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# Serendipitous Formation of 2*H*-Pyrazolo[3,4-*d*]pyridazin-7(6*H*)-ones from 3-Arylsydnones

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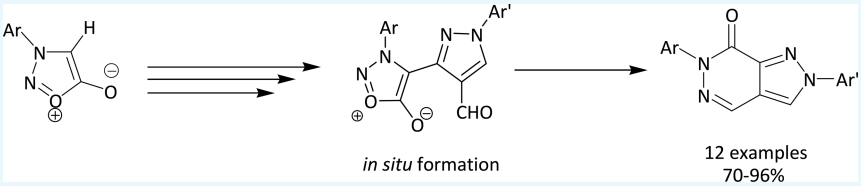
Supporting Information




**ABSTRACT:** Fused nitrogen heterocyclesnamely, pyrazolo[3,4-*d*]pyridazin-7(6*H*)-ones have been obtained by exploiting the 1,3-dipolar nature of *N*-arylsydnones, from hydrazones of 3-aryl-4-acetylsydnones *via* the Vilsmeier−Haack strategy. Facile intramolecular nucleophilic addition followed by $CO_2$ elimination under reflux or upon microwave irradiation was presented. Plausible mechanisms for the formation of the title compounds are proffered. Structure confirmatory evidence came from single-crystal X-ray crystallography.

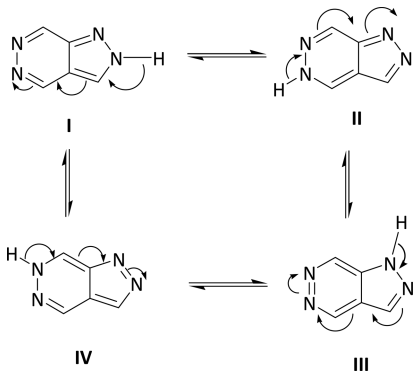
## INTRODUCTION

Mesoionic compounds are the five-membered heterocycles that cannot be represented by either a polar or covalent structure. Sydnones are the class of compounds that are mesoionic comprising nitrogen and oxygen atoms in the ring.[1−3] These are used as useful synthons in various reactions, particularly in 1,3-dipolar cycloaddition to yield a variety of nitrogen heterocycles. Huisgen and co-workers in 1962 reported a pioneering work of formation of pyrazoles by thermal 1,3-dipolar cycloaddition between sydnones as dipoles and alkynes as dipolarophiles. These may be considered as 1,3-dipoles that upon photolysis, yield nitrile imine intermediates or in the thermal reactions, act as cyclic azomethine imines. With acetylenic dipolarophiles, they undergo such cycloaddition reaction under thermal[4,5] or photochemical conditions[6−8] to yield pyrazole and/or pyrazolines. 3,4-Disubstituted sydnones upon photochemical reaction yield fused pyrazole derivatives.[9] Sydnone can also undergo transformations and delivers pyrazole via a [4 + 2] cycloaddition−retrocycloaddition with the expulsion of carbon dioxide. Nonsymmetrical alkynes resulted in the formation of two pyrazole products, with less or negligible regioselectivity.[10] A proper insight about the reactivity and recent advances of the popular mesoionic compound, namely, *N*-arylsydnone, has been extensively reviewed. Two recent reviews discuss the strategies involved in the sydnone−alkyne cycloaddition[12] and also their synthetic applications.[13]

More than a century has passed since $\alpha$-diazo derivatives of pyrazole have been discovered, but the five-membered heterocycle, pyrazole, has continued to be a star molecule because of its great interest in various fields.[14] Pyrazole and their derivatives possess a wide range of bioactivities.[15−21] Pyridazine and their analogues were thought worthwhile to study because they are available as a number of marketed drugs such as Hydralazine,[22] Minaprine,[23] and Cefozopran.[24] It has also been reported that pyridazine derivatives display anticancer,[25] anti-HIV,[26] antihypertensive,[27] antimicrobial, and antifungal activities.[28−30]

The combination of two pharmacophores into a single molecule is an established methodology for obtaining a potent molecule. Consequently, a design of efficient methods for the assembly of these fused nitrogen heterocycles is of

**Scheme 1. Tautomeric Structures of Pyrazolo[3,4-*d*]pyridazine**

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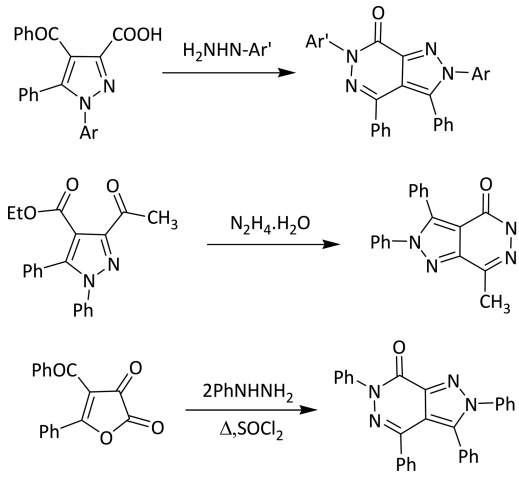
considerable interest, and many such approaches have been discussed in the literature. A useful method for the preparation of pyrazole and pyrazolopyridazine derivatives is the nucleophilic addition of hydrazines to 4-acyl-furandiones in boiling benzene.[31] Pyrazolopyridazine/ones have been obtained by various methods, that is, (i) pyrazole-3-carboxylic acid with 2,5-dichlorophenylhydrazine (**4**),[32] (ii) 1-phenyl-4-(2-thienylcarbonyl)-pyrazole-3-carboxylate (**5**),[33] and (iii) 4-benzoyl-5-phenyl-2,3-dihydro-2,3-furandione (**6**)[34] (Scheme 2). Three position isomers have been reported by different

**Scheme 2. Previous Reported Synthesis of Pyrazolopyridazines/ones (Yield = <70%)**




methods of synthesis such as pyrazolo[1,2-*a*]pyridazine-5,8-diones, pyrazolo[3,4-*d*]pyridazinones, and pyrazolo[4,3-*c*]-pyridazines.[35] One of the isomers, namely, pyrazolo[3,4-*d*]pyridazines, exhibits four tautomeric structures as shown in Scheme 1.

