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Note

Hypervalent iodine mediated synthesis of the heterocyclyl-1,3,4-oxadiazoles

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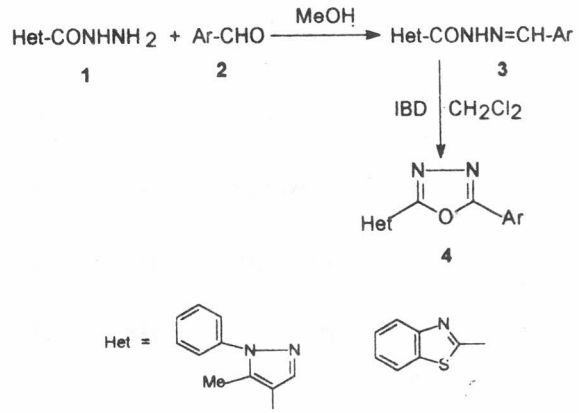
Oxidation of various heterocyclyl *N*-acylhydrazones **3a-j** with iodobenzene diacetate (IBD) in dichloromethane provides a facile method for the synthesis of heterocyclyl-1,3,4-oxadiazoles **4a-j.**

Hypervalent iodine (III) reagents have generated considerable interest in the recent years due to their applications in the synthesis of heterocyclic compounds[1-3]. In continuation of our efforts in developing I(III) mediated methods for the synthesis of heterocyclic compounds[4] we have focussed our attention to the synthesis of heterocyclyl-1,3,4-oxadiazoles. There are several methods reported in the literature for the synthesis of oxadiazoles from acylhydrazones, which include oxidation with lead tetraacetate (LTA)[5] or electrochemical oxidation of *N*-acylhydrazones of aldehydes[6].The iodobenzene diacetate (IBD) has also been employed for the synthesis of oxadiazoles from simple alkyl and phenyl acylhydrazones[7].

Our ongoing interest in the development of simpler hypervalent iodine mediated methodologies in heterocyclic synthesis[2], coupled with the significant biological importance of oxadiazoles in medicine and agrochemicals[8-11] prompted us to undertake the oxidation of the acylhydrazones of heterocyclic acid hydrazides. We report in this note the synthesis of heterocyclyl-1,3,4-oxadiazoles **4a-j** using IBD as an oxidizing reagent (cf. Scheme I).

Heterocyclyl *N*-acylhydrazones **3a-j** were prepared by the condensation of appropriate aldehydes with heterocyclyl acylhydrazines (Table I). The oxidative cyclization of aldehyde *N*-acylhydrazones **3a-j** to **4a-j** was effected by using



Scheme I

IBD and the results are summarized in Table II. It is to be noted that when Het is 4-(5-methyl-1-phenyl-pyrazolyl), the reaction is completed within 10 minutes at room temperature using one equivalent of IBD, whereas when Het is 2-benzothiazolyl, the reaction requires 30 minutes at reflux temperature, and two equivalents of IBD. A plausible mechanism for the conversion of **3** to **4** is outlined in Scheme II.

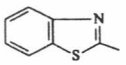
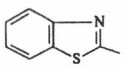
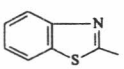
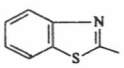
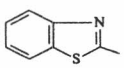
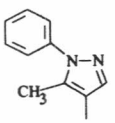
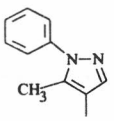
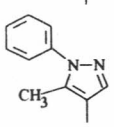
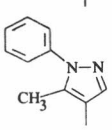
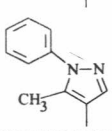
The intermediates **5** and **6** are suggested on the basis of oxidation of Schiff bases by IBD[12], and oxidative cyclisation of *N*-acylhydrazone[7]. In conclusion we find that IBD is a reagent of choice for the synthesis of heterocyclyl substituted 1,3,4-oxadiazoles, as compared to other reported methods which involve the use of toxic reagents like LTA[5]. In addition, this IBD mediated synthesis of 1,3,4-oxadiazoles is very facile and quick.

