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Microwave-Assisted Preparations of Amidrazones and Amidoximes

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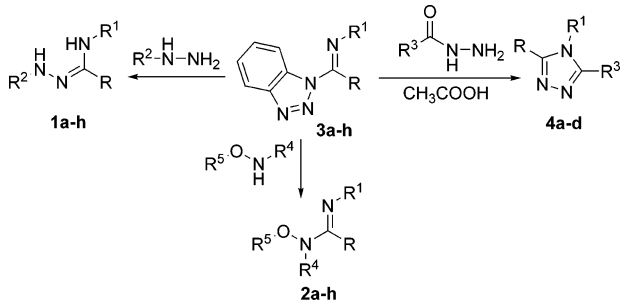

In an operationally straightforward and efficient method, amidrazones **1a**−**h** and amidoximes **2a**−**h** are prepared in yields of 65−87% from imidoylbenzotriazoles **3a**−**h** by microwave heating for 5−20 min with the appropriate hydrazine or hydroxylamine.

Introduction to Amidrazones

Amidrazones **1** display fungistatic, bacteriostatic, and antimycotic activity[1] and also function as herbicides[2] and lipoxygenase-1 inhibitors.[3] Amidrazones are used to prepare 1,2,4-triazines.[4]

Reactions of nitriles with hydrazines [Scheme 1, (i)] is frequently used for the preparation of amidrazones,[2,5−7] but the outcome depends on the nature of the nitrile,[7] and further reaction can give dihydrotetrazines and subsequently tetrazines.[5] Alternative methods (Scheme 1) for the synthesis of amidrazones avoid the use of nitriles by reaction of hydrazine with (ii) imidates or their salts (X = O, S; R^2 = Alk),[8a,b] (iii) imidoyl halides,[5,9] (iv) amides and thioamides in the presence of $POCl_3$,[4,10a,b] (v) dihydroxathiazoledioxides,[11] or (vi) ketenimines (R, R^1 = Ar).[12] Further routes to amidrazones include (vii) reaction of amines with hydrazonoyl halides (X = Cl, Br),[13a,13b,14] (viii) reduction of nitrazones by ammonium sulfide,[15a] or (ix) reduction of formazans (R, R^1 = Ar).[5] Two possible tautomers **1A** and **1B** exist for amidrazones (Scheme 2). If N^2 is substituted then amidrazones **1** are fixed in form **1B**; otherwise, spectral data[15c] suggest that amidrazones exist exclusively in form **1A** (Scheme 2).

Thus, amidrazones are of two major types: class I, which do not carry a substituent on N^2 and exist predominantly in structure **1A** (Scheme 1), and class II, which are substituted on N^2 and exist necessarily as **1B** (Scheme 1). Class I compounds can in turn be divided into eight subclasses (A−H) as shown in Table 1 (two mono-, three di-, three tri-, one tetra-substituted). Almost all of these subclasses could potentially be made by

(1) Modzelewska-Banachiewicz, B.; Matysiak, J.; Niewiadomy, A. *Eur. J. Med. Chem.* **2001**, *36*, 75.
(2) Haldeman, R. G.; Morin, L. T.; Matsuda, K. *Chem. Abstr.* **1963**, *58*, 11276.
(3) Clemens, F.; Drutkowski, G.; Wiese, M.; Frohberg, P. *Biochim. Biophys. Acta* **2001**, *1549*, 88.
(4) Schmidt, P.; Druey, J. *Helv. Chim. Acta* **1955**, *188*, 1560.
(5) Neilson, D. G.; Roger, R.; Heatlie, J. W. M.; Newlands, L. R. *Chem. Rev.* **1970**, *70*, 151.
(6) Matsuda, K.; Morin, L. T. *J. Org. Chem.* **1961**, *26*, 3783.
(7) Libman, D. D.; Slack, R. *J. Chem. Soc.* **1956**, 2253.
(8) (a) Haddad, M.; Dahan, F.; Legros, J. P.; Lopez, L.; Boisdon, M. T.; Barrans, J. *J. Chem. Soc., Perkin Trans. 2* **1992**, *4*, 671. (b) Weintraub, L.; Oles, S. R.; Kalish, N. *J. Org. Chem.* **1968**, *33*, 1679.
(9) Katritzky, A. R.; Nie, P. L.; Dondoni, A.; Tassi, D. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1961.
(10) (a) Rapoport, H.; Bonner, R. M. *J. Am. Chem. Soc.* **1950**, *72*, 2783. (b) Rätz, R.; Schroeder, H. *J. Org. Chem.* **1958**, *23*, 1931.
(11) Brown, H. C.; Cheng, M. T. *J. Org. Chem.* **1962**, *27*, 3240.
(12) Stevens, C. L.; Freeman, R. C.; Noll, K. *J. Org. Chem.* **1965**, *30*, 3718.
(13) (a) Fusco, R.; Rossi, S. *Tetrahedron* **1958**, *3*, 209. (b) Sharp, D. B.; Hamilton, C. S. *J. Am. Chem. Soc.* **1946**, *68*, 588.
(14) Drutkowski, G.; Donner, C.; Schulze, I.; Frohberg, P. *Tetrahedron* **2002**, *58*, 5317.
(15) (a) Jerchel, D. *Chem. Abstr.* **1953**, *52*, 11919. (b) Smith, R. F.; Johnson, D. S.; Abgott, R. A.; Madden, M. J. *J. Org. Chem.* **1973**, *38*, 1344. (c) Bahceci, S.; Yuksel, H.; Serdar, M. *Indian J. Chem. Sect. B* **2005**, *44*, 568. (d) Neunhoeffer, H.; Hammann, H. *Leibigs Ann. Chem.* **1984**, *2*, 283.

