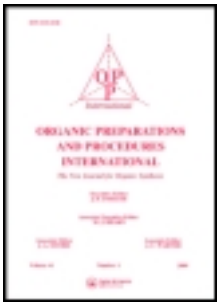


Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

AN EXPEDITIOUS SOLVENTLESS SYNTHESIS OF ISOXAZOLES

M. Kidwai [a] & P. Sapra [a]

[a] Department of Chemistry , University of Delhi , Delhi, 110007, INDIA

Published online: 18 Feb 2009.

To cite this article: M. Kidwai & P. Sapra (2001) AN EXPEDITIOUS SOLVENTLESS SYNTHESIS OF ISOXAZOLES, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 33:4, 381-386

To link to this article: http://dx.doi.org/10.1080/00304940109356606

Acknowledgement.- Financial support from the Chemical Faculty, Technical University of Gdańsk is gratefully acknowledged.

REFERENCES

1. R. Andruszkiewicz, S. Milewski and E. Borowski, *J. Enzyme Inhibition*, **9**,123 (1995)

2. R. Andruszkiewicz, R. Jedrzejczak, T. Zieniawa, M. Wojciechowski and E. Borowski, *ibid.*, **15**, 429 (2000)

3. J. Gumieniak, R. Andruszkiewicz, A. Czerwiński, J. Grzybowska and E. Borowski, *J. Antibiot.*, **36**, 1239 (1983)

4. R. Barfod, L. Bendahl, A. Hammershoi, D. K. Jensen, A. M. Sargeson and A. C. Willis, *J. Chem. Soc., Dalton Trans.*, 449 (**1999**)

5. L. D. Arnold, T. H. Kalantar and J. C. Vederas, *J. Am. Chem. Soc.*, **107**, 7105 (1985)

6. N. Kucharczyk, B. Badet and F. LeGoffic, *Synth. Comm.*, **19**, 1603 (1989)

7. E. S. Ratemi and J. C.Vederas, *Tetrahedron Lett.*, **35**, 7605 (1994)

8. R. F. Borch and A. I. Hassid, *J. Org. Chem.*, **37**, 1673 (1972)

9. Abbreviations used: Boc = *tert*-butoxycarbonyl, Z = benzyloxycarbonyl, Asn = (S)-asparagine, (S)-A_2pr = (S)-2,3-diaminopropanoic acid, Me = methyl, THF = tetrahydrofuran, MeOH = methanol, Et_2O = ethyl ether, PIDA = iodosobenzene diacetate

10. L. H. Zhang, G. S. Kauffman, J. A. Pesti and J. Yin, *J. Org. Chem.*, **62**, 6918 (1997)

****

AN EXPEDITIOUS SOLVENTLESS SYNTHESIS OF ISOXAZOLES

Submitted by M. Kidwai* and P. Sapra
(01/26/01)

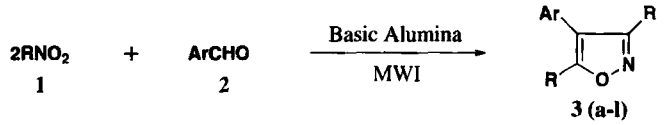
Department of Chemistry
University of Delhi, Delhi-110007, INDIA

In recent years, organic reactions on solid supports[1] and those assisted by microwaves[2] 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 pressure[5] 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 cycloaddition[10] and by reaction of aromatic aldehydes with phenylnitromethane[11] in presence of base. We now describe a microwave-accelerated solid state approach[12] 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) C_6H_5; b,j) 3-furyl; c) 4-$Me_2NC_6H_4$; d,k) 3-indolyl; e) 4-$MeOC_6H_4$
f, l) 4-ClC_6H_4; g) 3,4-$(OH)_2C_6H_3$; h) 3,4-$(OMe)_2C_6H_3$; i) 2-Cl-4-Me-3-quinolinyl
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 CH_2 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 ^{13}C 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_6H_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	$4\text{-}Me_2NC_6H_4$	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	$4\text{-}MeOC_6H_4$	Ph	92	145-147	3.0	80.71 (80.73)	5.18 (5.19)	4.31 (4.28)
3f	$4\text{-}ClC_6H_4$	Ph	94	154-156	2.5	76.13 (76.15)	4.22 (4.23)	4.22 (4.23)
3g	$3,4\text{-}(HO)_2C_6H_3$	Ph	92	164-166	2.0	76.61 (76.59)	4.58 (4.55)	4.22 (4.25)
3h	$3,4\text{-}(MeO)_2C_6H_3$	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	$4\text{-}ClC_6H_4$	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)). ^{13}C NMR spectra were recorded at 300 MHz on a Bruker Avancl 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})	^1H 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_5)
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 bath[16] 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 $MgSO_4$. Removal of the solvent under reduced pressure yielded the product which was purified by recrystallization from an acetone-methanol mixture.