Experimental Section

All melting points are uncorrected. ^{1}H NMR spectra in $CDCl_3$ were recorded on a 300 MHz spectrometer using TMS as an internal standard, IR spectra in KBr on a Perkin-Elmer 237B spectrometer, and mass spectra on a Hewlett-Packard GC/MS-5985 instrument. Compounds **1** were prepared through the reported procedure[13b].

Heterocyclyl acylhydrazones 3a-j: General Procedure. To an ethanolic solution of **1** (0.01 mole) was added corresponding benzaldehyde

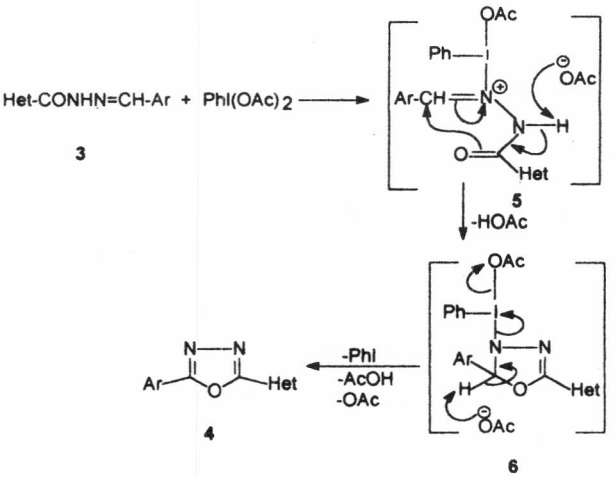
Table I—Physical data of compounds **3a-j**

Compd	Het	Ar	m.p. °C	Yield (%)
3a		Ph	220-21	89
3b		4-$CH_3C_6H_4$	201-02	90
3c		4-ClC_6H_4	230-31	93
3d		4-$OMeC_6H_4$	196-97	88
3e		4-$NO_2C_6H_4$	264	92
3f		Ph	185	78
3g		4-$CH_3C_6H_4$	190	82
3h		4-ClC_6H_4	188	81
3i		4-$OMeC_6H_4$	162	72
3j		4-$NO_2C_6H_4$	282	86

(0.011 mole) and the solution was refluxed for 1-2 hr. The solvent was evaporated *in vacuo* to half its volume and cooled to room temperature. The solid obtained was filtered and washed with ethanol. The physical data of **3a-j** are listed in Table I.

***N*-(2-Benzothiazoloyl) -*N'*-benzylidenehydrazine 3a** : ^{1}HNMR : δ 7.22-7.25 (m, 2H, ArH), 7.46-7.58 (m, 2H, benzothiazolyl C_5-H and C_6-H), 7.68-7.72 (d, 3H, ArH), 7.98-8.00 (dd, 1H, benzothiazolyl C_4-H), 8.05-8.10 (dd, 1H, benzothiazolyl C_7-H), 8.31 (s, 1H, –N=CH), 10.39(s, 1H; NH exchangeable with D_2O) ; IR (KBr/cm^{-1}) : 3210(NH), 1659(C=O), 1604, 1571(Ar) (Found : C, 64.01 ; H, 3.82; N, 15.02. $C_{15}H_{11}N_3OS$ requires C, 64.06 ; H, 3.91 ; N, 14.95%).

***N*-(2-Benzothiazoloyl) -*N'*-(4-methylbenzylidene)hydrazine 3b** : ^{1}HNMR : δ 2.38 (s, 3H, CH_3), 7.21-7.26 (m, 2H, ArH), 7.48-7.59 (m, 2H, benzothiazolyl C_5-H and C_6-H), 7.69-7.72 (d, 2H, ArH), 7.97-8.00 (dd, 1H, benzothiazolyl C_4-H), 8.06-8.09 (dd, 1H, benzothiazolyl C_7-H), 8.32 (s, 1H, –N=CH), 10.41(s, 1H, NH exchangeable with D_2O) (Found : C, 65.13; H, 4.13; N, 14.19. $C_{16}H_{13}N_3OS$ requires C, 65.08; H, 4.41; N, 14.33%).