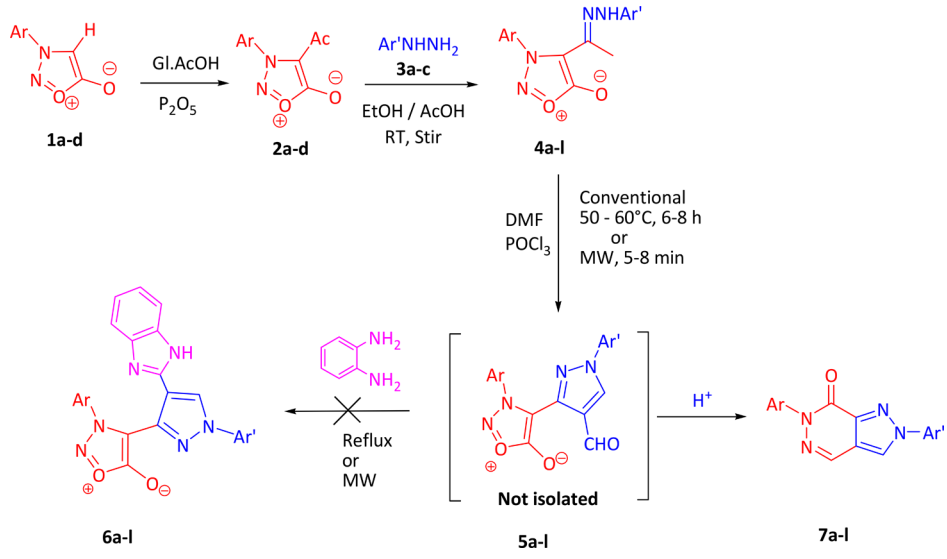
Several derivatives of pyrazolopyridazines exhibit potential activities such as antifungal,[36] antibacterial,[37] anti-inflammatory, analgesic, antihypoxic, antipyretic agents,[38] and antimicrobial actions.[39] Also, some pyrazolopyridazine derivatives are reported to be inhibitors of cyclin-dependent kinase 1 (CDK1),[40] phosphodiesterase 4 (PDE4) inhibitors, which are widely used in therapeutic treatment of inflammatory and immune disorders,[41] including glycogen synthase kinase 3 (GSK-3) inhibitors.[42]

During the course of our studies directed toward the design and synthesis of heterocycles employing a ring transformation of sydnones, we have recently reported the newer heterocyclic scaffolds using 3-arylsydnones **1a–d** as synthons.[43−47] We, herein, report the serendipitous formation of pyrazolo[3,4-*d*]pyridazin-7(6*H*)-ones (**7a–l**) from hydrazone of 3-aryl-4-acetylsydnones **2a–d** by intramolecular nucleophilic addition–elimination. The synthetic route for the synthesized compounds is outlined in Scheme 3.

## RESULTS AND DISCUSSION

Initially, our aim was cyclization of hydrazones **4a–l** by the Vilsmeier–Haack reaction to 3-(3-arylsydnon-4-yl)-1-aryl-1*H*-pyrazole-4-carbaldehydes **5a–l**, which was further planned to convert into benzimidazole derivatives **6a–l** by condensing with *o*-phenylenediamines. However, we did not get the expected aldehydes **5a–l** but ended up with an unexpected product. For example, when a hydrazone **4a** was reacted with DMF and $POCl_3$ at 50–60 °C, the product upon mass spectral analysis exhibited a molecular ion peak at 288 (*m*/*z*) instead of 332 (*m*/*z*), which is expected for a benzimidazole derivative **6a**. We analyzed the product for the possible structure by spectral analyses (IR, $^1$H and $^{13}$C NMR, GC–MS) as well as by single-crystal X-ray studies and were successful in establishing the structure of the compound as **7a**. The unusual reaction of forming fused ring, namely, pyrazolo[3,4-*d*]-pyridazin-7(6*H*)-ones **7a–l** via the Vilsmeier–Haack reagent,

**Scheme 3. Synthetic Route for Title Compounds 7a–l**[a]




[a]**7a**: Ar = $-C_6H_5$, Ar′ = $-C_6H_5$; **7b**: Ar = $-C_6H_5$, Ar′ = 4-Cl$-C_6H_4$; **7c**: Ar = $-C_6H_5$, Ar′ = 4-Br$-C_6H_4$; **7d**: Ar = 4-$CH_3O-C_6H_4$, Ar′ = $-C_6H_5$; **7e**: Ar = 4-$CH_3O-C_6H_4$, Ar′ = 4-Cl$-C_6H_4$; **7f**: Ar = 4-$CH_3O-C_6H_4$, Ar′ = 4-Br$-C_6H_4$; **7g**: Ar = 4-Cl$-C_6H_4$, Ar′ = $-C_6H_5$; **7h**: Ar = 4-Cl-$C_6H_4$, Ar′ = 4-Cl$-C_6H_4$; **7i**: Ar = 4-Cl$-C_6H_4$, Ar′ = 4-Br$-C_6H_4$; **7j**: Ar = 4-$H_3C-C_6H_4$, Ar′ = $-C_6H_5$; **7k**: Ar = 4-$H_3C-C_6H_4$, Ar′ = 4-Cl$-C_6H_4$; **7l**: Ar = 4-$H_3C-C_6H_4$, Ar′ = 4-Br$-C_6H_4$.



