Synthesis of 2,5-Diaryloxadiazinones

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Procedure (Note 1)

A. (Z)-2-(2-Benzoylhydrazineylidene)-2-phenylacetic acid (3). A single-necked (24/40 joint) 2000-mL round-bottomed flask is equipped with a Teflon-coated magnetic stir bar (4.0 x 1.5 cm, football-shaped). The flask is charged with benzohydrazide (1) (6.35 g, 46.6 mmol, 1 equiv) (Note 2) followed by deionized water (520 mL, 0.090 M) and left open to air. The reaction vessel is placed in a water bath maintained at 60 °C, and the reaction mixture is stirred at 750 rpm. The flask is fit with a 500-mL pressure equalizing addition funnel (Figure 1A). A separate, 1000-mL Erlenmeyer flask is charged with a Teflon-coated magnetic stir bar (7.5 cm x 1.5 cm), benzoylformic acid (2) (7.00 g, 46.6 mmol, 1 equiv) (Note 3), and deionized

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water (520 mL, 0.090 M). The mixture is stirred vigorously for 5 min (750 rpm) until the acid is fully dissolved, and the resulting benzyloformic acid solution is transferred into the addition funnel which is left open to air. The acid solution is then added dropwise into the stirring benzohydrazide solution over 1.5 h (Note 4). The mixture becomes progressively more heterogeneous as the product precipitates as a white solid over the course of the addition. When the addition is complete, the flask is fit loosely (Note 5) with a plastic stopper (Figure 1B) and stirring is maintained for 2.5 h at 60 °C.

![Figure 1. A) Reaction set-up for Step A. B) Reaction becomes increasingly turbid during addition and subsequent stirring (photos provided by submitters)](image)

After 2.5 h (Note 6), the reaction vessel is removed from the water bath and placed in a 0 °C ice bath where it is stirred at this temperature for 2 h (750 rpm) (Note 7). The solid is then collected by filtration in a Büchner funnel using ice-cold deionized water (3 x 50 mL) to transfer the solid into the funnel (Note 8). The resulting solid is transferred to an 8-dram vial which is
subsequently equipped with a vacuum adapter (24/40 joint) and dried under high vacuum at 40 °C (Note 9) to provide (Z)-2-(2-benzoylhydrazineylidene)-2-phenylacetic acid (3) as a white, amorphous solid (Figure 2, 11.17 g, 89%) (Notes 10, 11, 12, and 13).

Figure 2. Isolated hydrazone 3 (photo provided by submitters)

B. 2,5-Diphenyl-6H-1,3,4-oxadiazin-6-one (4). A single-necked (24/40 joint) 1000-mL round-bottomed flask is equipped with a Teflon-coated magnetic stir bar (4.0 x 1.5 cm, football-shaped). The apparatus is oven-dried and cooled to 23 °C under an atmosphere of argon (Note 14). The flask is charged with (Z)-2-(2-benzoylhydrazineylidene)-2-phenylacetic acid (3) (11.0 g, 41.0 mmol, 1 equiv), sealed with a rubber septum, and purged with argon (Note 15). The reaction vessel is then maintained under argon for the duration of the reaction. Hydrazone 3 is suspended in THF (410 mL, 0.10 M) (Note 16). The septum is removed, and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC•HCl) (8.64 g, 45.1 mmol, 1.1 equiv) (Note 17) is added quickly in one portion. The rubber septum with an argon inlet is restored without purging (Figure 3a).
After stirring for 16 h (750 rpm) at 23 °C (Notes 18 and 19) (Figure 3c), the reaction mixture is transferred into a 1000 mL separatory funnel. The residual precipitate is transferred into the separatory funnel using diethyl ether (3 x 50 mL aliquots), followed by deionized water (3 x 50 mL aliquots) (Note 20). The funnel is shaken, the layers are allowed to separate, and the aqueous layer is extracted with diethyl ether (2 x 75 mL) (Note 21). The combined organic layers are washed successively with a 2:1 mixture of deionized water : saturated NaCl solution (3 x 150 mL), followed by saturated NaCl solution (1 x 150 mL). The organic layer is dried over Na₂SO₄ (50 g) and filtered through a fritted Büchner funnel (Note 22) into a 1000 mL collection flask. The filtrate is concentrated on a rotary evaporator under reduced pressure (Note 23). The resulting yellow solid is collected in an 8-dram vial which is subsequently equipped with a vacuum adapter and dried under high vacuum at 30 °C (Note 24) to provide 2,5-diphenyl-6H-1,3,4-oxadiazin-6-one (4) as a yellow solid (9.7 g, 94% yield) (Figure 4) (Notes 25, 26, 27, 28, and 29).
Figure 4. Isolated 2,5-diphenyl-6H-1,3,4-oxadiazin-6-one (4) (photo provided by submitters)

