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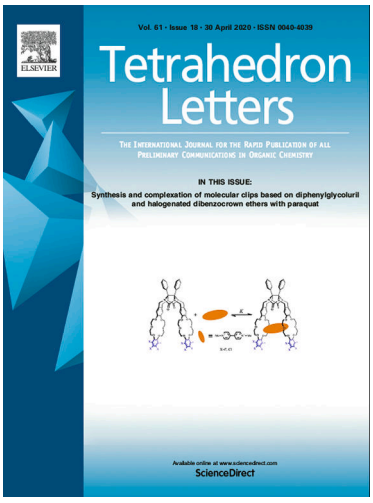


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# Dienaminodiones, new push-pull alkenes, from 3,4-dihydroxysalicylaldehyde-derived Schiff base

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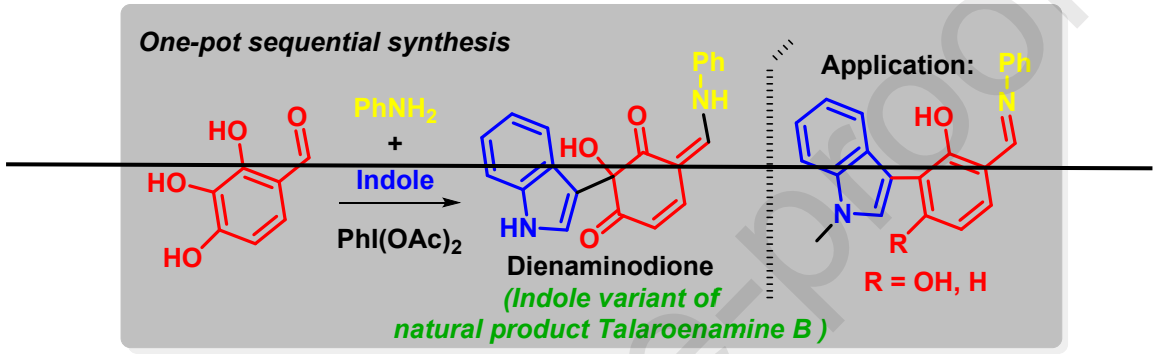
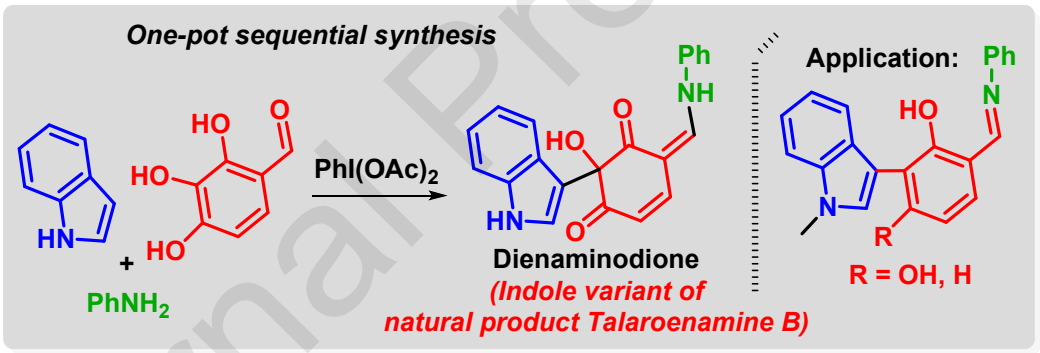



**Abstract:**

An atom-economical one-pot synthesis of a new push-pull dienaminodiones from a 3,4-dihydroxysalicylaldehyde-derived Schiff base and indoles in the presence of phenyliodine(III) diacetate is described. Variation of indoles and anilines constitute a broad substrate scope of the methodology with good to moderate yields. Formation of Schiff base followed by an indole addition to afford dienaminodione takes place in one-pot; thus, the present method serves as a sequential multicomponent reaction. The present work also serves as a methodology to afford indole variants of natural product talaroenamine B.

