NJC

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: M. Il'in, D. S. Bolotin, V. V. Suslonov and V. Yu. Kukushkin, *New J. Chem.*, 2018, DOI: 10.1039/C8NJ01682H.

View Article Online
DOI: 10.1039/C8NJ01682H

Facile Selective Synthesis of 2-Methyl-5-amino-1,2,4-oxadiazolium Bromides as Further Targets for Nucleophilic Additions

Mikhail V. Il'in,[a] Dmitrii S. Bolotin,[a,*] Vitalii V. Suslonov,[b] and Vadim Yu. Kukushkin[a]

[a] Institute of Chemistry, Saint Petersburg State University, Universitetskaya Nab. 7/9, Saint Petersburg, Russian Federation. E-mail: d.s.bolotin@spbu.ru

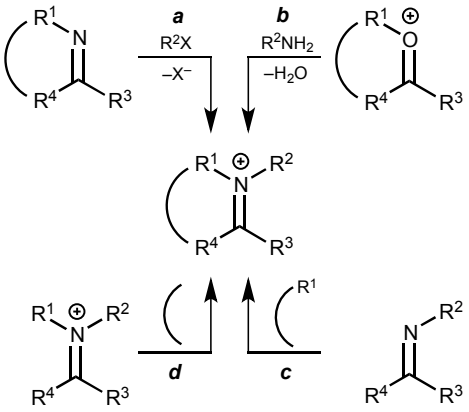
[b] Center for X-ray Diffraction Studies, Saint Petersburg State University, Universitetskii Pr., 26, Saint Petersburg, Russian Federation

Abstract

Reaction of aminonitrones $R^1C(NH_2)=N^+(Me)O^-$ (R^1 = Alk, Ar) with isocyanides R^2NC (R^2 = Alk, Ar; 1.2 equiv.) and Br_2 (1 equiv.) conducted in $CHCl_3$ (RT, 5 min) gives 2-methyl-5-amino-1,2,4-oxadiazolium bromides in good to excellent yields (65–95%; 16 examples). These species are highly electrophilically activated and 5-cyclohexylamino-2-methyl-3-phenyl-1,2,4-oxadiazolium bromide, taken as a model compound for the reactivity study, react rapidly under mild conditions with hydroxylamine, hydrazine, or benzamidine, to give 5-cyclohexylamino-3-phenyl-1,2,4-oxadiazole (88%), 5-cyclohexylamino-3-phenyl-1,2,4-triazole (95%), and 2-cyclohexylamino-4,6-diphenyl-1,3,5-triazine (64%), respectively. Treatment of the oxadiazolium salt with excess water provides *N*-benzoyl-*N*'-cyclohexylurea (95%).

View Article Online
DOI: 10.1039/C8NJ01682H

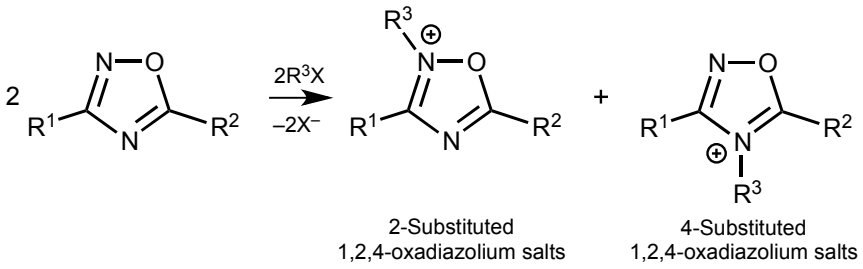
Cationic azaheterocyclic compounds are of importance due to their substantial synthetic potential and also their presence in natural products and functional materials.[1] Several general routes to construct such systems include direct protonation, alkylation, or vinylation of a nitrogen atom of azaheterocycles (**Scheme 1**, ***a***), formal displacement of the O^+ moiety in the cationic oxoheterocycles (***b***), heterocyclization via functionalization of side-chain accompanied by addition to the N atom (***c***), or cyclization of a side-chain of the acyclic N^+-containing moiety (***d***).[1e-g]



Scheme 1. General routes to cationic azaheterocycles.