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of “Prudent Practices in the Laboratory” (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical. See also “Identifying and Evaluating Hazards in Research Laboratories” (American Chemical Society, 2015) which is available via the associated website “Hazard Assessment in Research Laboratories” at https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with benzoylformic acid, benzohydrazide, tetrahydrofuran, diethyl ether, ethyl acetate, acetone, sodium sulfate, and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.
2. Benzohydrazide (98%) was purchased from Combi-Blocks and used as received.
3. Benzoylformic acid (97%) was purchased from Sigma Aldrich and used as received.
4. Addition of the benzoylformic acid solution is begun directly following its preparation, approximately 10 minutes after the benzohydrazide solution is introduced into the water bath.
5. The cap is lightly placed over the reaction flask to prevent possible contamination without rendering the flask airtight. The cap must not be secured tightly as to avoid heating a sealed system.
6. The progress of the reaction is monitored using TLC analysis on silica gel with 4:1 CH$_2$Cl$_2$:MeOH as eluent and visualization with a UV lamp (254 nm). The reaction spot was dried thoroughly under a stream of air to remove water before running the plate. Benzohydrazide has $R_f = 0.62$, benzoylformic acid has $R_f = 0.12$, and the hydrazone product has $R_f = 0.35$.

![TLC of crude reaction mixture after Step A](photo provided by submitters)

**Figure 5.** TLC of crude reaction mixture after Step A
(H = benzohydrazide, A = benzoylformic acid, C = co-spot of H, A, and R, R = reaction mixture) (photo provided by submitters)

7. Precipitation of the hydrazone can also be accomplished by storing the reaction flask in a −20 °C freezer until the water begins to freeze.
8. If any solid remains in the flask after washing, it can be scraped with a spatula and added to the Büchner funnel.
9. The product was dried under high vacuum (0.5 mmHg) in a 40 °C aluminum heating block for 14 h. The checkers used a vacuum oven (0.5 mmHg) at 40 °C for 14 h.

10. The product can be characterized, as follows: \(^1\)H NMR (400 MHz, (CD\(_3\))\(_2\)SO) \(\delta\): 7.41 – 7.47 (m, 3H), 7.57 (t, \(J = 7.5\) Hz, 2H), 7.61 – 7.74 (m, 3H), 7.87 (d, \(J = 7.6\) Hz, 2H), 12.82 – 12.87 (broad s, 1H); \(^{13}\)C NMR (100 MHz, (CD\(_3\))\(_2\)SO) \(\delta\): 127.6, 128.2, 128.3, 128.9, 129.4, 132.4, 132.8, 134.8, 164.0; IR (film) 3061, 2852, 2604, 1691, 1643, 1521, 1479, 1257, 1147, 925, 693 cm\(^{-1}\); HRMS (DART-TOF) \((m/z)\) \([M - H]\) calcd for C\(_{15}\)H\(_{11}\)N\(_2\)O\(_3\), 267.0775; found, 267.0784. mp 162 – 164 °C. Anal. Calcd. for C\(_{15}\)H\(_{12}\)N\(_2\)O\(_3\): C, 67.16; H, 4.51; N, 10.44. Found: C, 67.24; H, 4.49; N, 10.41.

11. The purity of 3 was determined to be >97 wt% by qNMR using trimethoxybenzene (Sigma-Aldrich, >99.9%) as the internal standard.

12. The procedure above delivers the hydrazone product in >97 wt% purity. However, if desired, the hydrazone can be recrystallized from boiling ethyl acetate (EMD Millipore, ACS grade) (500 mg crude product/100 mL EtOAc, wash with ice cold diethyl ether; 72% recovery). The checkers did not attempt to recrystallize the hydrazone product.

13. The checkers’ half-scale run resulted in 5.33 g (87% yield) of product.

14. The submitters flame-dried the apparatus under reduced pressure instead.

15. The submitters used a Schlenk line with nitrogen, with the flask evacuated and backfilled three times instead.

16. Tetrahydrofuran (99.9%) was purchased from Fischer Scientific and passed through an activated alumina column before use.

17. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride was purchased from Chem Impex (99.8%) and used without further purification.

18. The reaction mixture is initially cloudy and white following EDC addition and becomes increasingly yellow and homogeneous with stirring. At the 16 h time point, a gel-like precipitate is adhered to the flask walls (Figure 3C).

19. Reaction was monitored by TLC analysis on silica gel with 9:1 CH\(_2\)Cl\(_2\):MeOH as eluent and visualization with a UV lamp (254 nm) (Figure 6). Hydrazine starting material has \(R_f = 0.08\), and the oxadiazinone product has \(R_f = 0.96\).
20. The gel-like precipitate on the flask walls (Figure 7) is soluble in water and was transferred quantitatively into the separatory funnel using sonication (Branson 3510 Ultrasonic Cleaner) as required to facilitate dissolution.

