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Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazine and 1,3,4-Thiadiazine from Substituted Acetophenones and Acid Hydrazides Using [Hydroxyl(tosyloxy)iodo]benzene

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Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazine and 1,3,4-Thiadiazine from Substituted Acetophenones and Acid Hydrazides Using [Hydroxyl(tosyloxy)iodo]benzene

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Abstract: A novel and direct method for the efficient synthesis of 2,5-disubstituted 1,3,4-oxadiazines from the reactions of [hydroxy(tosyloxy)iodo]-benzene with substituted acetophenones, followed by the treatment with acid hydrazide and K_2CO_3, is reported. The methodology is also extended to the synthesis of 5-aryl-6*H*-1,3,4-thiadiazin-2-amine by using thiosemicarbazide under similar experimental conditions.

Keywords: Hydrazide, hypervalent iodine, 1,3,4-oxadiazine, α-tosyloxylation

INTRODUCTION

The 1,3,4-oxadiazines and 1,3,4-thiadiazine scaffolds play an important role as a component of antihypertensive, anticholesteremic, antibacterial, and antiviral agents.[1] They are also used in polycarbonate foams, hair shampoos, and skin cosmetics.[2] There are a limited number of literature reports for the general synthesis of 1,3,4-oxadiazines derivatives. The cathodic reduction of semicarbazones of phenacyl bromides using $LiClO_4$–dimethylformamide (DMF) system is demonstrated for the

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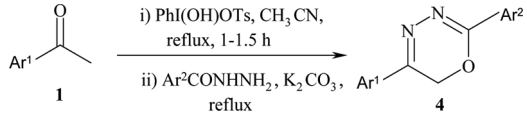
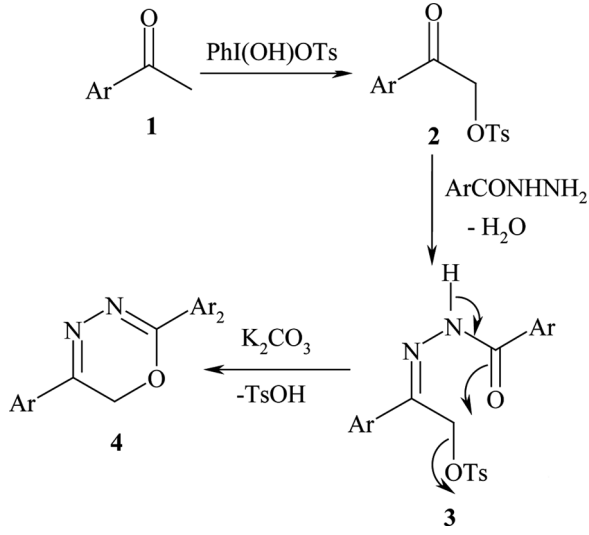


Scheme 1. Synthesis of 2,5-disubstituted 1,3,4-oxadiazine.

synthesis of fused 1,3,4-oxadiazines.[3] Another report involves the reaction of an excess of trifluoroacetic anhydride with arylaldehyde dimethylhydrazone to form 3,4-dihydro-*2H*-1,3,4-oxadiazines.[4] 2-Aryl-4*H*-1,3,4-oxadiazin-5(6*H*)-ones, which are known for the inhibition of monoamine oxidase, are synthesized from the reaction of 1-aroyl-2,2-bis(2-cyanoethyl)hydrazine with α-chloroacyl chloride.[5] Aromatic and heteroaromatic acid hydrazides reacted with oxalyl chloride in benzene or chloroform to give 2-aryl(hetaryl)-4*H*-1,3,4-oxadiazine-5,6-diones.[6] Recently, the reaction of cyanoacetylhydrazine with α-bromoacetophenone has been reported for the synthesis of 5-phenyl-2-acetonitrilo-1,3,4-oxadiazine.[7]

[Hydroxyl(tosyloxy)iodo]benzene (HTIB) is a versatile hypervalent iodine(III) reagent useful for α-tosyloxylation of enolizable ketones.[8] The resulting α-tosyloxyketone is known as an environmentally benign alternative to the toxic and lachrymatory α-haloketones. Because it is generally not necessary to isolate α-tosyloxyketone, it is utilized in situ as a strategic precursor for the one-pot synthesis of a wide range of



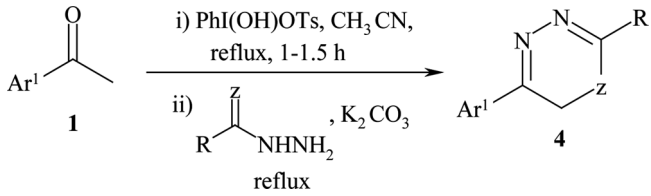
Scheme 2.

heterocycles such as thiazoles, selenazoles, oxazoles, imidazoles, pyrazoles, and benzofurans.[9] The application of HTIB has been hitherto unknown for the synthesis of 1,3,4-oxadiazines. In continuation of our interest in hypervalent iodine reagents,[10] herein we report a novel one-pot synthesis of 2,5-diaryl-6*H*-1,3,4-oxadiazine from various acetophenones and acid hydrazides using HTIB as the key reagent (Schemes 1 and 2).