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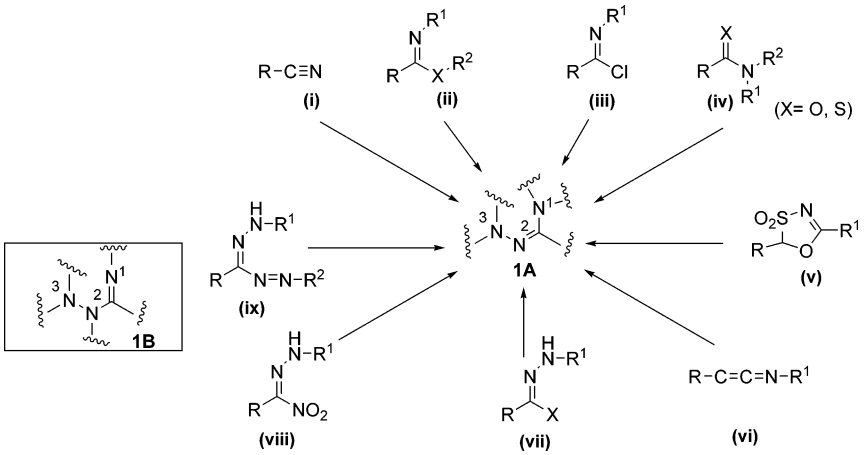
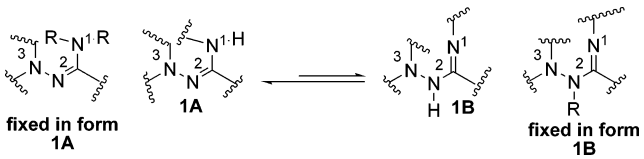
SCHEME 1. Preparative Routes to Amidrazones[a]



[a] Reagents: i−vi reactions with hydrazine; vii reaction with amine R, R^1, R^2 = alkyl or aryl.

SCHEME 2. Tautomeric Forms of Amidrazones



one or more of the existing methods; however, literature substructural searches showed no known examples of compounds of class G. The present work provides an easy access to novel class G in addition to classes A, B, D, and E. As to class II, a single example was reported for the preparation of such compounds as a hydroiodide salt in 75% yield.[15d]

Introduction to Amidoximes

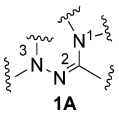
Amidoximes **2** are biologically active as antitumor agents,[16] antimalerial agents,[17] and nitric oxide synthase (NOS) substrates.[18,19] Amidoximes are prodrugs for amidines[20,21] and intermediates for the preparation of heterocycles such as oxadiazoles.[22] Tautomerism in simple amidoximes had been the subject of some debate, although most authors accept the structure of potentially tautomeric amidoximes to be the "amino oxime" form (**2A**) and not the "amino hydroxylamine" structure (**2B**) (Scheme 3).

Thus, similar to amidrazones, amidoximes **2** can be divided into two classes: class I, which do not carry a substituent on N^2 exist predominantly as structure **2A** (Scheme 3), and class II, which are substituted on N^2 exist necessarily as **2B** (Scheme 3). Common methods (Scheme 5) for the preparation of class I amidoximes include reactions of hydroxylamines with (i) nitriles,[23,24a−d] (ii) thioamides for the preparation of aromatic amidoximes,[23,25a,b] (iii) imidates,[26a,b] or (iv) amidines and their salts (49−52% yield).[26a,27] Alternative routes include (v) reaction of amines with hydroximic acid chlorides and oximinoethers,[23,26b,28a−d] (vi) reduction of oxyamidoximes,[23] (vii) platinum catalyzed reduction of nitrosolic and nitrolic acids,[23,29] (viii) aldol condensations of formamidoxime with aromatic aldehydes,[23] or (ix) oxadiazole ring cleavage.[30a,b] A single procedure for the preparation of class II amidrazones includes the reaction of imidoyl halides[31a] with arylnitrenium ion (Scheme 4).[31b] Moreover, *O*-substituted amidoximes are prepared directly by the reaction of amidoximes with methyl iodide or dimethyl sulfate to give *O*-methylamidoxime (22% yield)[32a,b] or acetylene to yield *O*-vinylamidoximes (80% yield).[33]

Amidoximes **2A** can be divided into five subclasses (two mono, two di, one tri) substituted as shown in Table 2. As to amidoximes **2B,** four subclasses (one mono, two di, one tri) can also exist as shown in Table 3. The 10 reported methods