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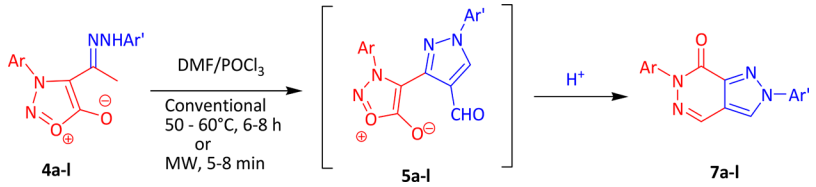
**Table 1. Synthesis of Fused Pyrazolopyridazin-7-ones (7a–l) from Hydrazones (3a–c) and DMF/$POCl_3$ under Optimized Conditions**




| | | | thermal | | microwave | |
|---|---|---|---|---|---|---|
| product | Ar **3(a–d)** | Ar′ **4(a–c)** | time (h) | yield[a] (%) | time (min) | yield[a] (%) |
| **7a** | $-C_6H_5$ | $-C_6H_5$ | 5 | 74 | 5 | 90 |
| **7b** | $-C_6H_5$ | $-4ClC_6H_4$ | 5 | 76 | 5 | 94 |
| **7c** | $-C_6H_5$ | $-4BrC_6H_4$ | 6 | 70 | 5 | 92 |
| **7d** | $4-CH_3OC_6H_4$ | $-C_6H_5$ | 6 | 74 | 7 | 95 |
| **7e** | $4-CH_3OC_6H_4$ | $-4ClC_6H_4$ | 5 | 72 | 7 | 95 |
| **7f** | $4-CH_3OC_6H_4$ | $-4BrC_6H_4$ | 5 | 70 | 7 | 95 |
| **7g** | $-4ClC_6H_4$ | $-C_6H_5$ | 7 | 73 | 6 | 96 |
| **7h** | $-4ClC_6H_4$ | $-4ClC_6H_4$ | 7 | 75 | 6 | 92 |
| **7i** | $-4ClC_6H_4$ | $-4BrC_6H_4$ | 8 | 71 | 6 | 95 |
| **7j** | $4-CH_3C_6H_4$ | $-C_6H_5$ | 6 | 70 | 8 | 91 |
| **7k** | $4-CH_3C_6H_4$ | $-4ClC_6H_4$ | 6 | 71 | 8 | 94 |
| **7l** | $4-CH_3C_6H_4$ | $-4BrC_6H_4$ | 7 | 73 | 8 | 96 |

[a]Isolated yield.

and an optimized condition under both conventional and microwave irradiation were established. This occurred by elimination of $CO_2$ and water via acid-catalyzed intramolecular nucleophilic addition–elimination in 3-aryl-4[(1-aryl-4-formyl-pyrazol-3-yl)]-sydnones **5a–l**, which was not isolated.

The reaction mixture was irradiated by microwave irradiation for 150 W at 120 °C. Interestingly, we observed the completion of the reaction within 5–8 min with excellent yields (94–96%) for all the title compounds **7a–l** (Table 1). Compared to conventional (6–7 h), microwave irradiation greatly reduced the reaction time from 6–7 h to 5–8 min. The yield of the product was also increased up to 94%. This report for pyrazolopyridazin-7-one analogues **7a–l** is more advantageous than other reported methods[32−34] as the synthetic method includes the shorter reaction time, easy workup, and excellent yields by using DMF/$POCl_3$ as a solvent. The proposed mechanism of conversion of hydrazone of 4-acetyl-3-arylsydnones **4a–l** to pyrazolo[3,4-*d*]pyridazin-7(6*H*)-ones **7a–l** is presented in Scheme 4. It is also interesting to note that 3-aryl-4-substituted sydnones have been used for ring transformation into various heterocycles.[11] This is the first protocol being reported for the ring transformation of hydrazone of 4-acetyl-3-arylsydnones **4a–l** upon the Vilsmeier–Haack reaction to ring transform into pyrazolo[3,4-*d*]pyridazin-7(6*H*)-ones **7a–l** directly in excellent yields.

The reaction followed a simple concerted mechanism. The mechanism of transformation of hydrazone of 3-arylsydnones **1a–d** to pyrazolo[3,4-*d*]pyridazin-7(6*H*)-ones (**7a–l**) occurred in three steps. In the first step, the Vilsmeier–Haack reagent **I** is formed *in situ* by the reaction of $POCl_3$ and DMF. This attacks on $CH_2$ of tautomer **II** to form intermediate **III** in step 2. Intermediate **III** undergoes elimination of HCl to form intermediate **IV**, which further undergoes removal of dimethyl amine followed by the attack of the Vilsmeier–Haack reagent **I** once again, which forms an aldehyde **5a–l** that was not possible to isolate. The reaction continued further as in the third step of Scheme 3 as intramolecular acid-catalyzed nucleophilic addition–elimination, which occurs through a protonated carbonyl group of aldehyde on pyrazole **VIII**. This is followed by elimination of $CO_2$ (cycloreversion) and water molecule from **IX** that gave the final compound **7a–l**.

