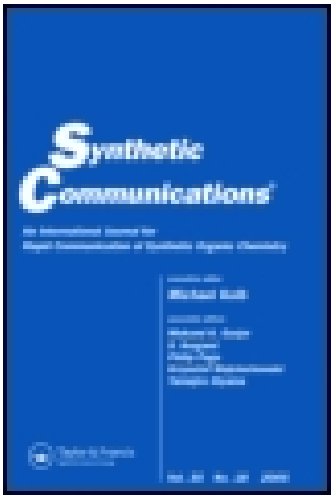


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Microwave-Assisted Synthesis of N,N′-Disubstituted Acetamidine Ligands

Phimphaka Harding [a], David J. Harding [a], Harry Adams [b] & Sujittra Youngme [c]

[a] Department of Chemistry, School of Science, Walailak University, Thasala, Thailand

[b] Department of Chemistry, University of Sheffield, Brook Hill, England

[c] Faculty of Science, Department of Chemistry, Khon Kaen University, Khon Kaen, Thailand

Published online: 14 Aug 2007.

To cite this article: Phimphaka Harding, David J. Harding, Harry Adams & Sujittra Youngme (2007) Microwave-Assisted Synthesis of N,N′-Disubstituted Acetamidine Ligands, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:16, 2655-2661, DOI: 10.1080/00397910701465164

To link to this article: http://dx.doi.org/10.1080/00397910701465164

Synthetic Communications®, 37: 2655–2661, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701465164

Microwave-Assisted Synthesis of *N,N′*-Disubstituted Acetamidine Ligands

Phimphaka Harding and David J. Harding
Department of Chemistry, School of Science, Walailak University, Thasala, Thailand

Harry Adams
Department of Chemistry, University of Sheffield, Brook Hill, England

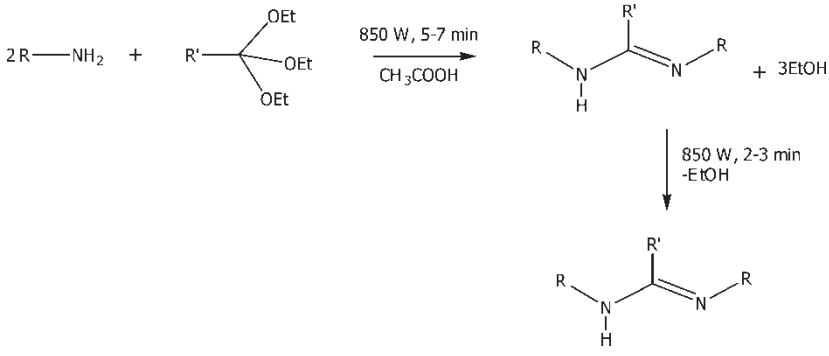
Sujittra Youngme
Faculty of Science, Department of Chemistry, Khon Kaen University, Khon Kaen, Thailand

Abstract: Under microwave activation, triethylorthoacetate reacts with the substituted anilines in the presence of acetic acid as a catalyst, producing acetamidine in moderate to high yields. The X-ray structures of the new amidines, *N,N′*-bis(3,5-dimethylphenyl)-acetamidine and *N,N′*-bis(*p*-tolyl)acetamidine, are also reported, revealing polymeric chains supported by intramolecular H-bonds.

Keywords: amidine, microwave-assisted synthesis, one pot

Recently, amidines have been used as bridging ligands for the preparation of transition-metal complexes, especially paddle-wheel complexes.[1–4] Rapid synthesis of increasingly complex amidines is therefore of prime importance. Taylor and Ehrhart reported an efficient synthesis of *N,N′*-disubstituted formamidines and acetamidines by refluxing ethyl orthoformate with alkylamines in the presence of acetic acid as a catalyst at high temperature and subsequent

Received October 14, 2006
Address correspondence to Phimphaka Harding, Department of Chemistry, School of Science, Walailak University, Thasala, Nakhon Si Thammarat 80161, Thailand. E-mail: kphimpha@wu.ac.th