(16) Flora, K. P.; Riet, B. V.; Wampler, G. L. *Cancer Res.* **1978**, *38*, 1291.
(17) Hynes, J. B.; Hack, L. G. *J. Med. Chem.* **1972**, *15*, 1194.
(18) Rehse, K.; Brehme, F. *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 375.
(19) Jousserandot, A.; Boucher, J. L.; Henry, Y.; Niklaus, B.; Clement, B.; Mansuy, D. *Biochemistry* **1998**, *37*, 17179.
(20) Weller, T.; Alig, L.; Beresini, M.; Blackburn, B.; Bunting, S.; Hadváry, P.; Müller, M. H.; Knopp, D.; Levet-Trafit, B.; Lipari, M. T.; Modi, N. B.; Müller, M.; Refino, C. J.; Schmitt, M.; Schönholzer, P.; Weiss, S.; Steiner, B. *J. Med. Chem.* **1996**, *39*, 3139.
(21) Clement, B. *Drug Metab. Rev.* **2002**, *34*, 565.
(22) Hamzé, A.; Hernandez, J. F.; Fulcrand, P.; Martinez, J. *J. Org. Chem.* **2003**, *68*, 7316.
(23) Eloy, F.; Lenaers, R. *Chem. Rev.* **1962**, *62*, 155.
(24) (a) Stephenson, L.; Warburton, W. K.; Wilson, M. J. *J. Chem. Soc. C* **1969**, *6*, 861. (b) Street, L. J.; Sternfeld, F.; Jelley, R. A.; Reeve, A. J.; Carling, R. W.; Moore, K. W.; McKernan, R. M.; Sohal, B.; Cook, S.; Pike, A.; Dawson, G. R.; Bromidge, F. A.; Wafford, K. A.; Seabrook, G. R.; Thompson, S. A.; Marshall, G.; Pillai, G. V.; Castro, J. L.; Atack, J. R.; MacLeod, A. M. *J. Med. Chem.* **2004**, *47*, 3642. (c) Kaboudin, B.; Navaee, K. *Heterocycles* **2003**, *60*, 2287. (d) Briggs, L. H.; Cambie, R. C.; Dean, I. C.; Rutledge, P. S. *Aust. J. Chem.* **1976**, *29*, 357.
(25) (a) Goldbeck, O. *Chem. Ber.* **1891**, 3658. (b) Tiemann, F. *Chem. Ber.* **1886**, 1668.
(26) (a) Pinner, A. *Ber. Dtsch. Chem. Ges.* **1884**, 184. (b) Bushey, D. F.; Hoover, F. C. *J. Org. Chem.* **1980**, *45*, 4198.
(27) Szczepankiewicz, W.; Borowiak, T.; Kubicki, M.; Suwiński, J.; Wagner, P. *Pol. J. Chem.* **2002**, *76*, 1137.
(28) (a) Baker, K. W. J.; Horner, K. S.; Moggach, S. A.; Paton, R. M.; Smellie, I. A. S. *Tetrahedron Lett.* **2004**, *45*, 8913. (b) Cragg, R. H.; Miller, T. J. *J. Chem. Soc., Dalton Trans.* **1982**, 907. (c) Gennet, D.; Zard, S. Z.; Zhang, H. *Chem. Commun.* **2003**, 1870. (d) Johnson, J. E.; Ghafouripour, A.; Arfan, M.; Todd, S. L.; Sitz, D. A. *J. Org. Chem.* **1985**, *50*, 3348.
(29) Wieland, H.; Bauer, H. *Ber.* **1906**, 1480.
(30) (a) Buscemi, S.; Cicero, M. G.; Vivona, N; Caronna, T. *J. Heterocycl. Chem.* **1988**, *25*, 931. (b) Gandolfi, R.; Gamba, A.; Grünanger, P. *Heterocycles* **1995**, *40*, 619.
(31) (a) Špirková, K.; Bučko, M.; Štankovský, S. *ARKIVOC* **2005**, *v*, 96. (b) Binding, N.; Heesing, A. *Chem. Ber.* **1983**, *116*, 1822.
(32) (a) Costa Leite, L. F. C.; Srivastava, R. M.; Cavalcanti, A. P. *Bull. Soc. Chem. Belg.* **1989**, *98*, 203. (b) Johnson, J. E.; Cornell, S. C. *J. Org. Chem.* **1980**, *45*, 4144.
(33) Trofimov, B. A.; Schmidt, E. Y.; Vasil'tsov, A. M.; Mikhaleva, A. I.; Zaitsev, A. B.; Morozova, L. V.; Gorskhov, A. G.; Henkelmann, J.; Arndt, J. D. *Synthesis* **2001**, *16*, 2427.