**Keywords:** Dienaminone • Push-pull effect • One-pot synthesis • Talaroenamine ~~analogs~~ • Oxidative transformation • *N*-salicylideneaniline Schiff base

**Introduction:**

The push-pull effect in alkenes flanked by electron-donating and electron-accepting substituents at either end of alkene constitute a conjugated system that enhances the polarity of C=C double bond, thus, has a decisive influence on the chemical reactivity of this class of compounds.[1] For instance, the push-pull effect in the β-enaminone conjugated system, which possesses a combined reactivity of enamine and enone, qualifies enaminones as suitable precursors in the synthesis of heterocycles.[2–4] Conjugated dienaminones are valuable intermediates for the synthesis of derivatives of pyridines,[5,6] azepinones,[7] by heteroannulation. Nair *et al.* synthesized a range of dienaminones from the reaction of vinamidinium salts with enolates,[8,9] and applied for the synthesis of spiro compounds.[10]

In one of the tautomeric form, *N*-salicylideneaniline Schiff base from salicylaldehyde exist as enaminone that equilibrates with enolimine tautomeric forms by proton transfer.[11] The enaminone form of Schiff base **I′** (Scheme 2), derived from 3,4-dihydroxysalicylaldehyde (3,4-DSA) and aniline, offers a unique 1,2-enediol segment that can participate in phenyliodine(III) diacetate (PIDA) mediated oxidative transformation. Herein, we report a one-pot sequential three-component condensation by PIDA mediated activation of highly stable Schiff base **1**~~,~~ and ~~subsequent treatment with~~ 1*H*-indole to afford~~ed~~ **2**, christened as dienaminodione (Scheme 1). A sequential one-pot multicomponent synthesis emerged as an excellent synthetic strategy with several reports in this area.[12–21] Dienaminodione **2** in *E*,*Z*-cyclic form, is an unprecedented variant of dienaminone. Besides synthetic potential, the enaminone motif serves as a therapeutic pharmacophore and provides a range of biological activities such as antitumor, antibacterial, and anticonvulsant agents.[22–25] Dienaminodione **2** bears a striking resemblance to the natural product talaroenamine B (Scheme 1).[26] Hence, the present work also serves as a methodology to generate talaroenamine analogs.

**Results and Discussion:**

In a first attempt, *N*-salicylideneaniline Schiff base **1** was generated in acetonitrile in a catalytic amount of acetic acid (Scheme 1). After concentration, the resulting imine in dichloromethane was sequentially added 1.5 equivalent each of *N*-methylindole and PIDA. In less than five minutes, a new polar product was observed over TLC, which was purified and characterized by 2D NMR analysis (see the Supporting Information) as dienaminodione **2** (Scheme 1). To generalize the use of this methodology for expedient access to dienaminodiones, optimization was attempted with 1*H*-indole in one-pot (Table 1). Schiff base

**1** can be generated in quantitative yield as a precipitate by condensation in water. Accordingly, in an initial attempt, Schiff base **1** precipitate obtained in water was decanted and dissolved in hexafluoroisopropanol (HFIP), followed by an addition of one equivalent each of 1*H*-indole and PIDA afforded dienaminodione **3a** in 52% yield (entry 1). The structure of dienaminodione **3a** was confirmed by single-crystal X-ray analysis (see the Supporting Information), which aided confirmation of the assigned structure of dienaminodione **2**. In a second attempt by variation of solvent to methanol, dienaminodione **3a** was produced with improved yield of 69% (entry 2). Variation of solvent combinations did not improve the yield of **3a** (entries 3-4). There was no improvement in yields by change of other iodine-based oxidants viz. ~~PIFA~~ $PhI(OCOCF_3)_2$, $I_2$, and ~~NIS~~ *N*-iodosuccinimide (entries 5-7). Attempts with a variation of other oxidants such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), ceric ammonium nitrate (CAN), *meta*-chloroperoxybenzoic acid (mCPBA)/PhI, and $K_2S_2O_8$/PhI did not afford dienaminodione **3a**. In all the successful attempts, *vide supra*, there is some unreacted 1*H*-indole; however, for the sake of atom-economy substrate scope was demonstrated with one equivalent each of 2,3,4-trihydroxybenzaldehyde, substituted anilines, and 1*H*-indoles in one-pot (Table 2).