21. The aqueous layer was extracted until no yellow color (indicative of the product oxadiazinone) appeared in the organic layer (2 x 75 mL diethyl ether extractions) (Figure 8).
22. A medium porosity fritted Büchner funnel under vacuum was used for filtration.

23. Rotary evaporation from 30 °C, 275 mmHg to 30 °C, 15 mmHg. Low pressure (15 mmHg) was maintained for only 1 min to thoroughly remove solvent from the solid residue without incurring vigorous boiling.

24. Product was dried under high vacuum (0.5 mmHg) in a 30 °C aluminum heating block for 14 h. The checkers used a vacuum oven (0.5 mmHg) at 30 °C for 14 h.

25. The checkers’ half scale run (starting with 5.2 g) resulted in 4.4 g (90% yield) of product.

26. The product can be characterized, as follows: ¹H NMR (400 MHz, CDCl₃) δ: 7.46 – 7.59 (m, 5H), 7.59 – 7.66 (m, 1H), 8.27 (d, J = 7.4 Hz, 2H), 8.32 (d, J = 7.4 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 127.5, 128.2, 128.6, 129.97, 129.04, 131.0, 132.0, 133.6, 148.1, 152.7, 157.5; IR (film): 3505, 3073, 3051, 1760, 1587, 1549, 1358, 1151, 797, 779, 689 cm⁻¹; HRMS—(DART-TOF) (m/z) [M + H]⁺ calcd for C₁₅H₁₁N₂O₂⁺, 251.0815; found, 251.0822. Anal. Calcd. for C₁₅H₁₁N₂O₂: C, 71.99; H, 4.03; N, 11.19. Found: C, 71.82; H, 4.13; N, 11.28.

27. The purity of 4 was determined to be >97 wt% by qNMR using trimethoxybenzene (Sigma-Aldrich, >99.9%) as the internal standard.
28. The procedure above delivers the oxadiazinone product in >97 wt% purity. However, if desired, the product can be recrystallized from hot acetone (EMD Millipore, ACS grade) (500 mg crude product/2 mL acetone in a sealed vial, rinsed with 2 mL cold ether; 91% recovery). The checkers did not attempt to recrystallize the oxadiazinone product.

29. Differential scanning calorimetry (DSC) of oxadiazinone 4 revealed degradation with an onset temperature of 140 °C (ΔH = 102 J/g), which occurs before any melting events.

Working with Hazardous Chemicals

The procedures in Organic Syntheses are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as “Prudent Practices in the Laboratory” (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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Discussion

The procedure described herein provides a simple protocol for the synthesis of 2,5-diaryloxadiazinones, valuable synthetic building blocks which have enabled the synthesis of substituted pyrones, lactones, and polyacenes. One particular field in which 2,5-diaryloxadiazinones have been utilized is in the synthesis of polycyclic aromatic hydrocarbons (PAHs) and their heterocyclic derivatives. Owing to their photophysical and electronic properties, PAHs have seen application in organic light-emitting diodes (OLEDs) (compounds 5, 6, 8–10), field effect transistors (OFETs), and photovoltaics (OPVs). One class of PAHs with proven utility is 9,10-diarylanthracenes and their heterocyclic counterparts. The parent compound, 9,10-diphenylanthracene (5, Figure 9), was first characterized in 1904 and has since found application in blue glowsticks and OLEDs.

![Chemical structures](image)

Figure 9. 9,10-Diarylanthracene derivatives with useful applications
Given the wide scope of applications enabled by 9,10-diarylanthracenes, syntheses of their derivatives, especially those incorporating heteroatoms, have been of interest. These syntheses often require strong acid or high temperatures to produce azaanthracene products, and routes to non-symmetric PAHs rely on lengthy linear synthetic sequences. A recent report leveraging oxadiazinones (Figure 10), constructed using the two-step condensation-cyclization procedure described above, provides an improved route to 9,10-diarylanthracenes and 9,10-diarylhetanthracenes.

The two step diaryloxadiazinone synthesis provides an entryway to non-symmetric 9,10-diaryl diazinones via a (Z) hydrazone intermediate which is cyclized in the presence of EDC. Use of EDC, as described above, circumvents the necessity of chromatography or iterative recrystallization as in previous protocols employing DCC. Notably, the chromatography-free protocol for oxadiazinone synthesis tolerates electron-rich (11), electron-poor (12), and heterocyclic (15 and 16) substrates. Further, this methodology allows for the incorporation of cross coupling handles such as aryl chlorides (14), allowing for elaboration of the PAH scaffold.