Scheme 1. Synthesis of acetamidine.

distillation at 80–150°C under low pressure to remove the by-product, ethanol, and excess starting material. However, this method is time-consuming, requiring lengthy refluxing and extensive workup to isolate the product.[5] In this communication, we report a novel method for the synthesis of *N,N′*-disubstituted acetamidines using a modified domestic microwave oven.[6,7]

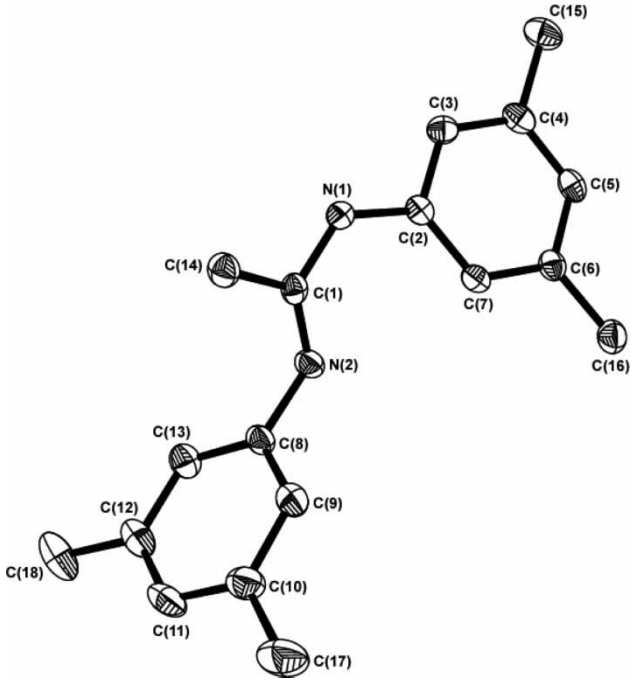


Figure 1. Molecular structure of **1** with thermal ellipsoids at 50% probability. Hydrogen atoms have been omitted for clarity.

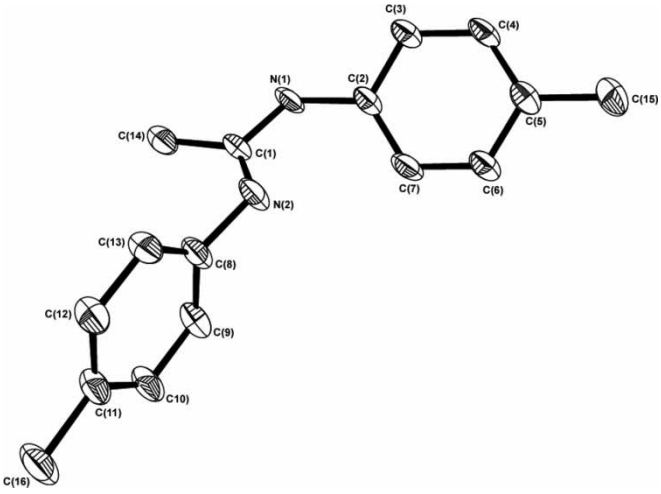


Figure 2. Molecular structure of **2** with thermal ellipsoids at 50% probability. Hydrogen atoms have been omitted for clarity.

Reflux of triethylorthoacetate and the desired aniline in the presence of acetic acid as a catalyst under microwave irradiation at 850 W for 5–7 min yields *N,N′*-disubstituted acetamidine, [RNC(Me)NHR] (R = 3,5-dimethylphenyl **1** and *p*-tolyl **2**), shown in Scheme 1. The by-product, EtOH, is easily removed by placing a receiver between the round-bottom flask and the condenser and heating under microwave conditions at 850 W for a further 2 or 3 min. The complete removal of EtOH is the key to high yield and purity of the product. In general, yields are comparable or increased by 10–20% and reaction times are shortened to minutes rather than hours, with isolated pure products obtained in most cases in less than an hour.

