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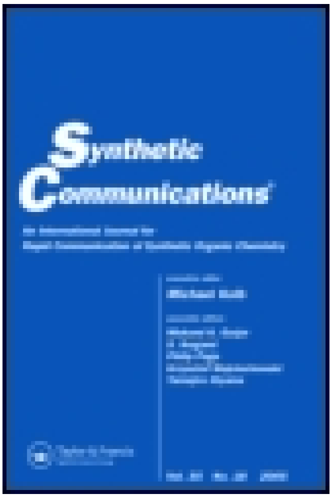

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N-Chlorosuccinimide/1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)-Mediated Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazoles

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N-CHLOROSUCCINIMIDE/1,8-DIAZABICYCLO[5.4.0] UNDEC-7-ENE (DBU)–MEDIATED SYNTHESIS OF 2,5-DISUBSTITUTED 1,3,4-OXADIAZOLES

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A mixture of N-chlorosuccinimide and 1,8-diazabicyclo[5.4.0]undec-7-ene oxidatively cyclizes structurally diverse acyl hydrazone, thereby providing an efficient and convenient method for the synthesis of various 2,5-disubstituted 1,3,4-oxadiazoles. The salient features of this method are mild reaction conditions, short reaction time, excellent yields, and simple workup procedure.

Keywords: Acyl hydrazones; N-chlorosuccinimide; 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); 1,3,4-oxadiazoles; oxidative cyclization

INTRODUCTION

1,3,4-Oxadiazoles are privileged structural units, not only in pharmaceutical chemistry[1–5] but also in pesticide chemistry[6,7] polymer chemistry,[8–10] and material science.[11–13] Because of these applications, the synthesis of 2,5-disubstituted 1,3,4-oxadiazoles has become a focus of synthetic organic chemistry. The most common approach toward preparation of 2,5-disubstituted 1,3,4-oxadiazoles involve cyclization of diacylhydrazines, prepared from the reaction of acyl hydrazide and acyl chloride. Several dehydrating agents such as thionyl chloride,[14,15] BF_3-(OEt_2),[16] 1,1,1,3,3,3-hexamethyldisilazane,[17] triflic anhydride,[18] phosphorus oxychloride,[19] phosphorus pentoxide,[20] polyphosphoric acid,[1b] sulfuric acid,[21] and zirconium chloride.[22] The most popular approaches are oxidative cyclization of acyl hydrazone using lead tetraacetate,[23] lead(IV) oxide,[24] potassium permanganate,[25] electrochemical methods,[26] iodobenzene diacetate (IBD),[27] chloroamine T,[28] cerric ammonium nitrate,[29] and trichloroisocyanuric acid.[30]

However, most of these processes have some disadvantages such as long reaction times, toxic or environmentally problematic by-products, laborious workup procedures, and/or poor yields.

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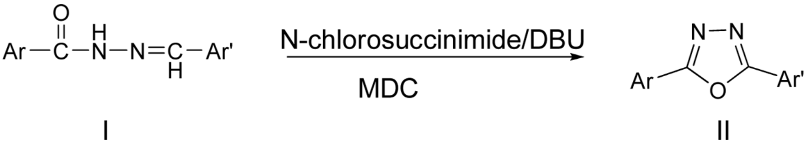
RESULTS AND DISCUSSION

As a part of our ongoing research on oxidation processes, we introduce N-chlorosuccinimide/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as an effective oxidant for oxidative cyclization of acyl hydrazone (I) to give 2,5-disubstituted 1,3,4-oxadiazoles (II) (Scheme 1).

N-Chlorosuccinimide and DBU mixture is used in oxidation processes;[31] hence, we explored the possibility of utilizing the N-chlorosuccinimide and DBU mixture as an oxidant for oxidative cyclization. N-chlorosuccinimide as well as DBU are commercially available at low cost. Reaction of acyl hydrazone (I) with N-chlorosuccinimide/DBU in dichloromethane (DCM) at room temperature to afforded 1,3,4-oxadiazoles in excellent yield within a short reaction time.

To check the effectiveness of the N-chlorosuccinimide and DBU mixture with different oxidants, we tried Dess–Martin periodinane (DMP), H_2O_2/HCl, and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as oxidants for oxidative cyclization. DCM was used as a solvent for DMP and DDQ, whereas acetonitrile was used for the H_2O_2/HCl reaction. The result revealed that DMP gave good yield but required excess molar quantity and therefore was not commercial viable. H_2O_2/HCl gave poor yield, and DDQ produced unwanted products. Thus, it is obvious from our study that the oxidizing performance of N-chlorosuccinimide/DBU was superior in this oxidative cyclization protocol (Scheme 1, Table 1).

The generality of oxidative cyclization of acyl hydrazone was checked by treating N-chlorosuccinimide/DBU with range of substituted and structurally diverse acyl hydrazone (I). Treatment of acyl hydrazone (I) bearing different substituents with N-chlorosuccinimide (1.5 eq.) and DBU (1.5 eq.) in DCM at room temperature to afforded 1,3,4-oxadiazoles in excellent yield (Table 2).