**Scheme 1.** Synthesis of dienaminodione **2**

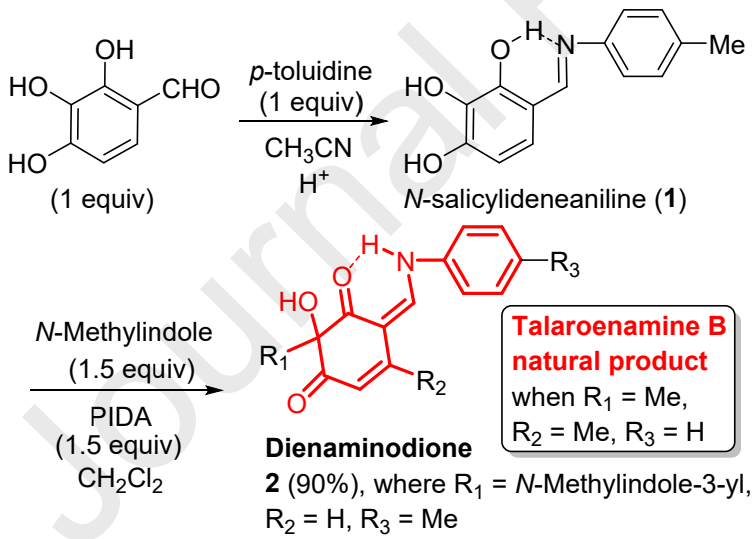
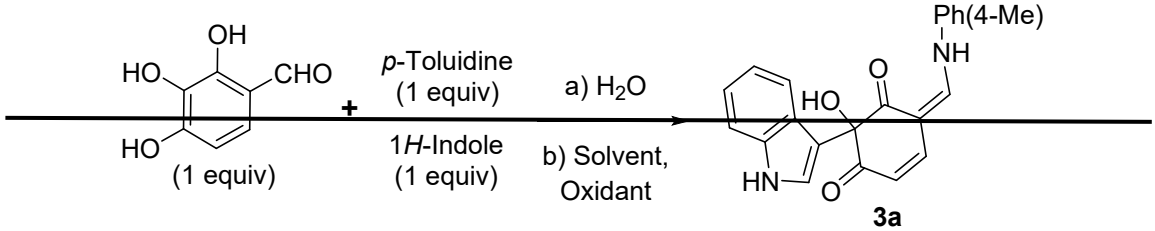
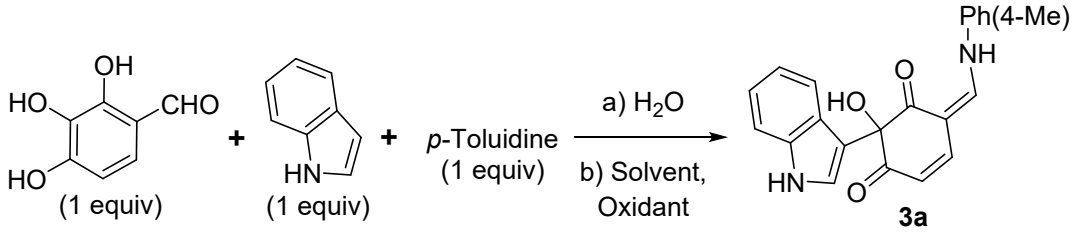



**Table 1.** Optimization of reaction conditions[a]






| entry | Oxidant (1 equiv) | Solvent | **3a**[b] (%, two steps) |
|---|---|---|---|
| 1 | PIDA | HFIP | 52 |
| 2 | PIDA | MeOH | 69 |
| 3 | PIDA | HFIP/DCM(1:1) | 43 |
| 4 | PIDA | MeOH/$H_2O$(9:1) | 27 |
| 5 | PIFA | MeOH | 11 |
| 6 | $I_2$ | MeOH | 18 |
| 7 | NIS | DCM | 11 |

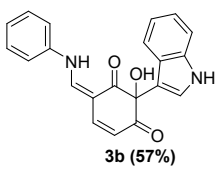
[a]Reaction conditions: All reactions were conducted at room temperature using undistilled solvents. 2,3,4-Trihydroxybenzaldehyde (0.39 mmol) and *p*-toluidine (0.39 mmol) are condensed in water (2 mL) to obtain a precipitate of *N*-salicylideneaniline **1**. Water was decanted, the precipitate was dissolved in a suitable solvent (2 mL) followed by sequential addition of 1*H*-indole (0.39 mmol) followed by PIDA (0.39 mmol). [b]Isolated yields (%) by column chromatography.