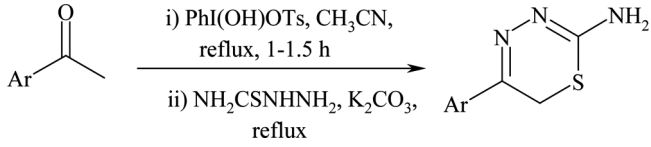
RESULTS AND DISCUSSION

Initially, the reaction of acetophenone with HTIB followed by treatment with benzoic hydrazide was carried out as a model reaction. In a typical experimental procedure, a mixture of acetophenone (2 mmol) and HTIB (2.2 mmol) was refluxed in CH_3CN (15 mL) for 1 h. After the formation of α-tosyloxyacetophenone as ascertained by thin-layer chromatography (TLC), benzoic hydrazide (2 mmol) and K_2CO_3 (2 mmol) were added to the reaction mixture and continued to reflux for an additional 6 h. The progress of the reaction was again monitored by TLC and after the usual workup procedure, the formation of 2,5-diphenyl-6*H*-1,3,4-oxadiazine in 74% yield was realized. The addition of K_2CO_3 in the latter stage of the

Table 1. Synthesis of 2,5-diaryl-6*H*-1,3,4-oxadiazine from substituted acetophenones and acid hydrazides using HTIB and K_2CO_3 in CH_3CN



Entry	R_1	R_2	Z	Product	Reaction time (h)	Yield (%)
1	C_6H_5-	C_6H_5-	O	**4a**	5	64
2	4-$CH_3C_6H_4$-	C_6H_5-	O	**4b**	5	58
3	4-$MeOC_6H_4$-	C_6H_5-	O	**4c**	5	63
4	4-BrC_6H_4-	C_6H_5-	O	**4d**	6	71
5	4-ClC_6H_4-	C_6H_5-	O	**4e**	5	64
6	4-$NO_2C_6H_4$-	C_6H_5-	O	**4f**	7	58
7	4-BrC_6H_4-	4-BrC_6H_4-	O	**4g**	5	68
8	C_6H_5-	NH_2	S	**4h**	7	61
9	4-$CH_3C_6H_4$-	NH_2	S	**4i**	8	65
10	4-ClC_6H_4-	NH_2	S	**4j**	8	63
11	4-BrC_6H_4	NH_2	S	**4k**	7	62



Scheme 3.

reaction was necessary for the requisite cyclization reaction of acid hydrazone of α-tosyloxyacetophenone to form 1,3,4-oxadiazine.

To demonstrate the generality of this method, we investigated the scope of this reaction under the optimized conditions, and the results are summarized in Table 1. As shown in Table 1, this method is equally effective for a wide range of acetophenones with both electron-donating and electron-withdrawing substituents.

The methodology was also extended to the synthesis of 5-aryl-6*H*-1,3,4-thiadiazin-2-amine from the reactions of substituted acetophenones with thiosemicarbazides using HTIB under similar experimental conditions (Scheme 3). In these cases (Table 1), the formation of 5-aryl-6*H*-1,3,4-thiadiazin-2-amine again took place in good to excellent yields. This method is more superior and flexible than the literature report of the heterocyclization of thiosemicarbazide with α-haloketone, which is a potentially toxic and lachrymatory compound.[11]

CONCLUSION

In summary, we have developed a general and direct method for an expeditious, one-pot synthesis of 2,5-diaryl-6*H*-1,3,4-oxadiazine and 5-aryl-6*H*-1,3,4-thiadiazin-2-amine from readily available substituted acetophenones and acid hydrazides using HTIB as the key oxidant. This method does not involves the use of any lachrymatory compounds, which are otherwise commonly reported in the literature for the synthesis of 1,3,4-oxadiazine and 1,3,4-thiadiazine derivatives.