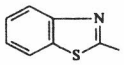
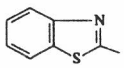
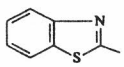
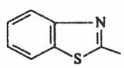
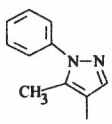
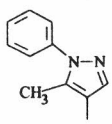
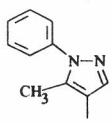
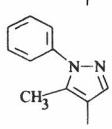
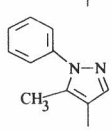
Scheme II

***N*-(2-Benzothiazoloyl)-*N'*-(4-methoxybenzylidene)hydrazine 3d:** ^{1}HNMR: δ 3.86 (s, 3H, $–OCH_3$), 6.94-6.98 (dd, 2H, ArH), 7.50-7.61 (m, 2H, benzothiazolyl C_5-H and C_6-H), 7.75-7.80 (d, 2H, ArH), 7.99-8.11 (m, 2H, benzothiazolyl C_4-H and C_7-H), 8.30 (s, 1H, N=CH), 10.33 (s, 1H, NH exchangeable with D_2O) (Found : C, 61.72 ; H, 3.97 ; N, 13.65. $C_{16}H_{13}N_3O_2S$ requires C, 61.74 ; H, 4.18 ; N, 13.51%).

***N*-(5-Methyl-1-phenyl-4-pyrazoloyl)- *N'*-benzylidenehydrazine 3f :** ^{1}HNMR : δ 2.64 (s, 3H, pyrazolyl C_5-CH_3), 7.39-7.71 (m, 10H, ArH), 7.88 (s, 1H, pyrazolyl C_3-H), 8.54 (s, 1H, N=CH), 9.41 (brs, 1H, NH, exchangeable with D_2O) (Found : C, 70.88 ; H, 4.92 ; N, 18.12. $C_{18}H_{16}N_4O$ requires C, 71.05 ; H, 5.26 ; N, 18.42%).

***N*-(5-Methyl-1-phenyl-4-pyrazoloyl)- *N'*-(4-methylbenzylidene)hydrazine 3g:** ^{1}HNMR: δ 2.37 (s, 3H, CH_3), 2.64 (s, 3H, pyrazolyl C_5-CH_3), 7.19-7.88 (m, 9H, ArH), 7.88 (s,1H, pyrazolyl C_3-H), 8.55 (s, 1H, N=CH), 9.75 (brs, 1H, NH exchangeable with D_2O) (Found : C, 71.52 ; H, 5.39 ; N, 17.48. $C_{19}H_{18}N_4O$ requires C, 71.69; H, 5.66; N, 17.61%).

Table II—Physical data of compounds **4a-j**

Compd	Het	Ar	m.p.(lit[13a].m.p.) °C	Yield %
4a*		Ph	176-77(177)	65
4b		4-$CH_3C_6H_4$	185-86	76
4c		4-ClC_6H_4	178(178)	66
4d		4-$OMeC_6H_4$	180-81(180)	72
4e		4-$NO_2C_6H_4$	230-31(234)	60
4f		Ph	174	71
4g		4-$CH_3C_6H_4$	146	73
4h		4-ClC_6H_4	199	68
4i		4-$OMeC_6H_4$	155	78
4j		4-$NO_2C_6H_4$	218	72

***4a** ; IR (KBr/cm^{-1}) : 1560, 1545 (Ar) ; Mass : m/z (M+1, CI) ; 280 (100), 279 (61.07), 253 (0.60), 250 (4.20), 240 (1.10), 238 (0.50), 237 (2.39), 224 (2.82), 223 (55.83).

Moreover, ^{1}H NMR spectra of **3** revealed the presence of exchangeable NH proton, which were absent in case of **4**.The characteristic C=O and N-H stretching of **3** were absent in IR spectra of **4**.

***N*-(5-Methyl-1-phenyl-4-pyrazoloyl)-*N'*-(4-chlorobenzylidene)hydrazine 3h:** ^{1}HNMR: δ 2.34 (s, 3H, pyrazolyl C_5-CH_3), 7.36-7.85 (m, 9H, ArH), 7.83 (s, 1H, pyrazolyl C_3-H), 8.49 (s, 1H, N=CH), 9.26 (brs, 1H, NH exchangeable with D_2O); Mass : m/z 338 (M^++2) (Found : C, 63.71; H, 4.18; N, 16.24. $C_{18}H_{15}ClN_4O$ requires C, 63.70 ; H, 4.44 ; N, 16.56%).

