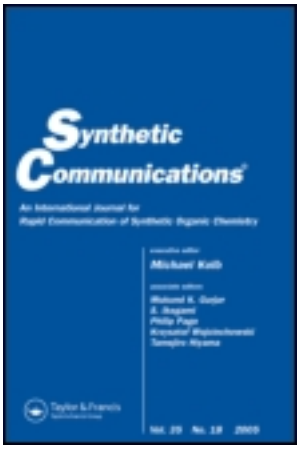

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Reaction of Oximes of α-Diketones with Diphosphorous Tetraiodide for Preparation of Oxadiazoles and Nitriles

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REACTION OF OXIMES OF α-DIKETONES WITH DIPHOSPHOROUS TETRAIODIDE FOR PREPARATION OF OXADIAZOLES AND NITRILES

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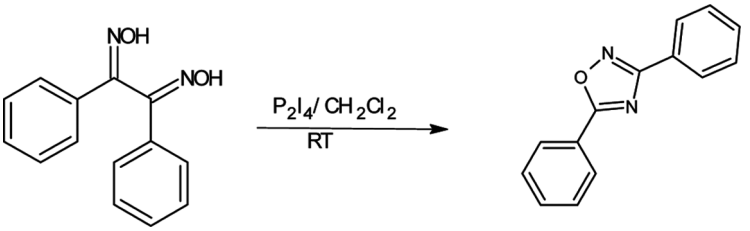
GRAPHICAL ABSTRACT



Abstract *The utility of diphosphorous tetraiodide as a new, mild, condensing agent for synthesis of oxadiazole is described. These data indicate the simple dehydration of oximes to 1,2,5-oxadiazole as well as the rearrangements of oximes to normal Beckmann product 1,2,4-oxadiazole. However, mono-oxime of benzil undergoes abnormal Beckman rearrangement to benzaldehyde as major product. The described method is simple and important for the synthesis of the oxadiazoles as well as for nitriles.*

Keywords Benzildioxime; benzonitrile; diphosphorus tetraiodide; oxadiazole

INTRODUCTION

Oxadiazoles are important class of heterocycle utilized in variety of bioactive molecules[1–3] including the metabotropic glutamate subtype 5 (mGlu5) receptor,[4] and muscarinic receptor (Fig. 1)[5] for the treatment of Alzheimer's disease.

Various approaches are developed for the preparation of oxadiazoles;[6] however despite ease of synthesis of dioximes from 1,2-diketone, their utilization for preparation of 1,2,4 and 1,2,5-oxadiazole has scarcely been reported. Previous reports for preparation of 1,2,5-oxadiazole from dioximes include use of diisopropyl azodicarboxylate (DIAD) in combination of triphenyl phospine[7] and crown ether in the presence of Bu^t OK,[8] whereas 1,2,4-oxadiazole is mainly prepared by Beckmann

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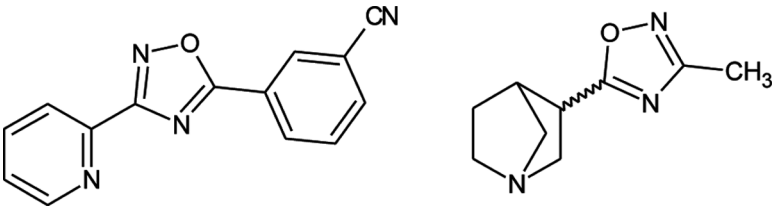


Figure 1. Bioactive molecules with oxadiazoles.

rearrangement using polyphosporic acid and thionyl chloride in liquid sulfur dioxide.[9] However, both these methods have not been studied on substituted benzil derivative.

Diphosphorus tetraiodide is a bright orange solid reagent of great interest in synthetic chemistry in several reactions.[10,11] The major driving force for these reactions is the formation of a P=O bond and the release of energy. It is a unique reagent able to promote substitution and dehydration as well as reduction reactions.

We previously reported utility of diphosphorus tetraiodide as an agent for decarboxylative bromination and synthesis of nitriles from acids.[12,13] To extend our previous work on diphosphorus tetraiodide, herein we report its approach to Beckmann rearrangement of both mono-oxime and dioxime of α -diketone.

