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AN EXPEDITIOUS SOLVENTLESS SYNTHESIS OF ISOXAZOLES

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9. Abbreviations used: Boc = *tert*-butoxycarbonyl, Z = benzyloxycarbonyl, Asn = (S)-asparagine, (S)-A₂pr = (S)-2,3-diaminopropanoic acid, Me = methyl, THF = tetrahydrofuran, MeOH = methanol, Et₂O = ethyl ether, PIDA = iodosobenzene diacetate
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AN EXPEDITIOUS SOLVENTLESS SYNTHESIS OF ISOXAZOLES

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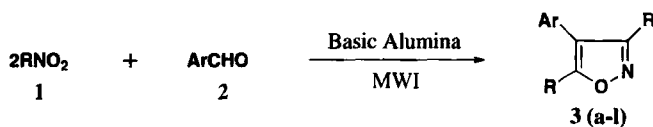
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In recent years, organic reactions on solid supports¹ and those assisted by microwaves² especially under solventless conditions,^{3,4} have attracted attention due to their enhanced selectivity, milder reaction conditions and associated ease of manipulation. Solid phase syntheses can address problems

in organic chemistry that cannot be solved through solution phase chemistry, namely the development of high pressure and the need for specialized sealed vessels as this strategy enables organic reactions to occur rapidly at atmospheric pressure⁵ in open vessels.

Isoxazole derivatives are useful structural components of many medicinal compounds,⁶ which have been reported as antimicrobial,⁷ spermicidal and anti-HIV active agents.⁸ A literature survey showed that isoxazoles have been prepared by number of methods such as reaction of ketones with hydroxylamines,⁹ 1,3-dipolar cycloaddition¹⁰ and by reaction of aromatic aldehydes with phenylnitromethane¹¹ in presence of base. We now describe a microwave-accelerated solid state approach¹² for the rapid assembly of isoxazoles.

Reaction of aromatic aldehydes with phenylnitromethane under microwave irradiation (MWI), on basic alumina afforded excellent yields (90-96%) of isoxazoles within 2-3 min. In contrast, the classical procedure for preparation of isoxazoles (50-60% yield) requires 5-18 h heating, an external base and solvents. Further, the use of basic alumina as solid support eliminates the need for an external base and solvents required in conventional method. The reaction of aromatic aldehydes with nitromethane is complete in same time with somewhat lower yield (82-85%) as compared to reaction with phenylnitromethane (see Table). The reaction of benzaldehyde and *p*-anisaldehyde with nitroethane under conventional conditions gave 73% and 69% respectively (with nitropropane, *p*-anisaldehyde gave a 78% yield); Best *et al.*¹³ also reported that aliphatic aldehydes gave poor yields (5-10%).



Ar = a) C₆H₅; b,j) 3-furyl; c) 4-Me₂NC₆H₄; d,k) 3-indolyl; e) 4-MeOC₆H₄
 f, l) 4-ClC₆H₄; g) 3,4-(OH)₂C₆H₃; h) 3,4-(OMe)₂C₆H₃; i) 2-Cl-4-Me-3-quinolyl
 a-i) R = Ph; j-l) R = Me

The formation of product is evidenced by the disappearance of a band due to the C=O of CHO at 1710-1685 cm⁻¹ and appearance of a band due to C=N of isoxazole at 1600-1630 cm⁻¹ in the IR spectra. The ¹H NMR of the products was devoid of the signal for CH₂ of phenylnitromethane at δ 3.9-4.0 and for the aldehydic protons at δ 10.20-10.50. Product formation was further confirmed by the presence of signals at δ 164-169 due to C-3, 110-116 due to C-4, and 157-160 due to C-5 of isoxazole ring in the ¹³C NMR spectra. These data are in accordance with those reported by Gavin *et al.*¹⁴ in that the chemical shifts of C-4 of isoxazole ring showed a smooth progression from 100.1-102.3 (no substituent), 109 (methyl substituent) to 110-117 (aryl substituent), which confirmed the presence of aryl substituent at C-4 and formation of isoxazole ring. The analytical and spectral data of products are given in Table 1 and 2 respectively. The isoxazoles prepared are shown in Table 1. All the synthesized compounds were screened for antifungal activity against fungi *A. niger* and *A. flavus* by paper disc diffusion method.¹⁵ Although all the isoxazoles displayed significant activity against both fungi,