The structures of pyrazolo[3,4-*d*]pyridazin-7(6*H*)-ones **7a–l** were confirmed by spectroscopic techniques, namely, IR, $^1H$ and $^{13}C$ NMR, GC–MS, single-crystal X-ray structure studies, and elemental analyses. The compounds have shown a strong adsorption band for carbonyl of pyridazinone and C=N of pyrazole ring at 1630–1679 and 1528–1609 $cm^{-1}$, respectively. In the case of $^1H$ NMR spectral analyses, the compounds exhibited a singlet in the range 9.94–10.06 ppm for pyridazin-7-one ($C_3$–H) ring and pyrazole ($C_4$–H) at 8.42–9.72 ppm. The aromatic protons of all phenyl rings appeared as multiplets in the range 7.36–7.70 ppm. In the case of $^{13}C$ NMR spectral study, compounds have shown the number of signals, which are consistent with number of magnetically nonequivalent carbon atoms in the compound, and in mass spectra, the synthesized compounds have shown the molecular ion peaks at their respective *m*/*z* values.

The crystalline nature of the compound is characterized by long range well-defined three-dimensional orders. An ORTEP view of the compound **7d** is presented in Figure 1. The crystal data and refinements are presented in Table S1 in Supporting Information. The X-ray structure clearly suggested that compound **7d** crystallized as a triclinic system.

## CONCLUSIONS

In summary, we have successfully established a fused ring for the first time from the sydnone in which the acid catalyzed intramolecular nucleophilic addition–elimination reaction provides an efficient means for the preparation of novel fused 2,6-diaryl-2*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-ones **7a–l** under a microwave-assisted condition in good yields. Formation of cyclized products along with formylation and intramolecular nucleophilic addition followed by an elimination sequence of reactions was presented. The other features



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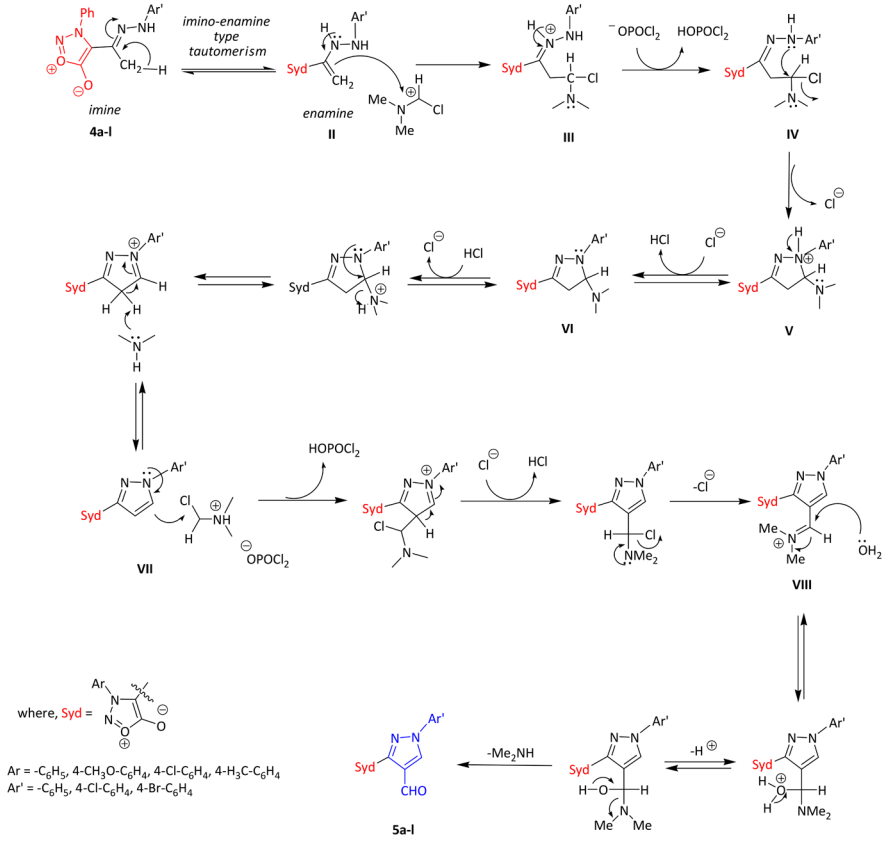
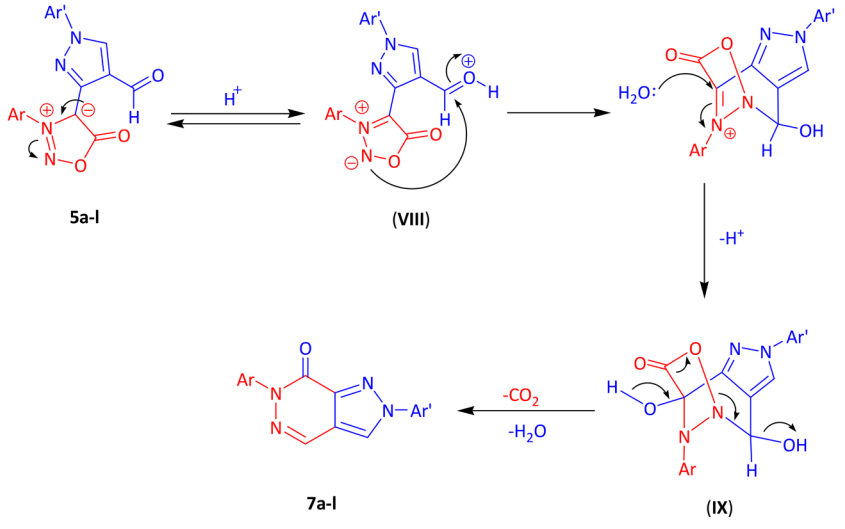
**Scheme 4. Plausible Mechanism for Formation of Pyrazolo[3,4-*d*]pyridazin-7(6*H*)-ones 7a−l**

**Step 1**: Formation of cyclized product along with formylation from *Vilsmeier-Haack* reagent (*chloriminium cation*)




**Step 2**: Acid-catalyzed intramolecular nucleophilic addition-elimination reaction




of this protocol include mild conditions, short reaction time, and easy workup.