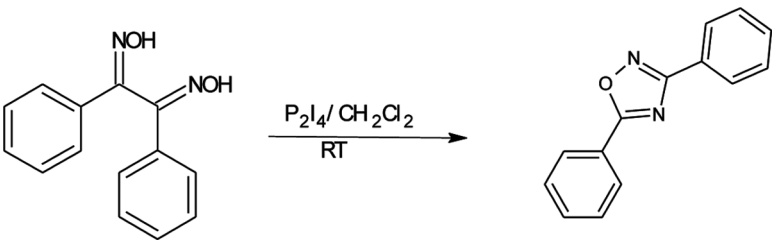
At the beginning, benzildioxime (1 equiv) was used as the starting material to investigate this reaction. It was found that when P_2I_4 was used as a reagent in the presence of CH_2Cl_2 as a solvent, the normal Beckmann product, 1,2,4-oxadiazole, could be obtained in 89% yield after the mixture was stirred at room temperature (Scheme 1).

The rearrangement in this case clearly follows the normal Beckmann path, where rearrangement occurs at one oximinogroup followed by cyclization to form the oxadiazole ring.

We also screen various solvents for this reaction. From Table 1, it is clearly indicated that chlorinated solvents are suitable for this reaction, where dichloromethane gives the greatest yield.

RESULTS AND DISCUSSION

Further scope of reaction was explored by using a variety of substituted 1,2-dioximes of α-diketones, and results are summarized in Table 2.



Scheme 1. Synthesis of oxadiazole from benzil dioxime.

Table 1. Effect of various solvents on the reaction of diphosphorus tetraiodide with dioxime of α-diketone

Entry	Solvent	Yield (%)
1	CH_2Cl_2	89
2	$CHCl_3$	75
3	CCl_4	72
4	CS_2	50
5	CH_3CN	No reaction

To check further effects of substitution on diketones, we took mono-substituted benzil for our study and recovered only oxadiazole as a product (Table 2, entry 2). Heterocyclic substitution on both side of dioxime gives the normal Beckmann product (Table 2, entry 3). Alkyl substitution on one or both sides of dioxime also results in formation of 1,2,4-oxadiazole as a product (Table 2, entries 4 and 5). Results clearly indicate that substitution on both rings of benzil dioxime does not give oxadiazoles but an abnormal Beckmann rearrangement to nitriles (Table 2, entries 6–8). This may be due to a steric effect.

The 1,2-cyclohexanedione dioxime does not give a normal Beckmann product but results in cyclohexano[*c*]1,2,5-oxadiazole (Table 2, entry 9). As explained by Tokura and coworkers,[9] Beckmann rearrangement in benzil dioxime is facilitated by its coplanar structure and participation of the phenyl ring in rearrangement, whereas cyclohexanedionedioxime prefers dehydration because of steric restriction to build an azilinium cation. The results obtained for dioximes of other cyclic α-diketone systems were similar to that of entry 9 (Table 2, entries 10–12).

To check the effect of diphosphorus tetraiodide on Beckmann rearangements of mono-oxime of α-diketones, we subjected benzil monooxime (1 equiv) with diphosphorus tetraiodide (0.25 equiv), and results are presented in Scheme 2. Previously benzil monooxime was reported[14] to undergo abnormal Beckmann rearrangement in the presence of polyphosphoric acid, which resulted in two major products, benzonitrile and benzoic acid. However, we got three products: benzaldehyde, benzonitrile, and benzoic acid in the ratio of 40:30:10. Thus, under our reaction conditions formation of benzaldehyde was quite unexpected.