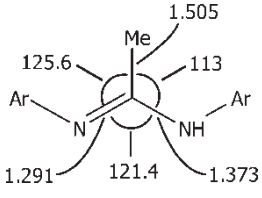
IR spectra of **1** and **2** show ν_{NH} at 3281 and 3301 cm^{-1} respectively. Additional bands are observed for the aromatic C═C and C-H stretches and are comparable with other reported amidines.[5] The ^1H NMR of the new amidine **1** reveals two singlets in the aromatic region and a doublet for the aromatic methyl groups slightly downfield of a singlet for the central amidine methyl group. The presence of two peaks for the aromatic methyl groups suggests that the acetamidine is asymmetric on the NMR timescale. The amino hydrogen is not observed in the NMR spectrum, presumably due to broadening.

Single-crystal X-ray diffraction studies of compounds **1** and **2** were undertaken, and the molecular structures are shown in Figs. 1 and 2 respectively, with selected bond lengths and angles given in Table 1 and crystal and refinement data in Table 2. The structures closely resemble one another, differing only in the substitution on the aromatic ring, and consequently the following discussion is limited to the structure of **1**. The amidine molecules adopt a

Table 1. Selected bond lengths (Å) and bond angles (°) of **1** and **2**

Length	Angle	**1**	**2**
N(1)–C(1)		1.3727(18)	1.363(3)
N(1)–C(2)		1.4122(18)	1.416(3)
N(1)–H(1)		0.8800	0.8800
N(2)–C(1)		1.2906(18)	1.295(3)
N(2)–C(8)		1.4293(18)	1.422(3)
C(1)–C(14)		1.505(2)	1.499(3)
	C(1)–N(1)–C(2)	129.46(12)	126.87(18)
	C(1)–N(1)–H(1)	115.3	116.6
	C(2)–N(1)–H(1)	115.3	116.6
	C(1)–N(2)–C(8)	118.61(12)	118.63(18)
	N(2)–C(1)–N(1)	121.42(13)	120.58(19)
	N(2)–C(1)–C(14)	125.55(13)	124.65(19)
	N(1)–C(1)–C(14)	113.03(12)	114.76(19)
	C(3)–C(2)–N(1)	123.90(13)	119.40(18)
	C(7)–C(2)–N(1)	116.46(13)	122.07(17)
	C(13)–C(8)–N(2)	120.05(14)	120.3(2)
	C(9)–C(8)–N(2)	120.66(14)	120.9(2)

trans-configuration with one of the aromatic rings orthogonal to the plane of the acetamidine core (see Figs. 1 and 2). This arrangement is preferred because of the presence of a weak intramolecular hydrogen bond between the H-atom on N(1) and the imine nitrogen, N(2), on a neighboring molecule. The H-bond length is 2.26(4) and 2.25(6) Å for **1** and **2** respectively. In contrast to other reported amidines, the H-bond forms a zigzag chain, in which neighboring amidines are almost orthogonal to one another, and *not* a dimer of molecules.[8] The N(2)–C(1) bond is considerably shorter than the N(1)–C(1) bond (1.291, cf. 1.373 Å) consistent with double and single carbon–nitrogen bonds respectively (Table 1).



In conclusion, we have successfully synthesized *N,N′*-disubstituted acetamidine ligands by microwave activation, reducing reaction times to a matter of minutes rather than hours. X-ray crystal structures reveal that the acetamidine molecules form polymeric chains through intramolecular hydrogen bonds. The synthesis of more complex acetamidines is currently under way in these laboratories.