## EXPERIMENTAL SECTION

**General Information.** All the reagents and chemicals were purchased from Spectrochem and Sigma-Aldrich. Melting points were measured in open capillaries and are uncorrected. The IR spectra were recorded by a Nicolet Impact 410 FTIR spectrometer using KBr pellets (range 4000−500 $cm^{-1}$). The $^{1}H$ NMR spectra were recorded at 400 MHz on a Bruker Avance FT NMR spectrometer in DMSO-$d_6$ solvent with tetramethylsilane (TMS) as internal standard. $^{13}C$ NMR spectra were recorded at 100 MHz on a Bruker Avance FT NMR spectrometer in DMSO-$d_6$ solvent with TMS as internal standard. The mass spectra were recorded on Shimadzu GC−MS operating at 70 eV. Thin-layer chromatography (TLC) was



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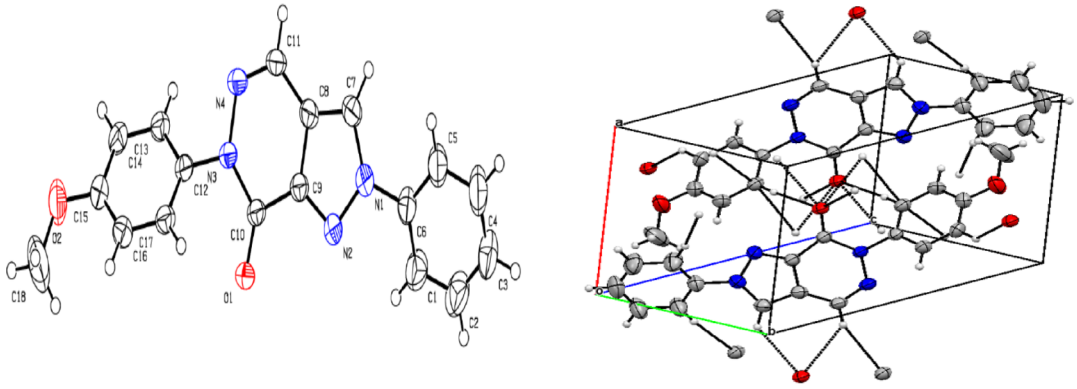


**Figure 1.** ORTEP structure of compound **7d** (displacement ellipsoids are drawn at the 50% probability level) and packing structure of compound **7d**.

performed on 0.20 mm Aluchrosep silica gel 60 F254 plates (SD Fine, Mumbai). Synthesis by microwave irradiation was carried out using a CEM Discover microwave synthesizer equipped with an IR sensor to monitor reaction temperatures.[48]

**Procedure for the Synthesis of 4-Acetyl-3-arylsydnones (2a−d).**[49] To a suspension of 5.20 g (0.0369 mol) of phosphorous pentoxide in dry xylene (20 mL) was added 2.00 g (0.0123 mol) of 3-arylsydnones **1a−d** in a two-necked RB flask equipped with a reflux condenser with a calcium chloride drying tube. The stirred mixture was heated to reflux on a water bath. Glacial acetic acid of about 0.80 mL (0.0123 mol) was added dropwise, and the reaction mixture was refluxed for 6 h during which the resultant clear brown solution turned black. After completion of the reaction, the reaction mixture was cooled to room temperature. Xylene was then decanted, and the remaining black residue was extracted twice with xylene (2 × 10 mL). Combined washings and decanted xylene were evaporated to obtain a pale yellow solid and recrystallized using ethanol to obtain pure compounds (**2a−d**).

**Procedure for the Synthesis of 1-(3-Arylsydnon-4-yl)ethylidene)-2-phenylhydrazines (4a−l).**[49] 4-Acetyl-3-arylsydnones **2a−d** (1.0 g, 0.005 mol) were dissolved in ethanol (10 mL), and about 3−4 drops of acetic acid were added. Aryl hydrazines **3a−c** (0.50 mL, 0.0049 mol) were then added, and the reaction mixture was refluxed for 2 h. The progress of the reaction was monitored by TLC, and after completion of the reaction, the separated solid was filtered, dried, and recrystallized from ethanol to obtain the compounds **4a−l**.

**Procedure for the Synthesis of 2,6-Diaryl-2*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-ones (7a−l).** DMF (1.16 mL, 0.015 mmol) in an RB flask was cooled to 0 °C, and $POCl_3$ (3.92 mL, 0.042 mmol) was added dropwise with constant stirring. To this adduct, 1-(3-arylsydnon-4-yl)-ethylidene)-2-phenylhydrazines **4a−l** (2.0 g, 0.006 mmol) was added and again stirred for 10 min. The resulting solution was heated on a water bath for 10−12 h. After completion of the reaction, the reaction mixture was cooled to RT and poured into crushed ice. The pale yellow solid separated was filtered and washed with water to obtain the compounds **7a−l**, which was recrystallized from ethanol.