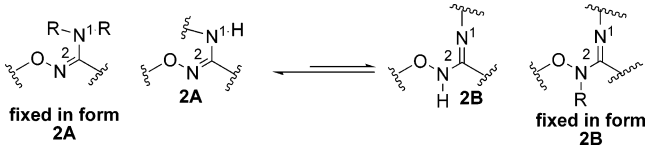
TABLE 1. Eight Class I Amidrazones Existing as 1A[a]



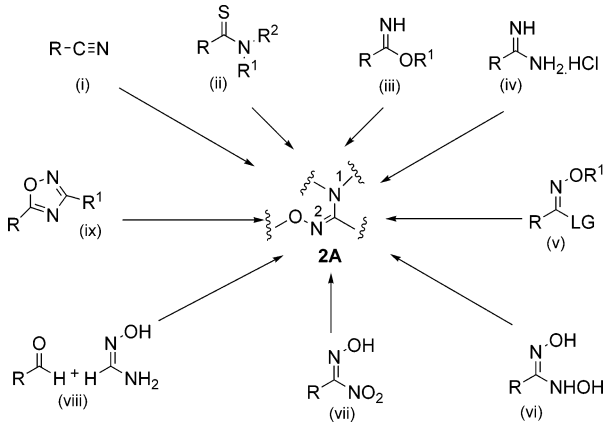
	mono-N-substituted		di-N-substituted			tri-N-substituted		tetra-N-substituted
subclass	A	B	C	D	E	F	G	H
method	N^1	N^3	N^1N^1	N^3N^3	N^1N^3	$N^1N^1N^3$	$N^1N^3N^3$	$N^1N^1N^3N^3$
i	N	R	N	R	N	N	N	N
ii	R	R	N	R	P	N	P	N
iii	R	R	N	P	R	N	P	N
iv	P	R	N	P	R	R	P	R
v	N	P	N	R	N	N	N	N
vi	R	P	N	P	P	N	P	N
vii	N	R	N	P	R	P	P	P
viii	N	R	N	P	N	N	N	N
ix	N	R	N	P	N	N	N	N
x	N	P	N	N	R	P	N	N
this work	R	P	N	P	R	N	P	N

[a] R: reported. P: possible but no example reported. N: not possible by reasons of valency.

SCHEME 3. Tautomeric Forms of Amidoximes

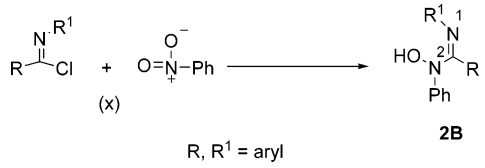


SCHEME 4. Preparative Routes to Amidoximes of Type 2A[a]



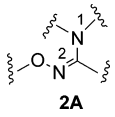
[a] Reagents: i−vi reactions with hydroxyamine or $RONH_2$; (v) reaction with amine R, R_1, R_2 = alkyl or aryl; (vi) reduction with SO_2; (vii) platinum-catalyzed reduction; (viii) aldol condensation; (ix) photorearrangement of oxazole ring.

SCHEME 5. Preparative Routes to Amidoximes of Type 2B



for the preparation of **2A** and **2B** (Schemes 4 and 5) generally target specific subclasses of amidoximes (Tables 2 and 3). We now report routes to many classes including class I′ where no examples have been reported to date.

TABLE 2. Five Subclasses of Amidoximes 2A[a]



	mono		di		tri
subclass	A′	B′	C′	D′	E′
method	N^1	O	N^1N^1	N^1O	N^1N^1O
i	N	P	N	N	N
ii	R	R	N	P	N
iii	N	P	N	N	N
iv	N	N	N	R	N
v	R	P	N	R	N
vi	N	P	N	N	N
vii	N	P	N	N	N
viii	N	P	N	N	N
ix	N	N	N	R	N
this work	R	P	N	R	N

[a] R: reported. P: possible but not reported. N: not possible by reasons of valency.

Results and Discussion

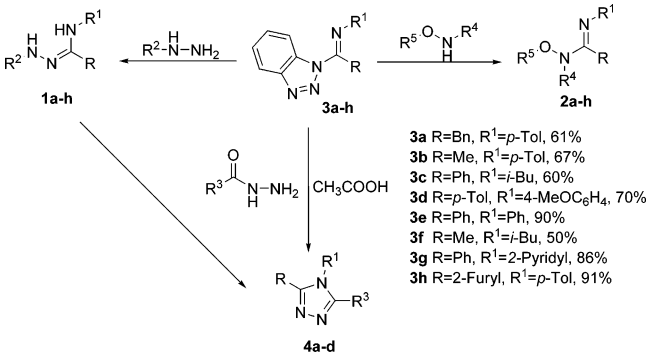
Imidoylbenzotriazoles **3** have become important as stable alternatives to the corresponding imidoyl chlorides.[34a−c] Recently, we reported a novel procedure for the preparation of amidines using imidoylbenzotriazoles.[35] We have now expanded the utility of imidoylbenzotriazoles to include the preparation of amidrazones **1a**−**h** and amidoximes **2a**−**h.**