Table 1. Analytical and Physical Data of Isoxazoles **3a-l**

Cmpd	Ar	R	Yield (%)	mp. (°C)	Time ^a (min.)	Elemental Anal. Found (Calcd) (%)		
						C	H	N
3a	C ₆ H ₅	Ph	91	210-212 ^b	2.0	84.83 (84.84)	5.07 (5.05)	4.73 (4.71)
3b	Furan-3-	Ph	96	162-164	2.5	79.41 (79.44)	4.54 (4.52)	4.89 (4.87)
3c	4-Me ₂ NC ₆ H ₄	Ph	90	140-142	3.0	81.18 (81.17)	5.90 (5.88)	8.21 (8.23)
3d	Indole-3-	Ph	93	168-170	2.0	82.13 (82.14)	4.78 (4.76)	8.35 (8.33)
3e	4-MeOC ₆ H ₄	Ph	92	145-147	3.0	80.71 (80.73)	5.18 (5.19)	4.31 (4.28)
3f	4-ClC ₆ H ₄	Ph	94	154-156	2.5	76.13 (76.15)	4.22 (4.23)	4.22 (4.23)
3g	3,4-(HO) ₂ C ₆ H ₃	Ph	92	164-166	2.0	76.61 (76.59)	4.58 (4.55)	4.22 (4.25)
3h	3,4-(MeO) ₂ C ₆ H ₃	Ph	93	152-154	3.0	77.34 (77.31)	5.33 (5.32)	3.94 (3.92)
3i	2-Cl-4-Me quinoline-3-	Ph	95	170-172	2.5	75.56 (75.53)	4.30 (4.28)	7.08 (7.05)
3j	Furan-3-	Me	85	45-47	2.5	62.22 (62.20)	3.70 (3.73)	10.37 (10.40)
3k	Indole-3-	Me	83	60-62	3.5	71.73 (71.70)	4.34 (4.31)	15.21 (15.25)
3l	4-ClC ₆ H ₄	Me	82	49-52	3.0	60.33 (60.31)	3.35 (3.32)	7.82 (7.79)

^a Total time of irradiation at 700 watts. ^b *lit.*¹⁷ mp. 211-212°C.

compounds **3b**, **3d**, **3h** and **3i** are the most active. In conclusion the salient feature of our approach is coupling microwaves with solvent-free technique keeping modernization and simplification of classical procedures, avoiding volatile and toxic organic solvents and bases, which make it a clean, efficient and economical technology for bioactive isoxazoles.

EXPERIMENTAL SECTION

Mps were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer FTIR-1710 spectrophotometer. ¹H NMR spectra were recorded at 90 MHz on a Perkin-Elmer R-32 spectrometer using TMS as internal reference (chemical shifts in δ (ppm)). ¹³C NMR spectra were recorded at 300 MHz on a Bruker Avanci spectrometer. Elemental analyses were performed on a Heraeus CHN-Rapid Analyser. Microwave irradiations were carried out in Padmini Essentia oven, Model Brownie at 2450 MHz. The average bulk temperature at the end of reaction was measured by inserting a thermometer in the reaction mixture.