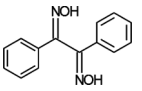
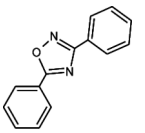
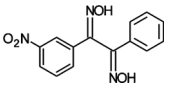
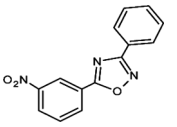
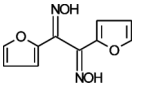
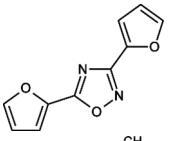
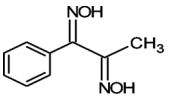
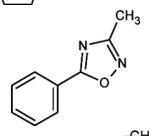
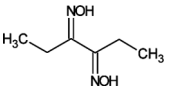
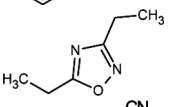
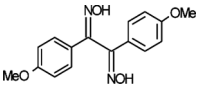
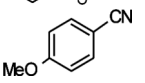
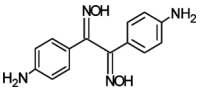
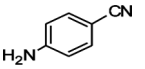
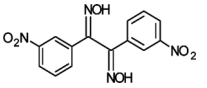
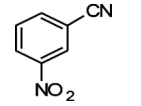
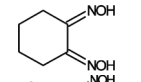
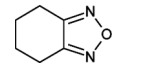
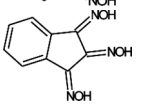
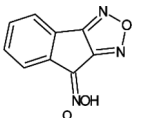
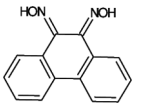
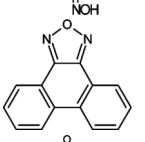
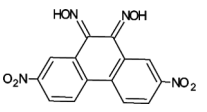
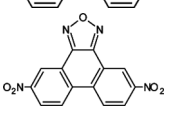
In conclusion, we have shown that 1,2,4-oxadiazole can be easily synthesized by corresponding dioximes of α-diketone in good yields whereas dioximes of cyclic α-diketones resulted in simple dehydration to 1,2,5-oxadiazole because of unfavorable conditions for rearrangement. The process is also useful for preparation of nitriles.

EXPERIMENTAL

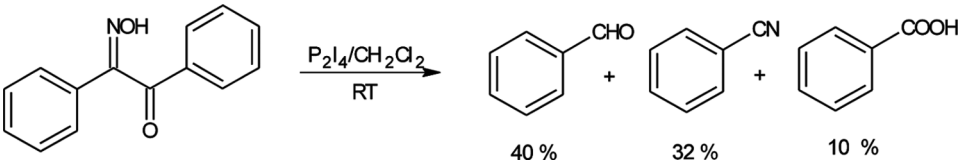
Representative Procedure for Synthesis of Oxadiazoles (Table 2, Entry 1)

Diphosphorus tetraiodide (285 mg, 0.5 mol) in anhydrous CH_2Cl_2 (10 mL) was stirred in a round-bottomed flask for 5 min to get a clear solution. Finally dioxime (240 mg, 1 mol) was added and stirring was continued at room temperature for

Table 2. Action of diphosphorus tetraiodide on dioxime of α-diketone[a]

Entry	Substrate (**a**)	Product (**b**)	Time (h)	Yield[b] (%)
1			3	89
2			3	76
3			3	80
4			3	85
5			4	79
6			2	90
7			2	89
8			2	85
9			2	90
10			2	85
11			2	87
12			2	80

[a]Reaction conditions: Substrate (1 mol) and P_2I_4 (0.5 mol) in dichloromethane at room temperature.
[b]Isolated yields after column chromatography and structures were confirmed by comparison of IR and ^{1}H NMR with authentic materials.



Scheme 2. Abnormal Beckmann rearrangement of mono-oxime of α-diketones.

2 h. After completion of the reaction thin-layer chromatography, (TLC), the reaction mixture was diluted with CH_2Cl_2(20 mL) and washed successively with 10% aq. ueous $NaHCO_3$(2×10 mL) and H_2O (3×10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue obtained was purified by silica-gel column chromatography (5% EtOAc–hexane) to afford pure product **1b**.