Imidoylbenzotriazoles **3a**−**h** (Scheme 6) were prepared in good yields (50−91%) from the reaction of secondary amide (1 equiv), oxalyl chloride (1 equiv), and benzotriazole (2 equiv) in the presence of pyridine.[35] The crude products were chromatographed, after washing with sodium carbonate, on basic alumina (EtOAc/Hex) to give pure imidoylbenzotriazoles **3a**−**h**

(34) (a) Katritzky, A. R.; Hayden, A. E.; Kirichenko, K.; Pelphrey, P.; Ji, Y. *J. Org. Chem.* **2004**, *69*, 5108. (b) Katritzky, A. R.; Huang, T.; Voronkov, M. V. *J. Org. Chem.* **2001**, *66*, 1043. (c) Katritzky, A. R.; Stevens, C. V.; Zhang, G. F.; Jiang, J.; De Kimpe, N. *Heterocycles* **1995**, *40*, 231.

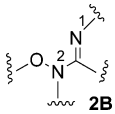
(35) Katritzky, A. R.; Cai, C.; Singh, S. K. *J. Org. Chem.* **2006**, *71*, 3375.

SCHEME 6. Reactions of Imidoylbenzotriazoles with Hydrazines and Hydroxylamines[a]



[a] For identity of R, R^1, and R^2, see Tables 4−6.

TABLE 3. Four Subclasses of Amidoximes 2B[a]



	mono	di		tri
subclass	F′	G′	H′	I′
method	N^2	N^2O	N^1N^2	N^1N^2O
X	N	N	R	N
this work	P	P	R	P

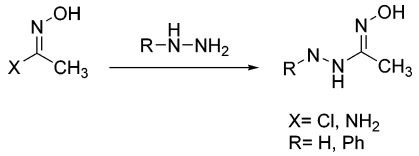
[a] R: reported. P: possible but not reported. N: not possible by reasons of valency.

(Scheme 6). Known **3a**−**e**,**g**,**h** and novel **3f** were fully characterized by ^{1}H and ^{13}C NMR spectroscopy and in the case of **3f** by elemental analysis. Most imidoylbenzotriazoles are easy to handle and keep indefinitely; however, we noted slow decomposition of 1-[phenyl(2-pyridinylimino)methyl]-1*H*-benzotriazole **3g** after 3 days.

Stirring 1 equiv of imidoylbenzotriazoles **3b**−**d**,**f** with 1.5 equiv of the corresponding hydrazine in the presence of a 7-fold excess of sodium sulfate for 5−20 min under microwave irradiation afforded amidrazones **1a**−**h** in 66−85% yields (Scheme 6 and Table 4). The progress of the reaction was monitored by TLC. Upon completion of the reaction, water was added to remove sodium sulfate. The organic layer was extracted with dichloromethane and then purified using column chromatography to give novel **1a**−**h** as colorless oils. Compound **1e** could be obtained only as a crude; attempted purification led to complete decomposition. Structures of novel **1a**−**h** were supported by NMR spectroscopy, mass spectroscopy, and elemental analysis. The carbonyl peaks of compounds **1c**,**f**−**h** were very broad in ^{13}C NMR probably because of intermolecular hydrogen bonding and/or tautomeric interconversion. The cyclic triazole structures were excluded for compounds **1a**−**h** by elemental analysis and MS. However, compound **1c** was smoothly converted into 4-(2-butyl)-3,5-diphenyl-4*H*-1,2,4-triazole[36] (**4e**) upon gentle heating (**1c** melted at 196−198 °C). Moreover, the melting point of **4e** obtained from heating **1c** was 176 °C, which is identical to that of 4-(2-butyl)-3,5-diphenyl-4*H*-1,2,4-triazole (see the Experimental Section).

(36) Gautun, O. R.; Carlsen, P. H. J. *Acta Chem. Scand.* **1991**, *45*, 609.

SCHEME 7. Preparative Routes to Aminoamidoximes



Amidrazones **1a**−**h** exhibit tautomerism; thus, it was hard to assign the NH protons, especially since they were not always visible.

Reacting imidoylbenzotriazole **3a**,**b**,**d** with hydrazides (R^3-$CONHNH_2$) in the presence of catalytic amounts of acetic acid under microwave conditions afforded cyclic 1,2,4-triazoles **4a**−**d**[37a−d] (Scheme 6 and Table 5) via a simple intramolecular condensation followed by the loss of one molecule of water. Upon completion of the reaction (5−10 min), the sample was diluted with dichloromethane and then purified using flash column chromatography to give **4a**−**d** in 77−100% yields. Novel **4a**−**d** were isolated as white microcrystals and characterized by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis.

Amidoximes **2a**−**h** were prepared in 65−81% yields from the reaction of imidoylbenzotriazoles **3a**−**f**,**h** with the corresponding hydroxylamines (Scheme 6 and Table 6). Utilizing microwave irradiation, reaction of imidoylbenzotriazole **3a**−**f**,**h** with hydroxylamines reached completion after 5−15 min. The reaction mixture was then dissolved in dichloromethane and washed with 10% aqueous Na_2CO_3. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue obtained was purified by gradient column chromatography (EtOAc/Hex) to obtain pure amidoximes **2a**−**h**. Structures of novel **2a**−**h** were supported by elemental analysis and ^{1}H and ^{13}C NMR spectra. The ^{1}H spectra no longer showed signals in the range of 7.0−8.2 ppm corresponding to the benzotriazole group. Some NH protons were not visible due to fast exchange.