**Procedure for Microwave-Assisted Synthesis of 2,6-Diphenyl-2*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-ones (7a−l).** In a sealed glass tube vial (30.0 mL), DMF (0.19 mL, 0.0025m mol) was taken and cooled to 0 °C, and $POCl_3$ (0.65 mL, 0.007 mol) was added dropwise with constant stirring. To this, 1-(3-arylsydnon-4-yl)ethylidene)-2-phenylhydrazines **4a−l** (0.5 g, 0.0016 mol) was added and again stirred for 10 min. The sealed vessel with the reaction mixture was prestirred for 30 s at room temperature. The reaction mixture was then irradiated by 150 W at 120 °C for about 5−8 min at medium stirring. The completion of the reaction was monitored by TLC using hexane:ethylacetate (7:3 drops) as an eluent. The reaction mixture was then quenched into crushed ice, and the crude product obtained was filtered, washed, and dried. It was recrystallized from ethanol to obtain pure crystals of the compounds **7a−l**.

*4-Acetyl-3-arylsydnone (**2a**).* Pale yellow solid; mp 141−143 °C; IR (KBr; $\bar{\nu}_{max}$, $cm^{-1}$): 1750 $cm^{-1}$ (C═O), $^1$H NMR (400 MHz, DMSO-$d_6$, ppm): 7.57−7.69 (m, 5H, Ar-H), 2.32 (s, 3H, $-CH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm): 183.9, 166.6, 135.5, 132.5, 129.7, 125.87, 107.5, 28.1. MS-EI (*m/z*): 204 $[M]^+$; analysis calcd (%) for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.81; H, 3.97; N, 13.73.

*1-(3-Arylsydnon-4-yl)ethylidene)-2-(4-bromopheny)-hydrazine (**4c**).* Yellow crystalline solid; mp 162−164 °C; IR (KBr; $\bar{\nu}_{max}$, $cm^{-1}$): 1660 $cm^{-1}$ (C═N), 1745 $cm^{-1}$ (C═O); $^1$H NMR (400 MHz, DMSO-$d_6$, ppm): 2.92 (s, 3H, $-CH_3$), 6.14−6.16 (d, 2H, Ar-H), 7.04−7.07 (d, 2H, Ar-H), 7.61−7.64 (m, 5H, Ar-H), 9.48 (s, 1H, N−H). $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm): 166.8, 144.6, 136.9, 131.7, 131.5, 130.3, 130.0, 125.8, 115.0, 110.8, 108.3, 31.2. MS-EI (*m/z*): 372 $[M]^+$, 374 $[M]^{+2}$; analysis calcd (%) for $C_{16}H_{13}N_4BrO_2$: C, 51.49; H, 3.51, N, 15.01. Found: C, 51.50; H, 3.50; N, 15.02.

*2,6-Diphenyl-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (**7a**).* Light yellow solid; mp 136−138 °C; IR (KBr; $\bar{\nu}_{max}$, $cm^{-1}$): 1673 (pyridazin, C═O), 1525 (CN); $^1$H NMR (400 MHz, DMSO-$d_6$, ppm): 9.89 (s, 1H, pyridazin C−H), 9.24 (s, 1H, pyrazolo C−H), 8.61 (d, 1H, *J* = 7.8 Hz, Ar-H), 8.04 (d, 1H, *J* = 8 Hz, Ar-H), 7.70−7.37 (m, 6H, Ar-H), 7.13 (d, 1H, *J* = 8.8 Hz, Ar-H), 7.03 (d, 1H, *J* = 8.8 Hz, Ar-H); $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm): 185.4 (pyridazin C═O), 154.9, 139.1, 131.3, 131.0, 129.7, 129.4, 128.8, 128.0, 126.6, 122.5, 119.8, 118.7; MS-EI (*m/z*): 288 $[M]^+$; analysis calcd (%) for $C_{17}H_{12}N_4O$: C, 70.82; H, 4.20; N, 19.43. Found: C, 70.85; H, 4.24; N, 19.46.

*2-(4-Chlorophenyl)-6-phenyl-2H-pyrazolo[3,4-d]-pyridazin-7(6H)-one (**7b**).* Yellow solid; mp 158−160 °C; IR (KBr; $\bar{\nu}_{max}$ $cm^{-1}$): 1675 (pyridazin, C═O), 1531 (CN); $^1$H NMR (400 MHz, DMSO-$d_6$, ppm): 9.89 (s, 1H, pyridazin C−H), 9.17 (s, 1H, pyrazolo C−H), 7.51−7.70 (m, 9H, Ar-H);



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$^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm): 185.6 (pyridazin, C=O), 166.8, 160.1, 137.5, 134.8, 132.9, 132.8, 130.1, 128.2, 126.1, 125.7, 124.1, 121.2; MS-EI ($m/z$): 324 $[M]^{+2}$, 322 $[M]^+$; analysis calcd (%) for $C_{17}H_{11}N_4ClO$: C, 63.26; H, 3.44; N, 17.36. Found: C, 63.32; H, 3.47; N, 17.44.

*2-(4-Bromophenyl)-6-phenyl-2H-pyrazolo[3,4-d]-pyridazin-7(6H)-one (**7c**).* Yellow solid; mp 166−168 °C; IR (KBr; $\bar{\nu}_{max}$, cm$^{-1}$): 1630 (pyridazin, C=O), 1554 (CN); $^1$H NMR (400 MHz, DMSO-$d_6$, ppm): 9.71 (s, 1H, pyridazin C−H), 9.00 (s, 1H, pyrazolo C−H), 7.33−7.52 (m, 9H, Ar-H); $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm): 183.2 (pyridazin C=O), 164.5, 157.9, 136.4, 132.4, 130.5, 130.4, 127.8, 123.7, 123.4, 121.8, 118.9, 99.7; MS-EI ($m/z$): 368 $[M]^{+2}$, 366 $[M]^+$; analysis calcd (%) for $C_{17}H_{11}N_4BrO$: C, 55.61; H, 3.02; N, 15.26. Found: C, 55.64; H, 3.05; N, 15.29.