EXPERIMENTAL

The required chemicals were purchased from commercial sources and were used without further purification. HTIB was prepared according to the literature procedure starting from (diacetoxyiodo)benzene.[12] ^1H and ^{13}C NMR spectra were recorded on a Bruker 400-MHz instrument using tetramethylsilane (TMS) as an internal standard in $CDCl_3$. Infrared

(IR) spectra were recorded on a Shimadzu Fourier transform (FT)–IR spectrophotometer.

General Procedure for the Synthesis of 2,5-Diaryl-6*H*-1,3,4-Oxadiazine

A mixture of the appropriate acetophenone (3 mmol) and HTIB (3 mmol) in CH_3CN (10 mL) was refluxed for 1–2 h. After the formation of α-tosyloxyketone as ascertained by thin-layer chromatograpy (TLC), a mixture of benzoic hydrazide (3 mmol) and K_2CO_3 (3 mmol) was added to the reaction mixture, which continued to reflux for an additional 6–8 h. The progress of the reaction was again monitored by TLC. After completion of the reaction, the mixture was diluted with water and extracted with $CHCl_3$ (3×15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude products, which were purified by column chromatography.

General Procedure for the Synthesis of 5-Aryl-6*H*-1,3,4-thiadiazin-2-Amine

The experimental procedure for the synthesis of 5-aryl-6*H*-1,3,4-thiadiazin-2-amine is identical as mentioned previously for the synthesis of 2,5-diaryl-6*H*-1,3,4-oxadiazine except that the use of thiosemicarbazide in place of benzoic hydrazide is required.

Characterization of the Products

2,5-Diphenyl-6*H*-1,3,4-oxadiazine (**4a**)

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.59$ (s, 2H, OCH_2), 7.46–7.53 (m, 4H, ArH), 7.58–7.65 (m, 2H, ArH), 7.97 (d, 2H, $J = 9.6$ Hz, ArH), 8.15 (d, 2H, $J = 8$ Hz, ArH). ^{13}C NMR ($CDCl_3$): $\delta = 66.52$, 127.87, 128.50, 128.94, 129.42, 130.01, 133.41, 133.97, 134.28, 166.09, 192.15. IR (KBr, cm^{-1}): 3020, 2934, 1600, 1573, 1215, 792. Anal. calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.28; H, 5.13; N, 11.83.

2-Phenyl-5-*p*-tolyl-6*H*-1,3,4-oxadiazine (**4b**)

^{1}H NMR ($CDCl_3$): $\delta = 2.42$ (s, 3H, $ArCH_3$), 5.54 (s, 2H, OCH_2), 7.26 (t, 1H, $J = 10.4$ Hz, ArH), 7.45 (t, 2H, $J = 10.4$ Hz, ArH), 7.57 (m, 2H,

$J = 8$ Hz, ArH), 7.84 (d, 2H, $J = 10.8$ Hz, ArH), 8.12 (d, 2H, $J = 10.4$ Hz, ArH). ^{13}C NMR ($CDCl_3$): $\delta = 191.71$, 166.10, 144.90, 133.35, 131.78, 130.14, 129.59, 129.47, 128.46, 127.95, 66.44, 21.81. IR (KBr, cm^{-1}): 3020, 2983, 1607, 1559, 1476, 1215, 793. Anal. calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.79; H, 5.67; N, 11.17.

5-(4-Methoxyphenyl)2-phenyl-6*H*-1,3,4-oxadiazine (**4c**)

^{1}H NMR ($CDCl_3$): $\delta = 3.87$ (s, 3H, OCH_3), 5.52 (s, 2H, OCH_2), 6.94 (d, 2H, $J = 11.6$ Hz, ArH), 7.42–7.57 (m, 3H, ArH), 7.93 (d, 2H, $J = 11.6$ Hz, ArH), 8.12 (d, 2H, $J = 9.2$ Hz, ArH). ^{13}C NMR ($CDCl_3$): $\delta = 55.57$, 66.27, 114.10, 127.29, 128.47, 128.93, 129.50, 130.18, 133.35, 164.07, 166.14, 190.59. IR (KBr, cm^{-1}): 3019, 2937, 1602, 1514, 1452, 1215, 797. Anal. calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.13; H, 5.27; N, 10.57.

5-(4-Bromophenyl)2-phenyl-6*H*-1,3,4-oxadiazine (**4d**)

^{1}H NMR ($CDCl_3$): $\delta = 5.51$ (s, 2H, OCH_2), 7.47 (t, 2H, $J = 9.6$ Hz, ArH), 7.58–7.65 (m, 3H, ArH), 7.81 (d, 2H, $J = 10.8$ Hz, ArH), 8.11 (d, 2H, $J = 10.4$ Hz, ArH). IR (KBr, cm^{-1}): 3019, 2931, 1587, 1215, 1125, 799. Anal. calcd. for $C_{15}H_{11}BrN_2O$: C, 57.16; H, 3.52; N, 8.89. Found: C, 57.14; H, 3.51; N, 8.93.