Aminoamidoximes and Diamidoximes. Aminoamidoximes **6** are compounds with both hydroxylamine and hydrazine moieties. Previous preparations of such compounds include reacting oxime chlorides[38a] or simple amidoximes[38b] with hydrazines to give aminoamidoximes in 21−30% yields (Scheme 7). Diamidoximes **7** are compounds with two hydroxylamine moieties, and to the best of our knowledge, they are not known in the literature.

Aminoamidoxime **6** and diamidoxime **7** were prepared starting from 1*H*-1,2,3-benzotriazol-1-ylmethanone oxime **5** (Scheme 8). Reagent **5** was prepared from the appropriate oxime (1 equiv), 1-chloro-1*H*-benzotriazole (1 equiv), and potassium *tert*-butoxide (1.1 equiv) in diethyl ether at −30 °C. The reaction was stirred at room temperature for 5 h before it was quenched with water and extracted with dichloromethane. Evaporating the organic layer afforded oxime **5** in 90% yield. Using a microwave, reagent **5** was reacted with the appropriate hydrazine or hydroxylamine under mild conditions (see the Experimental Section) to give **6** or **7**, respectively (Scheme 8). Novel **6** and **7** were isolated as viscous oils and were characterized by elemental analysis and ^{1}H and ^{13}C NMR spectra.

(37) (a) Wiedermannová, I.; Otyepka, M.; Styskala, J.; Slouka, J. *ARKIVOC* **2003**, *xv*, 65. (b) Riedl, Z.; Hajós, G.; Köver, P.; Kollenz, G. *ARKIVOC* **2003**, *v*, 62. (c) Wamhoff, H.; Tzanova, M. *ARKIVOC* **2003**, *ii*, 98. (d) Natarajan, A.; Guo, Y.; Arthanari, H.; Wagner, G.; Halperin, J. A.; Chorev, M. *J. Org. Chem.* **2005**, *70*, 6362.

(38) (a) Armand, J.; Bassinet, P. *J. Chem. Res. Synop.* **1980** 304. (b) Armand, J. *Compt. Seanc. Acad. Sci., Ser. C: Sci. Chim.* **1966**, *262*, 592.

TABLE 4. Preparation of Amidrazones 1a−h from 3b−d,f

imidoylbenzotriazole **3**	R	R^1	R^2	conditions (*T*, °C, power, W, time, min)	product	yield, %
3b	Me	*p*-Tol	H	95, 105, 10	**1a**	85
3b	Me	*p*-Tol	Ph	90, 120, 15	**1b**	70
3c	Ph	*i*-Bu	PhCO	120, 130, 15	**1c**	72
3d	*p*-Tol	4-$MeOC_6H_4$	Ph	80, 80, 10	**1d**	82
3f	Me	*i*-Bu	4-$NO_2OC_6H_4$	110, 120, 20	**1e**	68
3b	Me	*p*-Tol	PhCO	120, 125, 12	**1f**	66
3c	Ph	*i*-Bu	4-ClC_6H_4CO	160, 160, 12	**1g**	87
3f	Me	*i*-Bu	$COCH_3$	105, 115, 9	**1h**	80

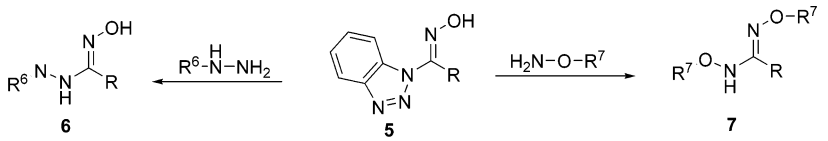
TABLE 5. Preparation of 1,2,4-Triazoles 4a−d from 3a,b,d

imidoylbenzotriazole **3**	R	R^1	R^3	conditions (*T*, °C, power, W, time, min)	product	yield, %
3a	Bn	*p*-Tol	Me	80, 120, 10	**4a**	77
3b	Me	*p*-Tol	*p*-Tol	80, 120, 5	**4b**	94
3d	*p*-Tol	4-$MeOC_6H_4$	*p*-Tol	80, 120, 5	**4c**	100
3d	*p*-Tol	4-$MeOC_6H_4$	Ph	80, 120, 10	**4d**	88

TABLE 6. Preparation of Amidoximes 2a−h

imidoylbenzotriazole **3**	R	R^1	R^4	R^5	conditions (*T*, °C, power, W, time, min)	product	yield, %
3a	Bn	*p*-Tol	H	H	100, 120, 5	**2a**	65
3b	Me	*p*-Tol	H	Bn	100, 120, 10	**2b**	79
3c	Ph	*i*-Bu	H	Me	100, 120, 5	**2c**	68
3c	Ph	*i*-Bu	Me	H	60, 120, 5	**2d**	81
3d	*p*-Tol	4-$MeOC_6H_4$	H	H	100, 120, 5	**2e**	78
3e	Ph	Ph	H	Me	80, 120, 5	**2f**	80
3f	Me	*i*-Bu	H	Bn	80, 120, 15	**2g**	68
3h	2-Furyl	*p*-Tol	Me	H	60, 100, 10	**2h**	73