*6-(4-Methoxyphenyl)-2-phenyl-2H-pyrazolo[3,4-d]-pyridazin-7(6H)-one (**7d**).* Chrome yellow solid; mp 168−170 °C; IR (KBr; $\bar{\nu}_{max}$, cm$^{-1}$): 1672 (pyridazin, C=O), 1525 (CN); $^1$H NMR (400 MHz, DMSO-$d_6$, ppm): 10.04 (s, 1H, pyridazin C−H), 8.44 (s, 1H, pyrazolo C−H), 7.53−7.48 (m, 5H, Ar-H), 7.01 (d, 2H, $J$ = 6.8 Hz, Ar-H), 6.98 (d, 2H, $J$ = 7.2 Hz, Ar-H), 3.90 (s, 3H, $OCH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm): 184.2 (pyridazin C=O), 162.2, 138.62, 130.5, 129.8, 129.7, 128.4, 127.2, 126.3, 124.3, 121.1, 119.5, 114.6, 55.8 (−$OCH_3$); MS-EI ($m/z$): 318 $[M]^+$; analysis calcd (%) for $C_{18}H_{14}N_4O_2$: C, 67.91; H, 4.43; N, 17.60. Found: C, 67.95; H, 4.45; N, 17.63.

*2-(4-Chlorophenyl)-6-(4-methoxyphenyl)-2H-pyrazolo-[3,4-d]pyridazin-7(6H)-one (**7e**).* Off-white solid; mp 155−157 °C; IR (KBr; $\bar{\nu}_{max}$, cm$^{-1}$): 1666 (pyridazin, C=O), 1532 (CN); $^1$H NMR (400 MHz, DMSO-$d_6$, ppm): 9.85 (s, 1H, pyridazin C−H), 9.20 (s, 1H, pyrazolo C−H), 7.40−7.71 (m, 6H, Ar-H), 7.01−7.07 (d, 2H, Ar-H), 3.77 (s, 3H, −$OCH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm): 185.5 (pyridazin C=O), 162.2, 138.8, 137.5, 133.0, 132.9, 130.2, 128.0, 127.2, 124.2, 121.3, 115.1, 101.8, 56.3 (−$OCH_3$); MS-EI ($m/z$): 354 $[M]^{+2}$, 352 $[M]^+$; analysis calcd (%) for $C_{18}H_{13}N_4ClO_2$: C, 61.28; H, 3.71; N, 15.88. Found: C, 61.32; H, 3.75; N, 15.94.

*2-(4-Bromophenyl)-6-(4-methoxyphenyl)-2H-pyrazolo-[3,4-d]pyridazin-7(6H)-one (**7f**).* Yellow solid; mp 158−160 °C; IR (KBr; $\bar{\nu}_{max}$, cm$^{-1}$): 1668 (pyridazin, C=O), 1528 (CN); $^1$H NMR (400 MHz, DMSO-$d_6$, ppm): 9.85 (s, 1H, pyridazin C−H), 9.20 (s, 1H, pyrazolo C−H), 7.53−7.71 (m, 6H, Ar-H), 7.07−7.10 (d, 2H, Ar-H), 3.75 (s, 3H, $OCH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm): 186.8 (pyridazin C=O), 163.5, 140.1, 138.8, 134.2, 134.1, 131.4, 129.3, 128.4, 125.4, 122.6, 116.4, 103.0, 57.6 (−$OCH_3$); MS-EI ($m/z$): 398 $[M]^{+2}$, 396 $[M]^+$; analysis calcd (%) for $C_{18}H_{13}N_4BrO_2$: C, 54.43; H, 3.30; N, 14.10. Found: C, 54.51; H, 3.36; N, 14.17.

*6-(4-Chlorophenyl)-2-phenyl-2H-pyrazolo[3,4-d]-pyridazin-7(6H)-one (**7g**).* White solid; mp 152−154 °C; IR (KBr; $\bar{\nu}_{max}$, cm$^{-1}$): 1679 (pyridazin, C=O), 1589 (CN); $^1$H NMR (400 MHz, DMSO-$d_6$, ppm): 9.94 (s, 1H, pyridazin C−H), 9.46 (s, 1H, pyrazolo C−H), 8.62 (d, 2H, $J$ = 8.4 Hz, Ar-H), 8.32 (d, 2H, $J$ = 8 Hz, Ar-H), 7.70−7.38 (m, 5H, Ar-H); $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm): 183.1 (pyridazin C=O), 169.6, 163.2, 139.9, 132.7, 126.6, 126.5, 126.1, 124.7, 122.2, 119.4, 106.2, 95.8; MS-EI ($m/z$): 324 $[M]^{+2}$, 322 $[M]^+$; analysis calcd (%) for $C_{17}H_{11}N_4ClO$: C, 63.26; H, 3.44; N, 17.36. Found: C, 63.32; H, 3.47; N, 17.41.