Scheme 1. Oxidative cyclization of acyl hydrazone using N-chlorosuccinimide and 1,8-diazabicyclo-[5.4.0]undec-7-ene.

Table 1. Effect of different oxidants on oxidative cyclization of acyl hydrazone

Sr. No.	Oxidant	Molar equivalent	Time (h)	Yield (%)
1	DMP	2.5	1.0	60
2	H_2O_2/HCl	1.2	1.0	15
3	DDQ	1.2	1.0	0
4	N-Chlorosuccinimide/DBU	1.2	0.5	85

Table 2. N-chlorosuccinimide/DBU-mediated synthesis of 2,5-disubstituted 1,3,4-oxadizoles

Entry	Ar	Ar″	Time (min)	Yield (%)	Melting point (°C)
A	C_6H_5	C_6H_5	30	85	138–140
B	C_6H_5	4-$CH_3OC_6H_4$	40	77	142
C	C_6H_5	4-$CH_3C_6H_4$	30	80	146–148
D	C_6H_5	4-ClC_6H_4	60	65	159
E	C_6H_5	4-pyridyl	60	60	151
F	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	45	70	149
G	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	35	72	178
H	4-$CH_3C_6H_4$	4-ClC_6H_4	25	65	204
I	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4$	45	70	160–161
J	4-$NO_2C_6H_4$	C_6H_5	60	45	206
K	3,5-$(CF_3)_2C_6H_3$	C_6H_5	60	60	164–166
L	3,5-$(CF_3)_2C_6H_3$	4-$CH_3OC_6H_4$	30	70	134–135

CONCLUSION

In summary, the present procedure involving N-chlorosuccinimide/DBU-mediated oxidative cyclization of acyl hydrazone (I) provides a convenient and synthetically useful method for preparation of various 2,5-disubstituted 1,3,4-oxadiazoles. The major advantages of this method over existing methods includes greater yield, shorter reaction time, simpler procedures, and commercial availability of N-chlorosuccinimide and DBU at a lower cost, which makes the process attractive for preparation of 1,3,4-oxadiazoles.

EXPERIMENTAL

Melting points are uncorrected and were determined with Buchi melting-point apparatus. Infrared (IR) spectra were recorded on a Shimadzu Hyper IR instrument as KBr pellets. ^1H NMR spectra were recorded on a Brucker 300-MHz spectrometer, and ^{13}C NMR were recorded on a 125-MHz spectrometer. Mass spectra (MS) were recorded on a MS-3200Q trap spectrometer. The reaction monitoring was accomplished by thin-layer chromatography (TLC) on silica-gel plates. All products have been previously described except entries K and L (Table 2).

Typical Procedure for Synthesis of 2,5-Disubstituted 1,3,4-Oxadiazole

N-chlorosuccinimide (1.5 mmol) was added to a stirred solution of acyl hydrazone (I) (1.0 mmol) in 5 ml DCM at room temperature; then DBU (1.5 mmol) was slowly added to reaction mixture, which continued to be stirred for the specified time (Table 2). After completion of the reaction as indicated by TLC, water (5 ml) was added and the product was extracted by DCM. The organic layer was washed with 5 ml 1 N HCl, 5 ml 10% sodium bicarbonate solution, and finally 5 ml saturated sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography (petroleum ether–ethyl acetate) to afford pure 1,3,4-oxadiazole.

Entry F: 2-(4-Methoxyphenyl)-5-(4-methylphenyl)-1,3,4-oxadiazole

IR (cm^{-1}): 1610, 1492, 1253, 1171, 1072, 835.1, 742. ^1H NMR: δ 2.44 (s, 3H), 3.89 (s, 3H), 7.01 (d, 2H), 7.31 (d, 2H), 7.99 (m, 4H). ^{13}C NMR : δ21.5, 55.3, 114.5, 116.2, 121.2, 126.8, 128.5, 129.5, 142.4, 164.4, 164.7. MS (EI): 267.2 (M^+).

Entry K: 2-(3,5-Bis(trifluoromethyl)phenyl)-5-phenyl-1,3,4-oxadiazole

IR (cm^{-1}): 1608, 1493, 1278, 1259, 1174, 1151, 906, 840. ^1H NMR: δ 7.60 (m, 3H), 8.07 (s, 1H), 8.18 (d, 2H), 8.60 (s, 2H). ^{13}C NMR: δ 123.19, 124.96, 125.6, 126.08, 126.81, 127.23, 129.23, 132.42, 133.26, 163.8, 164.5. MS (EI): 359 (M^+).

Entry L: 2-(3,5-Bis(trifluoromethyl)phenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole

IR (cm^{-1}): 1608, 1492, 1259, 1259, 1174, 1151, 906, 841. ^1H NMR: δ 3.92 (s, 3H), 7.05 (d, 2H), 8.05 (s, 1H), 8.10 (d, 2H), 8.58 (s, 2H). ^{13}C NMR: δ 55.6, 114.9, 118.1, 123.3, 124.7, 126.8, 129.1, 129.8, 132.1, 161.5, 164.1, 164.5. MS (EI): 389.2 (M^+).

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