Under the optimized conditions (entry 2, Table 1), Schiff bases derived from 2,3,4-trihydroxybenzaldehyde and aniline, para-substituted anilines with activating groups (alkyl, methoxy) afforded dienaminodiones **3b-e** in 51-62% yields. Schiff bases with para-halo-substituted anilines containing deactivating groups such as halides afforded dienaminodiones **3f-h** in 46-60% yields. The presence of an activating or deactivating group in the para-position of anilines does not have a significant bias in the yields of dienaminodione outcome. Attempts with ortho-substituted anilines also afforded dienaminodiones **3i-k** in moderate yields. Di-substituted anilines with activating or deactivating groups also produced dienaminodiones **3l-p** in similar yields. An attempt of variation in 1*H*-indole with 2-methyl-1*H*-indole, led to a decreased yield of dienaminodione **3q** to 37%. Attempts with 1*H*-indoles of varied substitutions also afforded dienaminodiones **3r-v** in moderate yields. Reaction with substituted *N*-methylindoles produced dienaminodiones **3w** and **3x** in 69% and 62% yields, respectively. Finally, reaction with *N*-methylpyrrole provided dienaminodione **3y** in 58% yield. Hence, the

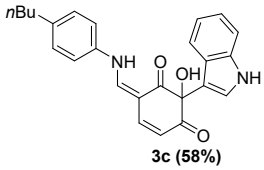
present work offers a broad substrate scope with a variation of anilines and indoles to produce dienaminodiones.

The plausible mechanistic pathway for the formation of dienaminodione **3** is provided in scheme-2. *N*-salicylideneaniline derived from 2,3,4-trihydroxybenzaldehyde and aniline exist in enolimine **I** (OH form) and enaminone **I′** (NH form) tautomeric forms.[11] Activation of enaminone **I′** with PIDA afford enol **II** or keto **II′** intermediates. Stronger acidity of 4-hydroxy group is credited with enhanced nucleophilic power, directing iodination with $PhI(OAc)_2$ to afford **II** or **II′**.[27] Elimination of phenyl iodide from **II** affords vicinal tricarbonyl **III**, with high electrophilic reactivity at the central carbonyl group,[28] which ensue 1*H*-indole addition to generate dienaminodione **3**. Alternatively, 1*H*-indole addition to keto **II′** intermediate and subsequent elimination of phenyl iodide affords **3**. Treatment of *N*-salicylideneaniline **1** with $NaBH_4$ in methanol provided the respective 2,3,4-trihydroxybenzaldehyde and aniline. Treatment of *N*-salicylideneaniline **1** with PIDA clearly showed the formation of a polar intermediate in TLC, but it was difficult to discern its structure by NMR; however, subsequent 1*H*-indole addition to the polar intermediate generated dienaminodione **3**. Treatment of polar intermediate with $NaBH_4$ in methanol afforded the respective 2,3,4-trihydroxybenzaldehyde and aniline, perhaps via *N*-salicylideneaniline. These control experiments suggest intermediacy of vicinal tricarbonyl **III** as the polar intermediate, further supported by reports on the addition of reactive aromatics such as indoles to ninhydrin, a vicinal tricarbonyl.[29] Unfortunately, attempts made with methylmagnesium bromide in place of 1*H*-indole to access natural product talaroenamine itself was futile.