Table 2, Entry 1. Mp 106 °C (lit.[15a] mp 108 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, 2H, $J = 7.6$ Hz), 8.01–7.97 (m, 2H), 7.74–7.70 (m, 1H), 7.67–7.57 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 162.5, 130.8, 130.2, 129.3, 128.9, 128.1, 127.2, 126.1, 123.3. (mp and ^{1}H and ^{13}C NMR match with literature.[15a])

Table 2, Entry 2. Mp 143 °C (lit.[15b] mp 145 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.04 (s, 1H), 8.54–8.56 (m, 1H), 8.47–8.49 (m, 1H), 8.22–8.19 (m, 2H), 7.80–7.76 (m, 1H), 7.59–7.53 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 167.1, 145.3, 132.2, 130.5, 129.4, 128.9, 127.7, 127.0, 126.3, 123.6, 121.1. (Mp and ^{1}H and ^{13}C NMR match with literature.[15b])

Table 2, Entry 3. Mp 103 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91–7.84 (m, 2H), 7.09–7.16 (m, 2H), 6.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1, 162.8, 152.2, 147.3, 140.4, 135.1, 115.2, 112.4, 105.6; IR (KBr): 1622, 1520, 1359, 721 cm^{-1}. Anal. calcd. for $C_{10}H_6N_2O_3$: C, 59.40; H, 2.97; N, 13.86. Found: C, 59.36; H, 2.93; N, 13.82.

Table 2, Entry 4. Mp 37 °C (lit.[15b] mp 38.1 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04–7.95 (m, 2H), 7.54–7.50 (m, 3H), 2.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175, 165.0, 131.8, 129.6, 127.3, 126.7, 12.4 (Mp and ^{1}H and ^{13}C NMR match with literature.[15b])

Table 2, Entry 5. Yellowish oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.80 (q, $J = 7.8$, 2H), 2.60 (q, $J = 7.8$, 2H), 1.28 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 159.1, 26.4, 21.2, 12.3, 10.1; IR (liquid film): 2950, 1585, 1530, 1380, 1271, 798 cm^{-1}. Anal. calcd. for $C_6H_{10}N_2O$: C, 57.14; H, 7.93; N, 22.22. Found: C, 57.11; H, 7.89; N, 22.18.

Table 2, Entry 9. Mp 27 °C (lit.[15c] mp 26 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.7–3.1 (m, 4H), 1.7–2.1 (m, 4H). (Mp and ^{1}H NMR match with literature.[15c])

Table 2, Entry 10. Mp 123 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.9–7.85 (m, 2H), 7.5–7.56 (m, 2H), 2.31 (b, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2, 147.1, 145.1, 133.2, 130.1, 129.0, 128.8, 123.2; IR (KBr): 3203, 3140, 1628, 1590, 1496,

1321, 1069 cm^{-1}; Anal. calcd. for $C_9H_5N_3O_2$: C, 57.75; H, 2.67; N, 22.45 Found: C, 57.70; H, 2.63; N, 22.40.

Table 2, Entry 12. Mp 189 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 8.82 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.2, 133.1, 132.1, 130.3, 129.7, 127.5, 120.1; IR (KBr): 1628, 1575, 1488, 1350, 780 cm^{-1}. Anal. calcd. for $C_{14}H_6N_4O_5$: C, 54.19; H, 1.93; N, 18.06. Found: C, 54.18; H, 1.89; N, 18.01.

Representative Procedure for Abnormal Beckmann Rearrangement of Monooxime

Diphosphorus tetraiodide (0.25 mol) in anhydrous CH_2Cl_2 was stirred in a round-bottomed flask for 5 min to get a clear solution. Mono-oxime (1 mol) was then added, and stirring was continued at room temperature for 2 h. The products were isolated by workup as described.