Acknowledgement.- One of the authors (PS) is thankful to CSIR New Delhi for the award of JRF.

REFERENCES

1. S. Deshayes, L. Marion, A. Loupy, J. L. Luche and A. Petit, *Tetrahedron*, **55**, 10851 (1999).

2. M. Kidwai and R. Kumar, *Org. Prep. Proced. Int.*, **30**, 451 (1998).

3. A. Oussaid, L. N. Thach and A. Loupy, *Tetrahedron Lett.*, **38**, 2451 (1997).

4. A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacqualt and D. Mathe, *Synthesis*, 1213 (**1998**).

5. D. C. Dittmer, *Chem. Ind.*, 779 (**1997**).

6. M. Nakatsuka, Y. Ueno, S. Okada and F. Nishikado, *Jpn. Kokai Tokkyo Koho JP*, 186,038 (2000); *Chem. Abstr.*, **133**, 84260k (2000).

7. R. Patil and J. S. Biradar, *Asian J. Chem.*, **11**, 1127 (1999); *Chem. Abstr.*, **132**, 279153q (2000).

8. S. Srivastava, L. K. Bajpai, S. Batra, A. P. Bhaduri, J. P. Maikhuri, G. Gupta and J. D. Dhar, *Bioorg. Med. Chem.*, **7**, 2607 (1999).

9. S. Singh, K. S. Avor, B. Pouw, T. W. Seale and G. P. Barmadjian, *Chem. Pham. Bull.*, **47**, 1501 (1999).

10. M. L. Fascio, V. J. Montesano and N. B. D'Accorso, *J. Carbohydr. Chem.*, **19**, 393 (2000).

11. P. Grunanger and P. Vita-Finzi, *The Chemistry of Heterocyclic Compounds*, Wiley, New York, volume **49** (1991).

12. M. Kidwai, P. Misra and B. Dave, *MGMC*, **23**, 401 (2000); M. Kidwai, K. R. Bhushan, P. Sapra, R. K. Saxena, and R. Gupta, *Bioorg. Med. Chem.*, **8**, 69 (2000); M. Kidwai, P. Misra and K. R. Bhushan, *Polyhedron*, **18**, 2641 (1999); M. Kidwai, P. Sapra and B. Dave, *Synth. Commun.*, **30**, 4479 (2000).

13. W. M. Best, E. L. Ghisalberti and M. Powell, *J. Chem. Res.(s)*, 388 (**1998**).

14. Gavin M. Buchan and Alan B. Turner, *J. Chem. Soc. Perkin Trans. 1*, 2115 (**1975**).

15. H. W. Seely and P. J. V. Denmark, *Microbes in Action*, W. H. Freeman & Co., USA, 1972.

16. G. Bram, A. Loupy and M. Majdoub, *Tetrahedron*, **46**, 5167 (1990).

17. Heim, *Ber.*, **44**, 2016 (1911).

****

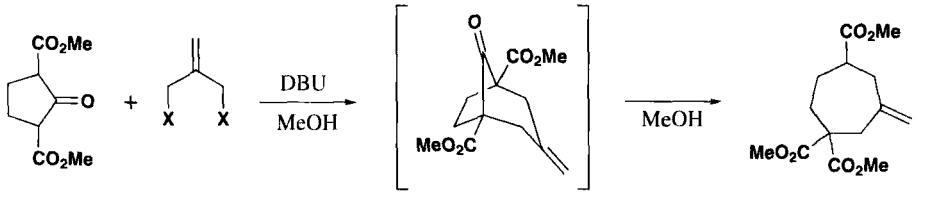
TWO-FOLD CYCLOALKYLATIONS OF A BICYCLO[3.3.0]OCTANE-3,7-DIONE

Submitted by (11/27/00)

Eckehard Volker Dehmlow*, Hans-Jörg Breyholz, Beate Neumann, and Hans-Georg Stammler

Fakultät für Chemie, Universität Bielefeld, Postfach 100 131, D-33501 Bielefeld, GERMANY
e-mail: dehmlow@post.uni-bielefeld.de; Fax:(xx49) 521-106-6146

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]



(1)

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