5-(4-Chlorophenyl)2-phenyl-6*H*-1,3,4-oxadiazine (**4e**)

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.54$ (s, 2H, OCH_2), 7.46–7.54 (m, 4H, ArH), 7.59–7.61 (m, 1H, $J = 12$ Hz, ArH), 7.91–7.93 (m, 2H, ArH), 8.10–8.15 (m, 2H, ArH). IR (KBr, cm^{-1}): 3019, 1593, 1559, 1423, 1215, 793. Anal. calcd. for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10; N, 10.35. Found: C, 66.52; H, 4.11; N, 10.33.

5-(4-Nitrophenyl)2-phenyl-6*H*-1,3,4-oxadiazine (**4f**)

^{1}H NMR ($CDCl_3$): $\delta = 5.58$ (s, 2H, OCH_2), 7.49 (t, 2H, $J = 7.6$ Hz, ArH), 7.61 (t, 1H, $J = 7.4$ Hz, ArH), 8.12–8.15 (m, 4H, ArH), 8.38 (d, 2H, $J = 8.8$ Hz, ArH). ^{13}C NMR ($CDCl_3$): $\delta = 66.56$, 123.71, 127.74, 128.60, 129.04, 130.01, 133.69, 138.72, 150.74, 165.94, 191.12. IR (KBr, cm^{-1}): 3019, 1599, 1559, 1530, 1459, 1216, 793. Anal. calcd. for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94; N, 14.94. Found: C, 64.08; H, 3.89; N, 14.91.

2,5-Bis(4-bromophenyl)-6*H*-1,3,4-oxadiazine (**4g**)

^{1}H NMR ($CDCl_3$): $\delta = 5.53$ (s, 2H, OCH_2), 7.98 (d, 2H, $J = 8.56$ Hz, ArH), 7.65 (d, 2H, $J = 8.08$ Hz, ArH), 7.83 (d, 2H, $J = 8.92$ Hz, ArH), 7.66 (d, 2H, $J = 9.24$ Hz, ArH). ^{13}C NMR ($CDCl_3$): $\delta = 65.94$, 127.59, 127.97, 128.59, 128.74, 130.83, 131.24, 131.67, 132.19, 164.57, 190.51. IR (KBr, cm^{-1}): 3020, 2943, 1384, 1590, 1216, 796. Anal. calcd. for $C_{15}H_{10}Br_2N_2O$: C, 45.72; H, 2.56; N, 7.11. Found: C, 45.71; H, 2.59; N, 7.09.

5-Phenyl-6*H*-1,3,4-thiadiazin-2-amine (**4h**)

^{1}H NMR ($CDCl_3$): $\delta = 1.61$ (br. s, 2H, NH_2), 2.30 (s, 2H, SCH_2), 7.29 (m, 2H, ArH), 7.42 (m, 2H, ArH), 7.78 (m, 1H, ArH). IR (KBr, cm^{-1}): 3422, 3241, 3149, 2957, 2925, 1585, 1506, 1280, 1095, 840, 762.

5-*p*-Tolyl-6*H*-1,3,4-thiadiazin-2-amine (**4i**)

^{1}H NMR ($CDCl_3$): $\delta = 1.59$ (br. s, 2H, NH_2), 2.32 (s, 2H, SCH_2), 2.41 (s, 3H, $ArCH_3$), 7.29 (d, 2H, $J = 8.16$ Hz, ArH), 7.57 (d, 2H, $J = 8.14$ Hz, ArH).

5-(4-Chlorophenyl-6*H*-1,3,4-thiadiazin-2-amine (**4j**)

^{1}H NMR ($CDCl_3$): $\delta = 1.57$ (br. s, 2H, NH_2), 2.31 (s, 2H, SCH_2), 7.29 (d, 2H, $J = 8.52$ Hz, ArH), 7.63 (d, 2H, $J = 8.61$ Hz, ArH).

5-(4-Bromophenyl-6*H*-1,3,4-thiadiazin-2-amine (**4k**)

^{1}H NMR ($CDCl_3$): $\delta = 1.69$ (br. s, 2H, NH_2), 2.34 (s, 2H, SCH_2), 7.33 (d, 2H, $J = 9.02$ Hz, ArH), 7.59 (d, 2H, $J = 9.02$ Hz, ArH). IR (KBr, cm^{-1}): 3419, 2956, 2925, 1590, 1480, 1403, 1095, 825, 757.

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