SCHEME 8. Preparation of Aminoamidoxime 6 and Diamidoxime 7



6 R=Ph, R^6=4-$NO_2C_6H_4$, Yield= 71%

7 R=Me, R^7=Bn, Yield= 64%

Conclusion

A simple, efficient, and broadly applicable synthetic methodology for the preparation of amidrazones and amidoximes under microwave conditions has been developed via the nucleophilic attack on imidoylbenzotriazoles by hydrazines or hydroxylamines. The easy accessibility of imidoylbenzotriazoles from the corresponding amide and the simple workup gives the approaches substantial utility.

Experimental Section

General Procedure for the Preparation of Imidoylbenzotriazoles 3a−h. To a solution of the corresponding amide (5.0 mmol) in dichloromethane (20 mL) was added dropwise at 0 °C pyridine (5.5 mmol) followed by oxalyl chloride (5.5 mmol) in dichloromethane (20 mL). Gas evolution was observed during the process. After the addition, the reaction was continued for 15 min, and then benzotriazole (10.5 mmol) was added in one portion to the reaction flask. The ice bath was removed to allow the reaction to continue at room temperature, and the reaction was monitored by TLC. The precipitated white solid was filtered off, and sodium bicarbonate solution (saturated) was added to dilute the reaction mixture. Aqueous workup gave a crude product that was purified by column chromatography on basic alumina, using hexanes/EtOAc (8:1) as eluent to give pure **3a−h** in good yields.

***N*-[(Benzotriazol-1-yl)ethylidene]-2-methyl-1-propanamine (3f).** Recrystallized from EtOAc/hex to give off-white microcrystals (50%): mp 63−65 °C; ^{1}H NMR δ 1.08 (d, J = 6.6 Hz, 6H), 2.03−2.14 (m, 1H), 2.74 (s, 3H), 3.41 (d, J = 6.6 Hz, 2H), 7.42 (t, J = 7.6 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 8.07 (d, J = 8.2 Hz, 1H), 8.48 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 14.4, 20.7, 29.9, 58.0, 115.6, 119.5, 124.8, 128.6, 131.3, 146.5, 153.5. Anal. Calcd for $C_{12}H_{16}N_4$: C, 66.64; H, 7.46; N, 25.90. Found: C, 66.36; H, 7.70; N, 25.89.

General Procedure for the Preparation of Amidrazones 1a−h. An intimate mixture of **3** (0.36 mmol), hydrazine (0.43 mmol), and sodium sulfate (anhydrous, 0.3 g) was stirred in a sealed tube (10 mL) under microwave irradiation (conditions vary in each case). After completion of the reaction as indicated by TLC, the reaction mixture was washed with 5% solution of Na_2CO_3 (2 × 15 mL) then the organic layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue obtained was either recrystallized from EtOAc/hex (unless indicated otherwise) or purified by column chromatography on silica gel with EtOAc/Hex to give pure **1a−h**.

***N*- (4-Methylphenyl)ethanehydrazonamide (1a):** viscous oil (85%); ^{1}H NMR δ 6.97 (d, J = 8.4 Hz, 2H), 6.62 (d, J = 8.4 Hz, 2H), 4.8 (br s, 1H), 2.42 (s, 3H), 2.23 (s, 3H); ^{13}C NMR δ 143.3, 129.7, 125.5, 124.1, 115.2, 20.4, 10.0. Anal. Calcd for $C_9H_{13}N_3$: C, 66.23; H, 8.03; N, 25.74. Found: C, 66.47; H, 8.21; N, 25.70.

General Procedure for the Preparation of Amidoximes 2a−h. (In the case of **2b**, the compound was directly purified by column without workup). A mixture of the appropriate **3** (0.35 mmol) (see Scheme 6 and Table 6), hydroxylamine hydrochloride (0.4 mmol),

and Et_3N (0.4 mmol) was stirred in a sealed tube (10 mL) under microwave irradiation (conditions vary in each case). The mixture was dissolved in dichloromethane and washed with 10% solution of Na_2CO_3 (2 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue obtained was purified by gradient column chromatography with EtOAc/Hex or recrystallized from EtOAc/hexanes (unless specified otherwise) to give pure **2a**−**h**.

***N′*-Hydroxy-*N*-(4-methylphenyl)-2-phenylethanimidamide (2a).** Recrystallized from EtOAc/hexanes to give off-white microcrystals (65%): mp 140−142 °C; ^{1}H NMR δ 7.14−7.18 (m, 3H), 7.00−7.05 (m, 4H), 6.81 (d, J = 8.2 Hz, 2H), 3.58 (s, 2H), 2.30 (s, 3H); ^{13}C NMR δ 152.6, 136.1, 135.8, 135.0, 129.4, 128.7, 128.2, 126.4, 125.7, 35.04, 20.84. Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.77; H, 6.80; N, 11.95.