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REFERENCES

1. Diana, G. D.; Volkots, D. L.; Nitz, T. J.; Bailey, T. R.; Long, M. A.; Vescio, N.; Aldous, S.; Pevear, D. C.; Dutko, F. J. Oxadiazoles as ester bioisosteric replacements in compounds related to disoxaril antirhinovirus activity. *J. Med. Chem.* **1994**, *37*, 2421.
2. Borg, S.; Vollinga, R. C.; Labarre, M.; Payza, K.; Terenius, L.; Luthman, K. Design, synthesis, and evaluation of Phe-Gly mimetics: Heterocyclic building blocks for pseudopeptides. *J. Med. Chem.* **1999**, *42*, 4331.
3. Guo, S.; Song, Y.; Huang, Q.; Yuan, H.; Wan, B.; Wang, Y.; He, R.; Beconi, M. G.; Franzblau, S. G.; Kozikowski, A. P. Identification, synthesis, and pharmacological evaluation of tetrahydroindazole-based ligands as novel antituberculosis agents. *J. Med. Chem.* **2010**, *53*, 649.
4. Roppe, J.; Smith, N. D.; Huang, D.; Tehrani, L.; Wang, B.; Anderson, J.; Brodkin, J.; Chung, J.; Jiang, X.; King, C.; Munoz, B.; Varney, M. A.; Prasit, P.; Cosford, N. D. Discovery of novel heteroarylazoles that are metabotropic glutamate subtype 5 receptor antagonists with anxiolytic activity. *J. Med. Chem.* **2004**, *47*, 4645.
5. Street, L. J.; Baker, R.; Book, T.; Kneen, C. O.; MacLeod, A. M.; Merchant, K. J.; Showell, G. A.; Saunders, J.; Herbert, R. H.; Freedman, S. B.; Harley, E. A. Synthesis and biological activity of 1,2,4-oxadiazole derivatives: Highly potent and efficacious agonists for cortical muscarinic receptors. *J. Med. Chem.* **1990**, *33*, 2690.
6. Kayukova, L. A. Synthesis of 1, 2, 4-oxadiazoles (a review). *Pharm. Chem. J.* **2005**, *39*, 539.
7. Tron, G. C.; Pagliai, F.; Grosso, E. D.; Genazzani, A. A.; Sorba, G. Synthesis and cytotoxic evaluation of combretafurazans. *J. Med. Chem.* **2005**, *48*, 3260.
8. Hosokawa, G.; Ohta, T.; Okamoto, Y.; Murahashi, S. I. Alkylation of ketoxime with dichloromethane using bases under phase-transfer conditions: Formation of methylene dioxime and novel heteromacrocyclic compounds. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 194.

9. Tokura, N.; Tada, R.; Yokoyama, K. Formation of cyclohexano[*c*]1,2,5-oxadiazole from 1,2-cyclohexanedione dioxime: An attempted Beckmann rearrangement with thionyl chloride in liquid sulfur dioxide. *Bull. Chem. Soc. Jpn.* **1961**, *34*, 270.
10. Demirdji, S. H.; Jaddadin, M. J.; Issidorides, C. H. Facile synthesis of furans from 2-ene-1,4-diones by diphosphorus tetraiodide. *J. Heterocycl. Chem.* **1985**, *22*, 495.
11. Shigemasa, Y.; Ogawa, M.; Sashiwa, H.; Saimoto, H. A new method for the deprotection and reduction of dithioacetals. *Tetrahedron Lett.* **1989**, *30*, 1277
12. Telvekar, V. N.; Chettiar, S. N. A novel system for decarboxylative bromination. *Tetrahedron Lett.* **2007**, *48*, 4529.
13. Telvekar, V. N.; Rane, R. A. A novel system for the synthesis of nitriles from carboxylic acids. *Tetrahedron Lett.* **2007**, *48*, 6051
14. Conley, R. T.; Mikulski, F. A. Abnormal Beckmann rearrangement in polyphosphoric acid, I: Benzil monoxime and related oximes. *J. Org. Chem.* **1959**, *26*, 97.
15. (a) Rostamizadeh, S.; Ghaieni, H. R.; Aryan, R.; Amani, A. One-pot synthesis of 3,5-disubstituted 1,2,4-oxadiazoles directly from nitrile and hydroxylamine hydrochloride under solvent-free conditions using potassium fluoride as catalyst and solid support. *Synth. Commun.* **2010**, *40*, 3084; (b) Augustine, J. K.; Akabote, V.; Hegde, S. G.; Alagarsamy, P. PTSA-$ZnCl_2$: An efficient catalyst for the synthesis of 1,2,4-oxadiazoles from amidoximes and organic nitriles. *J. Org. Chem.* **2009**, *74*, 5640; (c) Cere, V.; Dal Monte, D.; Sondri, E. Catalytic hydrogenation of benzo[2.1.3]oxadiazoles. *Tetrahedron* **1972**, *28*, 3271.