*2,6-Bis(4-chlorophenyl)-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (**7h**).* Yellow solid; mp 148−150 °C; IR (KBr; $\bar{\nu}_{max}$, cm$^{-1}$): 1669 (pyridazin, C=O), 1556 (CN); $^1$H NMR (400 MHz, DMSO-$d_6$, ppm): 9.86 (s, 1H, pyridazin C−H), 9.18 (s, 1H, pyrazolo C−H), 7.53−7.67(m, 6H, Ar-H), 7.36−7.38 (d, 2H, Ar-H); $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm): 185.2 (pyridazin C=O), 160.1, 143.0, 137.5, 133.0, 132.3, 130.5, 130.2, 125.4, 124.2, 121.3, 121.1, 106.1; MS-EI ($m/z$): 356 $[M]^{+4}$, 354 $[M]^{+2}$, 352 $[M]^+$; analysis calcd (%) for $C_{17}H_{10}N_4Cl_2O$: C, 57.16; H, 2.82; N, 15.69. Found: C, 57.22; H, 2.91; N, 15.74.

*2-(4-Bromophenyl)-6-(4-chlorophenyl)-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (**7i**).* Chrome yellow solid; mp 154−156 °C; IR (KBr; $\bar{\nu}_{max}$, cm$^{-1}$): 1672 (pyridazin, C=O), 1567 (CN); $^1$H NMR (400 MHz, DMSO-$d_6$, ppm): 9.89 (s, 1H, pyridazin C−H), 9.17 (s, 1H, pyrazolo C−H), 7.54−7.70 (m, 8H, Ar-H); $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm): 185.6 (pyridazin C=O), 135.8, 133.0, 132.6, 130.1, 129.7, 126.8, 125.8, 124.1, 121.5, 121.2, 112.5, 105.3; MS-EI ($m/z$): 400 $[M]^{+4}$, 398 $[M]^{+2}$, 396 $[M]^+$; analysis calcd (%) for $C_{17}H_{10}N_4Br_2O$: C, 50.84; H, 2.51; N, 13.95. Found: C, 50.90; H, 2.57; N, 13.98.

*2-Phenyl-6-p-tolyl-2H-pyrazolo[3,4-d]pyridazin-7(6H)-one (**7j**).* Off-white solid; mp 168−170 °C; IR (KBr; $\bar{\nu}_{max}$, cm$^{-1}$): 1664 (pyridazin, C=O), 1609 (CN); $^1$H NMR (400 MHz, DMSO-$d_6$, ppm): 10.05 (s, 1H, pyridazin C−H), 8.44 (s, 1H, pyrazolo C-H), 7.48−7.34 (m, 5H, Ar-H), 7.32 (d, 2H, $J$ = 7.4 Hz, Ar-H), 7.29 (d, 2H, $J$ = 8 Hz, Ar-H), 2.40 (s, 3H, $CH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm): 184.3 (pyridazin C=O), 167.1, 142.8, 138.5, 130.4, 130.1, 129.8, 128.4, 124.7, 119.4, 119.1, 117.3, 101.2, 21.5 ($CH_3$); MS-EI ($m/z$): 302 $[M]^+$; analysis calcd (%) for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53. Found: C, 71.58; H, 4.75; N, 18.59.

*2-(4-Chlorophenyl)-6-p-tolyl-2H-pyrazolo[3,4-d]-pyridazin-7(6H)-one (**7k**).* Off white solid; mp 147−149 °C; IR (KBr; $\bar{\nu}_{max}$, cm$^{-1}$): 1676 (pyridazin, C=O), 1558 (CN); $^1$H NMR (400 MHz, DMSO-d$_6$, ppm): 9.85 (s, 1H, pyridazin C−H), 9.18 (s, 1H, pyrazolo C−H), 7.36−7.67 (m, 8H, Ar-H), 2.34 (s, 3H, $CH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm): 185.5 (pyridazin, C=O), 151.9, 143.0, 138.7, 137.5, 133.0, 132.3, 130.5, 130.2, 125.4, 124.2, 121.3, 102.4, 21.4 ($CH_3$); MS-EI ($m/z$): 336 $[M]^{+2}$, 334 $[M]^+$; analysis calcd (%) for $C_{18}H_{13}N_4ClO$: C, 64.19; H, 3.89; N, 16.64. Found: C, 64.23; H, 3.92; N, 16.66.

*2-(4-Bromophenyl)-6-p-tolyl-2H-pyrazolo[3,4-d]-pyridazin-7(6H)-one (**7l**).* Yellow solid; mp 186−188 °C; IR (KBr; $\bar{\nu}_{max}$, cm$^{-1}$): 1674 (pyridazin, C=O), 1531 (CN); $^1$H NMR (400 MHz, DMSO-$d_6$, ppm): 9.86 (s, 1H, pyridazin C−H), 9.18 (s, 1H, pyrazolo C−H), 7.36−7.68(m, 8H, Ar-H), 2.34 (s, 3H, $CH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$, ppm): 185.5 (pyridazin C=O), 166.8, 143.0, 139.2, 137.9, 132.9, 132.3, 130.5, 125.4, 124.2, 121.6, 121.2, 101.8, 21.8 (−$CH_3$); MS-EI ($m/z$): 380 $[M]^{+2}$, 378 $[M]^+$; analysis calcd (%) for $C_{18}H_{13}N_4BrO$: C, 56.71; H, 3.44; N, 14.70. Found: C, 56.76; H, 3.49; N, 14.75.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b02013.

Scanned copies of $^1$H NMR and $^{13}$C NMR, mass spectra for newly synthesized compounds **7a**−**7l**, ORTEP X-ray



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crystal structure, and CIF files of crystallographic data for **4a** (PDF)

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### Notes

The authors declare no competing financial interest.

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