***N*-(5-Methyl-1-phenyl-4-pyrazoloyl)-*N'*-(4-methoxybenzylidene)hydrazine 3i:** ^{1}HNMR: δ 2.64 (s, 3H, pyrazolyl C_5-CH_3), 3.85 (s, 3H, OCH_3), 7.10-7.66 (m, 9H, ArH), 7.79 (s, 1H, pyrazolyl C_3-H), 8.53(s, 1H, N=CH), 8.97(s, 1H, NH exchangeable with D_2O) (Found : C, 68.22 ; H, 5.11 ; N, 16.44. $C_{19}H_{18}N_4O_2$ requires C, 68.26 ; H, 5.38 ; N, 16.76%).

***N*-(5-Methyl-1-phenyl-4-pyrazoloyl)-*N'*-(4-nitrobenzylidene)hydrazine 3j:** ^{1}HNMR: δ 3.00 (s, 3H, pyrazolyl C_5-CH_3), 7.45-8.25 (m, 10H, ArH and pyrazolyl C_3-H), 8.48 (1H, s, N=CH), 11.61 (1H, s, NH, exchangeable with D_2O) (Found: C, 61.65 ; H, 4.12 ; N, 19.92. $C_{18}H_{15}N_5O_3$ requires C, 61.89 ; H, 4.29 ; N, 20.04%).

Heterocyclyl-1,3,4-oxadiazoles 4a-j : General Procedure. To a stirred solution of **3** (10 mmoles) in dichloromethane (10 mL) was added IBD (10

moles, when Het = 5-methyl-1-phenyl-4-yl and 20 mmoles, when Het = 2-benzothiazolyl) and the mixture was stirred at room temperature in the case of former and refluxed for 10 to 30 min. on a water-bath in the case of latter. Concentration of the mixture *in vacuo,* followed by recrystallization from ethanol or purification by column chromatography on silica gel using petroleum ether-ethyl acetate as an eluant gave pure products. Physical data of **4a-j** are listed in Table II.

2-Benzothiazolyl-5-(4-tolyl)-1,3, 4-oxadiazole 4b: ^{1}HNMR : δ 2.46 (s, 3H, CH_3), 7.35-7.55 (d, 2H, ArH), 7.58-7.63 (m, 2H, benzothiazolyl), 8.00-9.27 (m, 4H, benzothiazolyl and ArH) (Found : C, 65.51 ; H, 3.48 ; N, 14.22. $C_{16}H_{11}N_3OS$ requires C, 65.53 ; H, 3.75 ; N, 14.33%).

2-(5-Methyl-1-phenyl-4-pyrazolyl)- 5-phenyl-1,3,4-oxadiazole 4f : ^{1}HNMR : δ 2.74 (s, 3H, pyrazolyl C_3-CH_3), 7.47-8.14 (m, 10H, ArH), 8.18 (s, 1H, pyrazolyl C_3-H) (Found : C, 71.42 ; H, 4.54 ; N, 18.32. $C_{18}H_{14}N_4O$ requires C, 71.52 ; H, 4.63 ; N, 18.54%).

2-(5-Methyl-1-phenyl-4-pyrazolyl)- 5-(4-tolyl)-1,3,4-oxadiazole 4g: ^{1}HNMR: δ 2.44 (s, 3H, CH_3), 2.73 (s, 3H, pyrazolyl C_5-CH_3), 7.26-7.99 (m, 9H, ArH), 8.17 (s, 1H, pyrazolyl C_3-H) ; Mass : m/z 316 (M^+) (Found : C, 71.98 ; H, 4.91 ; N, 17.46. $C_{19}H_{16}N_4O$ requires C, 72.15 ; H, 5.06 ; N, 17.72%).