Table 2. Spectral Data of Isoxazoles **3a-l**

Cmpd	IR (cm ⁻¹)	¹ H NMR (CDCl ₃) δ	δ ¹³ C NMR (CDCl ₃)			
			C3	C4	C5	Others
3a	1620 (C=N)	7.3-8.0 (m, 15H, Ar-H)	169.0	116.4	159.9	130.8 (C1'), 129.2 (C2',6'), 128.4 (C3',5'), 127.2 (C4')
3b	1630 (C=N)	4.82 (s, 1H, C-4 of furan), 6.37 (s, 1H, C-5 of furan), 6.43 (s, 1H, C-2 of furan), 7.5-8.1 (m, 10H, Ar-H)	165.2	108.2	157.6	145.2 (C2 of furan), 106.6 (C3 of furan), 111.4 (C4 of furan), 141.7 (C5 of furan), 130.2 (C1'), 129.3 (C2',6') 128.2 (C3',5'), 127.1 (C4')
3c	1600 (C=N)	7.2-7.9 (m, 14H, Ar-H), 2.2 (s, 6H, N-CH ₃)	168.4	112.3	160.5	121.4 (C1'), 129.2 (C2',6'), 122.2 (C3',5'), 169.2 (C4'), 50.3 (NCH ₃)
3d	1625 (C=N)	7.15 (s, 1H, H-2 of indole), 7.3-8.1 (m, 14H, Ar-H), 9.1 (brs, 1H, NH of indole)	166.6	110.4	158.3	125 (C2 of indole), 117.2 (C3 of indole), 126.2 (C3'), 125.1 (C4') 127.5 (C5'), 128 (C6'), 140.5 (C7'), 138.2 (C8')
3e	1610 (C=N)	3.20 (s, 3H, OCH ₃), 7.15-7.85 (m, 14H, Ar-H)	169.1	116.2	159.9	122.6 (C1'), 128.2 (C2',6'), 114.3 (C3',5'), 159.0 (C4'), 55.3 (OMe)
3f	1615 (C=N)	7.2-7.9 (m, 14H, Ar-H)	164.3	115.6	160.2	133.4 (C1'), 130 (C2',6'), 128.9 (C3', 5'), 128.2 (C4')
3g	1635 (C=N)	4.83 (s, 2H, H-3',4'), 7.4-7.9 (m, 13H, Ar-H)	165.0	116.2	158.4	125.3 (C1'), 129.4 (C2', 5'), 126.4 (C6'), 140.2 (C3', 4')
3h	1630 (C=N)	3.41 (s, 6H, OCH ₃ -3',4'), 7.3-8.0 (m, 13H, Ar-H)	169.1	116.3	160.5	124.6 (C1'), 129.2 (C2',5'), 130.3 (6'), 159.4 (C3',4'), 55.3 (OMe)
3i	1635 (C=N)	3.15 (s, 3H, CH ₃ -4'), 7.4-8.2 (m, 14H, Ar-H)	164.3	113.3	159.6	165.2 (C2'), 130.9 (C3'), 137.9 (C4'), 127 (C5'), 126.8 (C6'), 129.2 (C7'), 130.3 (C8'), 140.3 (C9'), 130.2 (C10')
3j	1625 (C=N)	4.90 (s, 1H, C-4 of furan), 6.32 (s, 1H, C-5 of furan), 6.62 (s, 1H, C-3 of isoxazole), 6.78 (s, 1H, C-2 of furan), 7.10 (s, 1H, C-5 of isoxazole)	167.3	115.2	158.5	147.2 (C2 of furan), 109.6 (C3 of furan), 110.4 (C4 of furan), 141.5 (C5 of furan),
3k	1630 (C=N)	6.69 (s, 1H, C-3 of isoxazole) 7.12 (s, 1H, C-5 of isoxazole) 7.20-7.9 (m, 5H, indole), 9.1 (brs, 1H, NH of indole)	169.6	116.3	159.0	123 (C2'), 119.2 (C3'), 125.2 (C4'), 127.7 (C5'), 129 (C6'), 140.9 (C7')
3l	1620 (C=N)	6.71 (s, 1H, C-3 of isoxazole) 7.09 (s, 1H, C-5 of isoxazole) 7.2-7.6 (m, 4H, Ar-H)	165.3	116.7	160.0	133.0 (C1'), 130.5 (C2',6'), 128.3 (C3', 5'), 128.7 (C4')

4-Substituted-3,5-diphenyl-1,2-isoxazoles (3a-i). Typical Procedure.- Basic alumina (40 g) was added to a solution of benzaldehyde (2.0 g, 4.41 mmol) and phenylnitromethane (6.37 g, 9.3 mmol) in acetone (10 ml) at room temperature. The reaction mixture was thoroughly mixed and the adsorbed material was dried in air (beaker), placed in an alumina bath¹⁶ inside the microwave oven and irradiated intermittently at 0.5 min intervals at 140° for the specified time (Table 1). Upon completion of the reaction as determined by TLC examination, the mixture was cooled to room temperature and the product was extracted into diethyl ether (3x15 ml). The ethereal extract washed with brine and dried over MgSO₄. Removal of the solvent under reduced pressure yielded the product which was purified by recrystallization from an acetone-methanol mixture.

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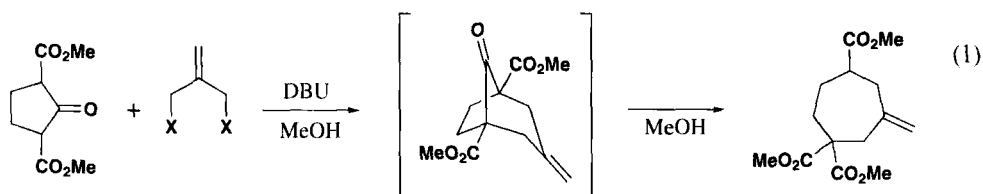
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TWO-FOLD CYCLOALKYLATIONS OF A BICYCLO[3.3.0]OCTANE-3,7-DIONE

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An elegant three-step one-pot ring enlargement of dimethyl cyclopentanone-2,5-dicarboxylate with 2-halomethylallyl halides to give cycloheptane derivatives was reported quite recently by Rodriguez *et al.* (Eq. 1)^{1,2} Our interest in double ring enlargements of substituted bicyclo[3.3.0]octanes to bicyclo[5.5.0]dodecanes as possible intermediates for certain polycycles,^{3,4} prompted us to apply this new reaction to compound **1**.⁵



When **1** was treated with two equivalents of dichloro compound **2a** and five eq. of DBU, a tarry mixture was formed from which a low yield (3%) of crystals could be obtained. The product had the composition of $C_{24}H_{26}O_{10}$ and thus could not be the desired mixture of compounds **5a** and **5b** (Scheme 1). On the other hand, two molecules of **2** had been incorporated. The ^{13}C NMR spectrum included twenty four signals. There were indications for the presence of four methyl esters, one keto group, and three double bonds, and consequently the new compound could not be the precursor **3** either. The