![Reaction Scheme](image)

**Figure 10.** Oxadiazinones accessed via the two-step condensation-cyclization procedure. Yield reported is over two steps.
Diaryloxadiazinones facilitate the construction of the anthracenyl core found in many functional PAHs via sequential aryne Diels–Alder/retro-Diels–Alder processes with concomitant extrusion of N\textsubscript{2} and CO\textsubscript{2}. This sequence relays the substitution of the oxadiazinone to the central ring of the resulting anthracene scaffold. This synthetic sequence has enabled the construction of 9,10-diarylhetanthracenes bearing differential substitution at the 9 and 10 positions (17–19, Figure 11) as well as anthracenyl derivatives incorporating indole (20), naphthalene (21), and pyran (22) motifs.

2,5-Diphenyl-6H-1,3,4-oxadiazin-6-one (4) and related oxadiazinones accessible via the procedure described here are valuable building blocks for the assembly of PAH materials. This modular and facile protocol for their synthesis should enable the scalable synthesis of this class of compounds and facilitate further investigation of their physical properties.
Figure 11. 9,10-Diarylanthracene derivatives accessed from oxadiazinones; *Yield reported over two steps from corresponding oxadiazinone; †Yield reported from corresponding pyrone intermediate
References

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13. Condensation of arylhydrazides and benzylicformic acid has been shown to yield almost exclusively the Z isomer of the resulting hydrazone: Țîntaș, M. L.; Diac, A. P.; Soran, A.; Terec, A.; Grosu, I.; Bogdan, E. *J. Mol. Struct.* 2014, 1058, 106–113.

**Appendix**

**Chemical Abstracts Nomenclature (Registry Number)**

- Benzohydrazide; (613-94-5)
- Benzylicformic acid; (611-73-4)
- 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; (25952-53-8)

Andrew Kelleghan received his B. S. in Chemical and Biomolecular Engineering from University of California, Berkeley in 2018, where he carried out research under the advisement of Professor Phillip Messersmith. He then moved to the University of California, Los Angeles where he is currently a second-year graduate student in Professor Neil K. Garg’s laboratory. His graduate studies primarily focus on developing synthetic methods utilizing strained cyclic allenes.
Katie Spence received her B.A. in Chemistry and Psychology from Williams College in 2018. As an undergraduate, she studied the formation of atmospheric organic aerosol and completed a senior thesis on this topic under the advisement of Professor Anthony Carrasquillo. She is currently a second-year graduate student in Professor Neil K. Garg’s lab at University of California, Los Angeles where she develops synthetic methodologies employing strained intermediates.

Neil Garg is a Professor of Chemistry and the Kenneth N. Trueblood Endowed Chair at the University of California, Los Angeles. His laboratory develops novel synthetic strategies and methodologies to enable the total synthesis of complex bioactive molecules.

Kyan D’Angelo was born in Toronto, ON. He received his B.Sc. and M.Sc. degrees from the University of Toronto where he conducted research in the laboratory of Professor Mark Taylor on catalytic stereoselective glycosylation reactions. In 2016, he began his Ph.D. studies under the supervision of Professor Mohammad Movassaghi at the Massachusetts Institute of Technology. His current research focuses on the total synthesis of alkaloid natural products.
Edward Jin is currently an undergraduate at the Massachusetts Institute of Technology, pursuing a degree in chemistry and mathematics. He has an interest in organic chemistry and is currently conducting research in Professor Mohammad Movassaghi’s laboratory.
Proton NMR spectrum of (Z)-2-(2-benzoylhydrazinylidene)-2-phenylacetic acid in DMSO-d6 (400 MHz)
Carbon NMR spectrum of (Z)-2-(2-benzoylhydrazineylidene)-2-phenylacetic acid in DMSO-\textit{d6} (100 MHz)
wt = (mg_{std} \times MW_{cpd} \times \text{normalized NMR ratio} \times P_{std}) / (mg_{cpd} \times MW_{std})

= [17.8 \times 268.27 \times (2/3.01) \times (3/2) \times 0.999] / [25.8 \times 168.19]

= 1.007
Proton NMR spectrum of 2,5-Diphenyl-6H-1,3,4-oxadiazin-6-one in CDCl₃ (400 MHz)
Carbon NMR spectrum of 2,5-Diphenyl-6H-1,3,4-oxadiazin-6-one in CDCl₃ (100 MHz)
\[ wt = \frac{m_{\text{std}} \times M_{\text{cpd}} \times (\text{normalized NMR ratio}) \times P_{\text{std}}}{m_{\text{cpd}} \times M_{\text{std}}} \]

\[ = \frac{17.3 \times 250.26 \times (1/3.02) \times 3 \times 0.999}{25.6 \times 168.19} \]

\[ = 0.990 \]