2-(5-Methyl-1-phenyl-4-pyrazolyl)- 5-(4-chlorophenyl)-1,3,4-oxadiazole 4h : ^{1}HNMR : δ 2.74 (s, 3H, pyrazolylC_5-CH_3), 7.45-8.09 (m, 9H, ArH), 8.16 (s, 1H, pyrazole C_3-H) ; Mass : m/z 336 (M^+) (Found : C, 64.12 ; H, 3.71 ; N, 16.57. $C_{18}H_{13}ClN_4O$ requires C, 64.28 ; H, 3.86 ; N, 16.66%).

2-(5-Methyl-1-phenyl-4-pyrazolyl)- 5-(4-anisyl)-1,3,4-oxadiazole 4i : ^{1}HNMR : δ 2.73 (s, 3H, pyrazolyl C_5-CH_3), 3.89 (s, 3H, OCH_3), 7.01-8.07 (m, 9H, ArH), 8.16 (s, 1H, pyrazolyl C_3-H) (Found : C, 68.32 ; H, 4.52 ; N, 16.78. $C_{19}H_{16}N_4O$ requires C, 68.67 ; H, 4.81 ; N, 16.86%).

2-(5-Methyl-1-phenyl-4-pyrazolyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole 4j: ^{1}HNMR: ($CDCl_3$+DMSO); δ 2.76 (s, 3H, pyrazolyl C_5-CH_3), 7.45-8.42 (m, 10H, ArH and pyrazolyl C_3-H) (Found :C, 62.02 ; H, 3.63 ; N, 20.34. $C_{18}H_{13}N_5O_3$ requires C, 62.24 ; H, 3.74 ; N, 20.17%).

* Compounds **4a-e** are reported in the literature except **4b** and **4f-j** which were synthesized for the first time.

Acknowledgement

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References

1 (a) Moriarty R M & Prakash O, *Adv Heterocycl Chem*, 69, **1998**, 1.
(b) Prakash O & Singh S P, *Aldrichimica Acta,* 27, **1994,** 15.
2 (a) Prakash O, Saini N & Sharma P K, *Synlett* (*Account*), **1994,** 221.
(b) Prakash O, Saini N & Sharma P K, *Heterocycles*, 38, **1994**, 409.
3 (a) Prakash O, Saini N & Goyal S, *J Chem Soc, Perkin. Trans 1*, **1992**, 707.
(b) Prakash O & Goyal S, *Synthesis*, **1991**, 629.
4 (a) Singh S P, Prakash O & Kumar D, *J Chem Res (S),* **1993**, 244. (b) Prakash O, Singh S P, Saini R K & Kumar D, *Synthetic Commun*, 25, **1995**, 3363.
(c) Prakash O, Sharma V & Sadana A, *Synth Commun*, 27, **1997**, 3371.
5 Stolle R, *J Prakt Chem*, 73, **1906**, 277.
(b) Baltazzi E & Wysocki A, *J Chem Ind* (London), **1963**, 1080.
6 Chiba T & Mitsuhiro O, *J Org Chem*, 57, **1992**, 1375.
7 Rui-Yang & Li-Xin Dai, *J Org Chem*, 58, **1993**, 3381.
8 Andotra C S, Langer T C, Dharm S & Kaur P, *Ind J Pharm Sci*, 55, **1993**, 19.
9 Gupta A K S, Garg M & Chandra U, *J Indian Chem Soc LVI*, **1974**, 1230.
10 Adelstein C H, Yen G W, Dajani E Z & Bianchi R G, *J Med Chem*, 19, **1976**, 1221.
11 (a) Hetzheim A & Mockel K, *Adv Heterocycl Chem*, 7, **1966**, 183.
(b) Behr L C, *Chem Heterocycl Compd*, 17, **1962**, 263.
(c) Varma R S, Saini R K & Prakash O, *Tetrahedron Lett*, 38, **1997**, 2621.
12 Narasimhabarathi S, Sunndaram S & Venkatasubramanian K, *Indian J Chem*, 15B, **1977**, 376.
13 (a) Sawhney S N, Singh J & Bansal O P, *J Indian Chem Soc, LI*, **1974**, 888.
(b) Campaigne E E & Van Verth J E, *J Org Chem*, 23, **1958**, 1344.