General Procedure for the Preparation of 4a−d. A mixture of the appropriate **3** (0.5 mmol) and the corresponding hydrazine (0.51 mmol) in the presence of a catalytic amount of CH_3COOH (1−2 drops) was stirred in sealed tube (10 mL) under microwave irradiation (conditions vary in each case). The mixture was dissolved in dichloromethane and washed with 10% solution of Na_2CO_3 (2 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue obtained was recrystallized from the appropriate solvent (designated below) to give pure **4a**−**d** as white microcrystals.

3-Benzyl-5-methyl-4-(4-methylphenyl)-4*H*-1,2,4-triazole (4a). Recrystallized from $CHCl_3$/MeOH to give white microcrystals (77%): mp 60−61 °C; ^{1}H NMR δ 7.21 (d, J = 8.2 Hz, 2H), 7.14−7.16 (m, 3H), 6.93−6.97 (m, 2H), 6.81 (d, J = 8.2 Hz, 2H), 3.97 (s, 2H), 2.42 (s, 3H), 2.21 (s, 3H); ^{13}C NMR δ 153.6, 151.9, 139.8, 135.7, 131.0, 130.2, 128.4, 128.2, 126.7, 126.5, 31.4, 21.1, 10.9. Anal. Calcd for $C_{17}H_{17}N_3$: C, 77.54; H, 6.51; N, 15.96. Found: C, 77.09; H, 6.56; N, 15.94.

Conversion of *N*-Benzoyl-*N*-isobutylbenzenecarbohydrazonamide (1c) into 4-(2-Butyl)-3,5-diphenyl-4*H*-1,2,4-triazole (4e). Compound **1c** was prepared according to the general procedure for preparation of compounds **1a**−**h**. Compound **4e** was prepared according to the general procedure for preparation of compounds **4a**−**d**. Compound **1c** (0.3 mmol) was heated in a tube on a hot-stage apparatus until it started melting (mp = 196 °C). The melted solid was then cooled and dissolved in dichloromethane (1 mL). TLC showed no evidence of stating material **1c**. Melting point, spectral data, and elemental analysis of the obtained solid agreed with the values reported for compound **4e**.

4-(2-Butyl)-3,5-diphenyl-4*H*-1,2,4-triazole (4e). Recrystallized from ethanol to give white crystals (88%): mp176−177 °C; ^{1}H NMR δ 7.70−7.66 (m, 4H), 7.57−7.50 (m, 6H), 3.97 (d, J = 4.0 Hz, 2H), 1.61−1.49 (m, 2H), 0.52 (d, J = 4.0 Hz, 6H); ^{13}C NMR δ 155.8, 129.8, 128.8, 128.7, 127.7, 53.3, 28.4, 20.0. Anal. Calcd for $C_{18}H_{19}N_3$: C, 77.95; H, 6.90; N, 15.15. Found: C, 77.67; H, 7.00; N, 15.24.

General Procedure for the Preparation of 6 and 7. An intimate mixture of oxime **5** (0.42 mmol), the appropriate hydrazine or hydroxylamine (1.05 mmol), and sodium sulfate (anhydrous, 0.1 g) was stirred in sealed tube (10 mL) under microwave irradiation (115W) at approximately 110 °C (indications) for 10 min. After completion of the reaction, as indicated by TLC, the reaction mixture was dissolved in dichloromethane (10 mL) and then washed with a 5% solution of Na_2CO_3 (2 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue obtained was washed with benzene to give the corresponding products as viscous oils.

***N*-Hydroxy-*N*-(4-nitrophenyl)benzenecarbohydrazonamide (6):** oil (71%); ^{1}H NMR δ 8.2 (d, J = 9.0 Hz, 1H), 8.07 (d, J = 9.0 Hz, 1H), 7.71−7.68 (m, 2H), 7.44−7.37 (m, 3H), 7.14 (d, J = 9.3 Hz, 1H), 6.62 (d, J = 9.0 Hz, 1H); ^{13}C NMR δ 155.8, 144.7, 133.4, 131.0, 128.7, 127.2, 124.7, 119.9, 111.9. Anal. Calcd for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.58; H, 4.53; N, 20.18.

***N*-*N′*-Bis(benzyloxy)ethanimidamide (7):** oil (64%); ^{1}H NMR δ 7.91 (br s, 1H), 7.30−7.35 (m, 10H), 4.94 (s, 2H), 4.74 (s, 2H), 1.92 (s, 3H); ^{13}C NMR δ 154.6, 137.6, 135.6, 129.0, 128.5, 128.3, 128.1, 127.8, 78.6, 75.7, 14.1. Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.08; H, 6.75; N, 10.69.

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Supporting Information Available: Characterization data for compounds **1b**−**h**, **2b**−**h**, and **4b**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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