Table 2. Crystal and refinement data for RNC(Me)NHR (R = 3,5-dmp **1** and *p*-tolyl **2**)

Parameter	**1**	**2**
Empirical formula	$C_{18}H_{22}N_2$	$C_{16}H_{18}N_2$
Formula weight	266.38	238.32
Temperature	100(2) K	100(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Orthorhombic	Orthorhombic
Space group	Pbca	Pbca
Unit cell dimensions	a = 8.5708(9) Å, $\alpha = 90^\circ$ b = 15.7448(16) Å, $\beta = 90^\circ$ c = 23.201(2) Å, $\gamma = 90^\circ$	a = 12.390(3) Å, $\alpha = 90^\circ$ b = 9.1300(18) Å, $\beta = 90^\circ$ c = 23.950(5) Å, $\gamma = 90^\circ$
Volume	3130.8(6) $Å^3$	2709.2(9) $Å^3$
Z	8	8
Density (calculated)	1.130 Mg/m^3	1.169 Mg/m^3
Absorption coefficient	0.066 mm^{-1}	0.069 mm^{-1}
F(000)	1152	1024
Crystal size	0.32 × 0.18 × 0.14 mm^3	0.32 × 0.10 × 0.09 mm^3
Theta range for data collection	1.76 to 27.53°	1.70 to 30.98°
Index ranges	$-11 \le h \le 11$, $-19 \le k \le 17$, $-30 \le l \le 29$	$-16 \le h \le 17$, $-13 \le k \le 13$, $-29 \le l \le 34$
Reflections collected	38695	53317
Independent reflections	3545 [R(int) = 0.0706]	4217 [R(int) = 0.1169]
Completeness to $\theta = 27.53^\circ$	98.2%	100.0%
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	0.9908 and 0.9791	0.9938 and 0.9782
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	3545/0/186	4217/0/167
Goodness of fit on F^2	1.048	1.032
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0491, wR2 = 0.1134	R1 = 0.0875, wR2 = 0.1903
R indices (all data)	R1 = 0.0733, wR2 = 0.1250	R1 = 0.1884, wR2 = 0.2347
Largest diff. peak and hole	0.266 and −0.294 e. $Å^{-3}$	0.026(3)

EXPERIMENTAL

A modified domestic microwave oven with a computer controller and infrared thermometer was used for all experiments (details of the microwave reactor are available at http://www.science.mju.ac.th/chemistry/research/weerachai/

reactor_eng.htm). Melting points were determined on a Stuart SMP3. Infrared spectra (as KBr discs) were recorded on a Perkin-Elmer Spectrum One infrared spectrophotometer in the range of 400–4000 cm^{-1}. ^{1}H and ^{13}C-^{1}H NMR spectra were recorded on a Bruker 300-MHz FT-NMR spectrometer in $CDCl_3$ with $SiMe_4$ as an internal standard. Elemental analyses and electrospray ionization mass spectrometry (ESI MS) were carried out by the staff of the School of Chemistry, University of Bristol, U.K.

Synthesis of *N*,*N*′-Bis(3,5-dimethylphenyl)acetamidine (1)

Method A

A mixture of triethylorthoacetate (2.0 cm^3, 10.4 mmol), 3,5-dimethylaniline (1.6 cm^3, 20 mmol), and acetic acid (0.5 cm^3) was placed in a microwave oven equipped with a reflux condenser and heated at 850 W for 7 min. A receiver was placed between the flask and the condenser, and the mixture was heated under microwave conditions at 850 W for a further 2 or 3 min. The volume was reduced under vacuum to yield a thick oil, and *n*-hexane (10 cm^3) was added. The solution was cooled to 0°C, resulting in colorless crystals (1.21 g, 45%).

Method B

Triethylorthoacetate (1 cm^3, 5.2 mmol), 3,5-dimethylaniline (0.78 cm^3, 10 mmol), and acetic acid (0.04 cm^3) were refluxed at 135°C for 2 h. The orange solution was distilled at 140°C in vacuo to remove EtOH and starting material. The orange crystals were washed with cool *n*-hexane, giving colorless crystals and an orange solution. The mixture was stored at −20°C overnight. The colorless crystals were filtered and dried in air; yield 0.619 g (47%).