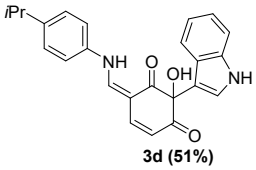
**Table 2.** Substrate scope of dienaminodiones **3**[a]



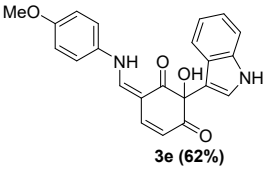

**3b (57%)**



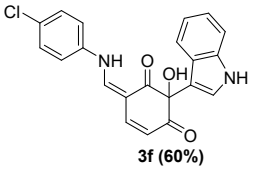

**3c (58%)**



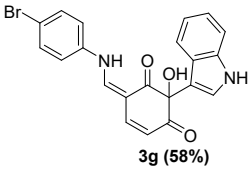

**3d (51%)**



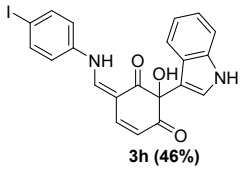

**3e (62%)**



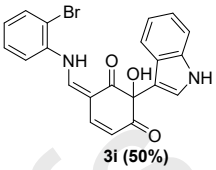

**3f (60%)**



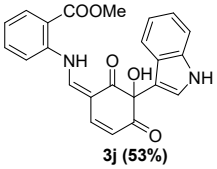

**3g (58%)**



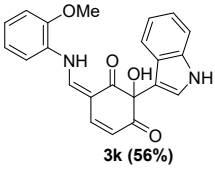

**3h (46%)**



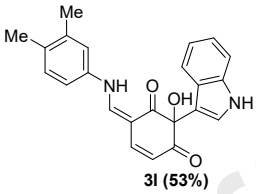

**3i (50%)**



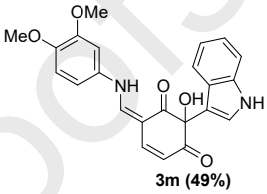

**3j (53%)**



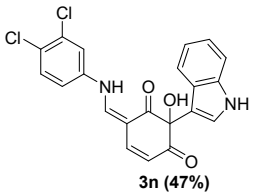

**3k (56%)**



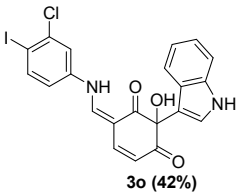

**3l (53%)**



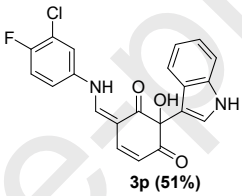

**3m (49%)**



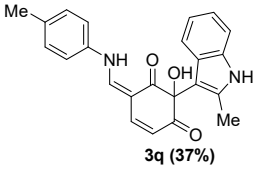

**3n (47%)**



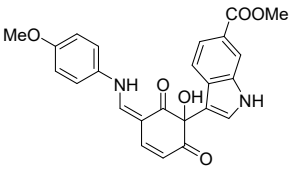

**3o (42%)**



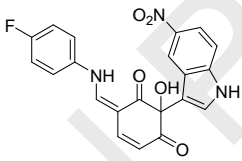

**3p (51%)**



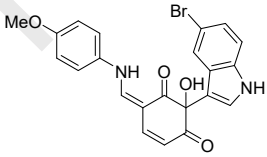

**3q (37%)**



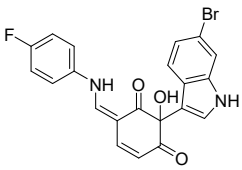

**3r (59%)**



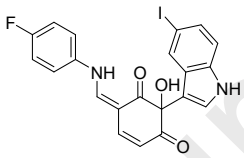

**3s (53%)**



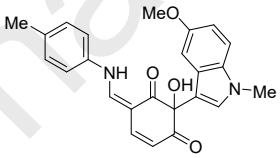

**3t (63%)**



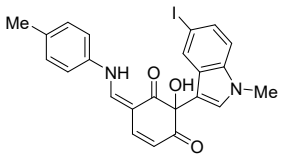

**3u (62%)**



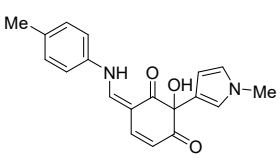

**3v (60%)**




**3w (69%)**



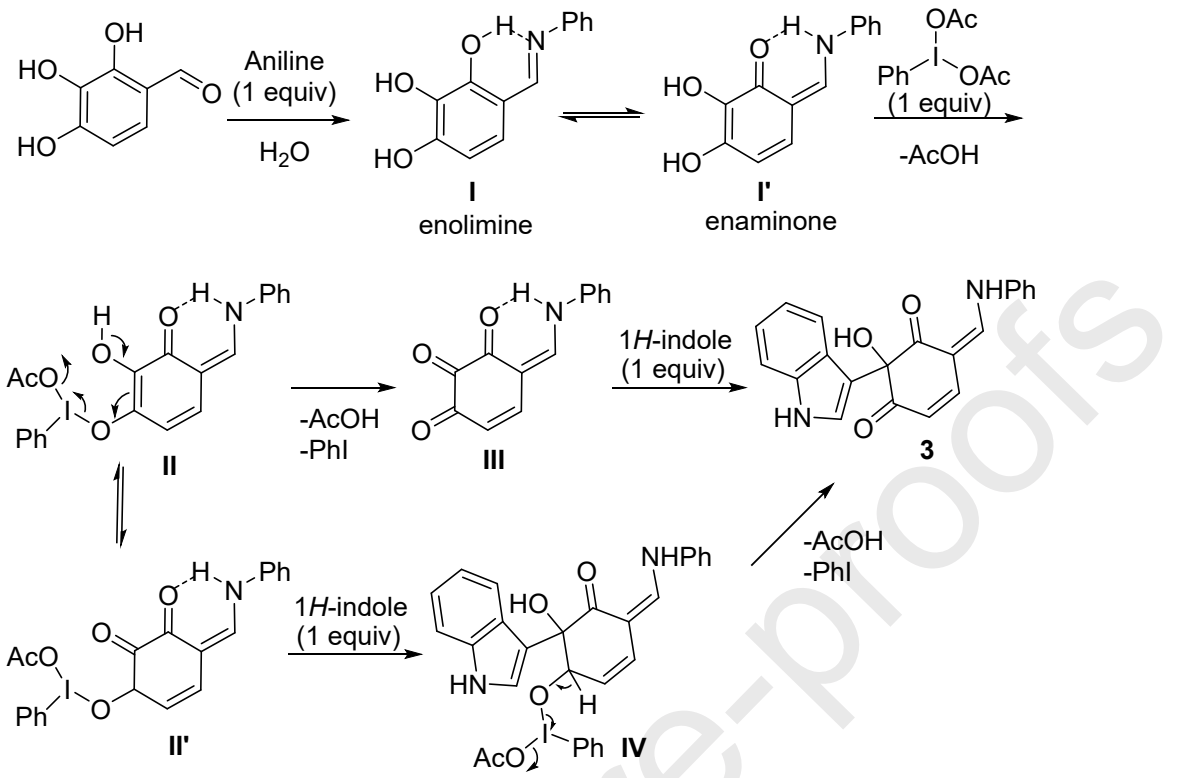

**3x (62%)**




**3y (58%)**

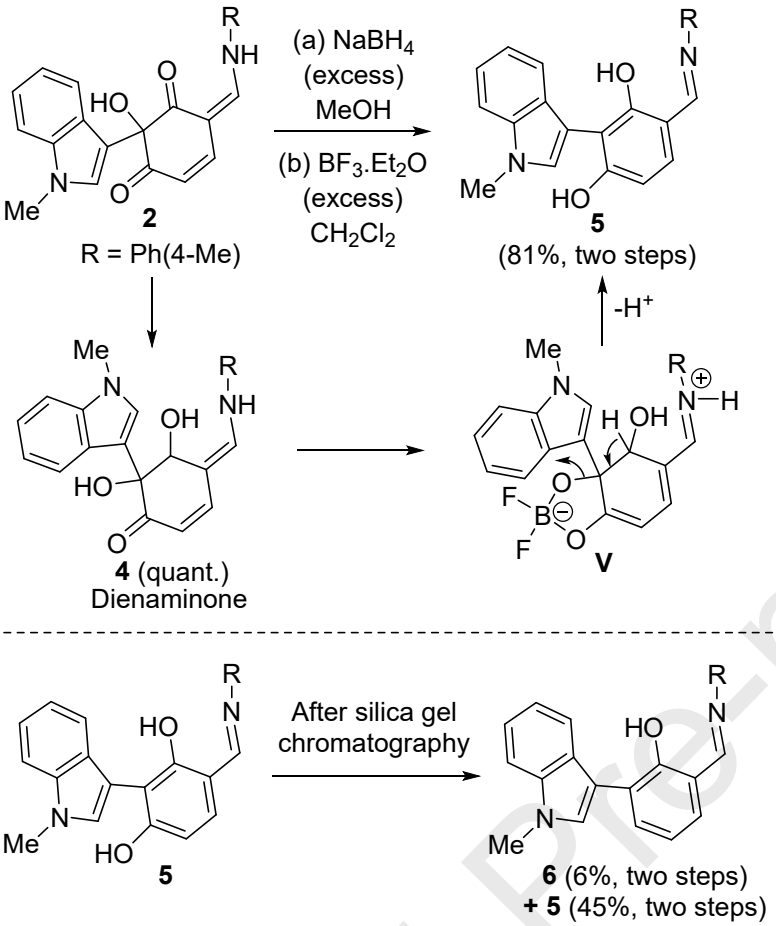
[a]Isolated yields (%) by column chromatography.

