (dd, $J = 3.8$, 4.7 Hz, 1H), 3.29–3.33 (m, 1H), 3.75 (dd, $J = 3.0$, 7.0 Hz, 1H), 4.08 (d, $J = 2.9$ Hz, 1H), 4.64 (d, $J = 3.2$ Hz, 1H), 4.65 (partially merged d, 1H), 4.73 (d, $J = 12.0$ Hz, 1H), 5.95 (d, $J = 3.5$ Hz, 1H), 7.25–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.6 (CH_3), 27.2 (CH_3), 47.3 (CH_2), 48.6 (CH), 72.7 (CH_2), 82.1 (CH), 82.5 (CH), 83.1 (CH), 105.8 (CH), 112.2 (C), 128.0 ($2 \times$ CH), 128.3 (CH), 128.9 ($2 \times$ CH), 137.8 (C); ESIMS, m/z: 315 $(M+Na)^+$. Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.58; H, 6.77. For **22**: $[\alpha]_D^{30}$ +6.3 (c 0.55, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.33 (s, 3H), 1.49 (s, 3H), 3.00 (dd, $J = 5.4$, 11.7 Hz, 1H), 3.17–3.37 (m, 2H), 3.53 (dd, $J = 5.7$, 13.6 Hz, 1H), 3.62 (d, $J = 4.4$ Hz, 1H), 3.79 (dd, $J = 5.6$, 11.3 Hz, 1H), 4.10 (d, $J = 3.8$ Hz, 1H), 4.52 (d, $J = 2.2$ Hz, 1H), 5.07–5.27 (m, 2H), 5.78–5.98 (m, merged with a d, $J = 3.2$ Hz, at δ 5.92, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 22.5 (CH), 26.6 (CH_3), 27.4 (CH_3), 57.5 (CH_2), 63.5 (CH_2), 72.2 (CH), 83.5 (CH), 92.2 (CH), 107.0 (CH), 112.0 (C), 117.7 (CH_2), 134.9 (CH); ESIMS, m/z: 374 $(M+Na)^+$. Anal. Calcd for $C_{12}H_{18}INO_3$: C, 41.04; H, 5.17; N, 3.99. Found: C, 40.86; H, 5.00; N, 3.80.
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17. Prepared via oxidation of the C-3 OH of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, Wittig reaction with $Ph_3P{=}CHCO_2Et$, selective removal of the 5,6-acetonide, vicinal diol cleavage and stereocontrolled reduction[26] of the double bond along with the aldehyde group with $LiAlH_4$.
18. Reduction in the yield of **18** is due to the parallel dehydroiodination of the intermediate iodide to form the 3-*O*-vinyl product (60%) [^1H NMR ($CDCl_3$, 300 MHz): δ 1.33 (s, 3H), 1.52 (s, 3H), 3.82–3.96 (m, 3H), 4.18–4.20 (m, 1H), 4.38–4.42 (m, 2H), 4.60 (d, $J = 3.6$ Hz, 1H), 5.94 (d, $J = 3.3$ Hz, 1H), 6.37 (dd, $J = 7.0$, 14.0 Hz, 1H)].
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