Mp 160–161.5°C. IR (KBr, cm^{-1}) 3301 w, 3270 w, 3152 w, 3096 w, 2917 w, 2861 w, 1636 s, 1567 s, 1467 s, 1344 s, 1157 s, 1047 m, 846 s, 691 s, 654 s. ^{1}H NMR ($CDCl_3$) δ 6.78 (s, 3H, *H*-Ar), 6.68 (s, 3H, *H*-Ar), 2.28 (s, 12H, Ar-*CH*$_3$), 1.98 (s, 3H, *CH*$_3$). ^{13}C NMR ($CDCl_3$) δ 155.07, 144.01, 139.52, 125.69, 120.05, 21.67, 18.85. Found: C, 81.5; H, 8.3; N, 10.6. $C_{18}H_{22}N_2$ calcd.: C, 81.2; H, 8.3; N, 10.5. Electrospray ionization (ESI) mass data: m/z 267 $[M + H]^+$.

Synthesis of *N*,*N*′-Bis(p-tolyl)acetamidine (2)

A mixture of triethylorthoacetate (2.0 cm^3, 10.4 mmol), *p*-toluedine (2.12 g, 19.8 mmol), and acetic acid (0.5 cm^3) was placed in a microwave oven equipped with a reflux condenser and heated at 850 W for 5 min. A receiver

was placed between the flask and the condenser, and the mixture was heated under microwave conditions at 850 W for a further 2 or 3 min. The volume was reduced under vacuum to yield a thick oil, and *n*-hexane (10 cm^3) was added. The solution was cooled to 0°C, resulting in off-white crystals (1.66 g, 70%).

Mp 102–103°C. IR (KBr, cm^{-1}): 3281 br, 3021 w, 2922 w, 2856 w, 1639 s, 1595 s, 1514 s, 1375 s, 1219 s, 1016 w, 817 s, 655 m, 506 s. ^{1}H NMR ($CDCl_3$) δ 7.14–7.05 (m, 8H, *H*-Ar), 2.32 (s, 6H, *CH*$_3$), 2.00 (s, 3H, *CH*$_3$). ^{13}C NMR ($CDCl_3$) δ 180.87, 137.99, 135.64, 130.23, 124.07, 21.24, 17.39. Found: C, 74.6; H, 7.4; N, 10.4. $C_{16}H_{18}N_2 \cdot 0.75H_2O$ calcd.: C, 74.6; H, 7.8; N, 11.1. Electrospray ionization (ESI) mass data: m/z 239 $[M + H]^+$.

ACKNOWLEDGMENTS

We thank the Thailand Research Fund (MRG4780116) for financial support. The University of Bristol is also gratefully acknowledged for CHN analysis and MS services, and Weerachai Phutdhawong is acknowledged for assistance with the microwave reactor.

REFERENCES

1. Jiang, X.; Bollinger, J. C.; Lee, D. *J. Am. Chem. Soc.* **2005**, *127*, 15678.
2. Abdou, H. E.; Mohamed, A. A.; Fackler, Jr., J. P. *Inorg. Chem.* **2005**, *44*, 166.
3. Nelkenbaum, E.; Kapon, M.; Eisen, M. S. *Organometallics* **2005**, *24*, 2645.
4. Schmit, J. A. R.; Arnold, J. *J. Chem. Soc., Dalton Trans.* **2002**, 3454.
5. Taylor, E. C.; Ehrhart, W. A. *J. Org. Chem.* **1963**, *28*, 1108.
6. Phutdhawong, W.; Buddhasukh, D.; Pyne, S. G.; Rujiwatra, A.; Pakawatchai, C. *Synth. Commun.* **2006**, *36*, 881.
7. Phutdhawong, W.; Buddhasukh, D. *Molecules* **2005**, *10*, 1409.
8. Cotton, F. A.; Lei, P.; Murillo, C. A.; Wang, L.-S. *Inorg. Chim. Acta* **2003**, *349*, 165.