**Scheme 2.** Plausible mechanistic pathway for the formation of dienaminodione




In an attempt to demonstrate the synthetic utility of dienaminodione **2**, treatment with $NaBH_4$ led to 1,2-reduction product **4** in quantitative yield (Scheme 3), confirmed by 2D NMR analysis (see the Supporting Information). Further treatment of dienaminone **4** with a Lewis acid such as $BF_3.Et_2O$, led to aromatization to afford imine **5** in 81% over two steps. Structural confirmation of imine **5** was carried out by 2D NMR analysis (see the Supporting Information). As observed over TLC, dienaminodione **2** is polar than dienaminone **4**, which in turn is polar than imine **5**. The polarity of dienaminodione **2** is attributed to the push-pull effect. Though the imine **5** was obtained in pure form without purification, as evident from TLC and NMR, an attempt to pass it through silica gel column chromatography led to the partial formation of a non-polar product along with imine **5**. Structural characterization of this non-polar product by 2D NMR analysis (see the Supporting Information), surprisingly, confirmed an unusual loss of C3-OH of imine **5** to obtain imine **6**. The plausible mechanistic pathway of formal reduction to imine **6** during contact of imine **5** with silica gel is depicted in scheme-S1 (see the Supporting Information), which warrants a detailed mechanistic investigation in an independent study. Dienaminodione **3a** was also subjected to the same series of reaction conditions (Scheme 3); however, the obtained imines exhibited a complex NMR.

**Scheme 3.** Synthetic utility of dienaminodione **2**




## Conclusions

In conclusion, an unprecedented synthesis of polyfunctional dienaminodione **2** paves the way for further diversification and warrants its utility in synthesis and biological activity. The present methodology was superior in the generation of dienaminodiones with indoles and related nucleophilic heteroaromatics, demonstrated with *N*-methylpyrrole. Though attempts with alkyl/phenyl Grignard reagents failed in this method, triumph with indoles makes the methodology essential owing to the significance of indoles in medicinal chemistry. Hence, exploring the biological potential of the library of the dienaminodiones will be pursued. The synthetic transformation of dienaminodione **2** to imine **5** opens a new avenue in nucleophilic aromatic substitution of a polyhydroxy system by PIDA mediated oxidative transformations of Schiff bases.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Acknowledgements**

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**Appendix A. Supplementary data**

Supplementary data to this article can be found online.

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**Highlights:**

- Atom-economical one-pot synthesis of new push-pull dienaminodiones by a sequential multicomponent reaction
- Broad substrate scope of the methodology by variation of indoles and anilines
- The present work also serves as a methodology to afford indole variants of natural product talaroenamine B.

**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.