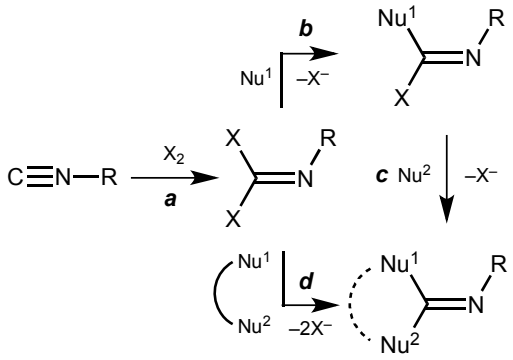
Direct derivatization of 1,2,4-oxadiazoles generally yields two isomeric products, namely, 2- and 4-substituted 1,2,4-oxadiazoles (**Scheme 2**). While 4-substituted 1,2,4-oxadiazoles can be selectively prepared via the reaction of chloroximes and highly reactive nitrilium salts,[2] selective generation of 2-substituted 1,2,4-oxadiazolium salts has not yet been achieved. The only reported synthetic route to 2-substituted 1,2,4-oxadiazolium salts is the alkylation of 1,2,4-oxadiazoles which required either relatively harsh conditions (Me_2SO_4, 110 °C, 4 h) or the use of $(Me_3O)[BF_4]$ (a very reactive and moisture-sensitive alkylation agent) and gave ca. 1:1 mixture 2-alkyl- and 4-alkyl-1,2,4-oxadiazolium salts.[3]

View Article Online
DOI: 10.1039/C8NJ01682H



Scheme 2. The alkylation of 1,2,4-oxadiazoles.

Reactions involving the so-called isocyanide dihalides, $X_2C{=}NR$ (X = Cl, Br, I; IUPAC name: carbonimidic dihalides) – generated in situ from isocyanides and X_2 (**Scheme 3**, ***a***) – typically lead to coupling of the CNR moiety with one (***b***) or two (***c***, ***d***) nucleophilic centers (**Scheme 3**). These reactions have been employed for generation of some *neutral* heterocycles (other than 1,2,4-oxadiazoles),[4] but not *positively charged* heterocyclic systems.



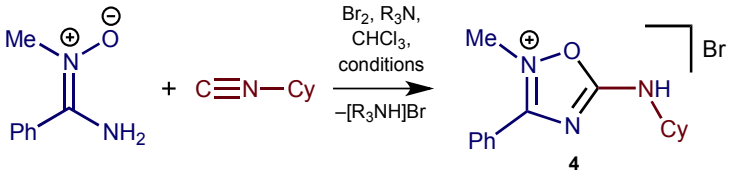
Scheme 3. Utilization of isocyanide dihalides for the reaction with two nucleophilic centers.

In this work, we report a novel synthetic strategy for selective generation of 2-substituted 5-amino-1,2,4-oxadiazolium salts (R = Me) that is based on condensation between aminonitrones and isocyanide dibromides. We have also found these 1,2,4-oxadiazolium salts to readily react with various nucleophiles, viz. hydroxylamine, hydrazine, benzamidine, water, to furnish 1,2,4-oxadiazole, 1,2,4-triazole, 1,3,5-triazine, or ureide, respectively, in high yields.

View Article Online
DOI: 10.1039/C8NJ01682H

For the purpose of finding optimal reaction conditions, $PhC(NH_2)=N^+(Me)O^-$ and CyNC were chosen as model substrates. Our initial experiments indicated that passing Cl_2 through a stirred solution of the aminonitrone $PhC(NH_2)=N^+(Me)O^-$ and CyNC in acetonitrile (RT, 15 min) gave the expected 2-methyl-5-cyclohexylamino-1,2,4-oxadiazolium chloride (23% ^{1}H NMR yield) along with a mixture of by-products from which the starting aminonitrone hydrochloride was isolated in 32% yield. We believe that relatively low yield of the desired product obtained in the initial experiment was due to protonation of the aminonitrone (by HCl formed), which reduced nucleophilicity of the latter. Therefore we reasoned that addition of a base scavenger might improve the outcome of the reaction. After substantial experimentation involving variation of base, X_2, and solvent we found that substantially better yields (as judged by ^{1}H NMR) of the target 1,2,4-oxadiazoium salt **4** (**Scheme 4**) were obtained via the use of Et_3N and Br_2 in $CHCl_3$, whereas much lower yields were obtained with inorganic bases (M_2CO_3, M = Na, K, Cs) and Cl_2 or I_2. While the product yield obtained with Et_3N was nearly quantitative (by ^{1}H NMR; **Table 1**; Entries 1–2), its isolation from the reaction mixture presented a problem as it was poorly separable from $[Et_3NH]Br$. Changing the base to Bn_3N solved the problem and the pure product was isolated in 93%. Upon variation of the reaction time we found that 5 min was sufficient for the completion of the reaction (Entries 2–4) and the use 1.2 eqiv. of CyNC gave the optimal results (Entries 4–6).

Table 1. Optimization of the reaction conditions.

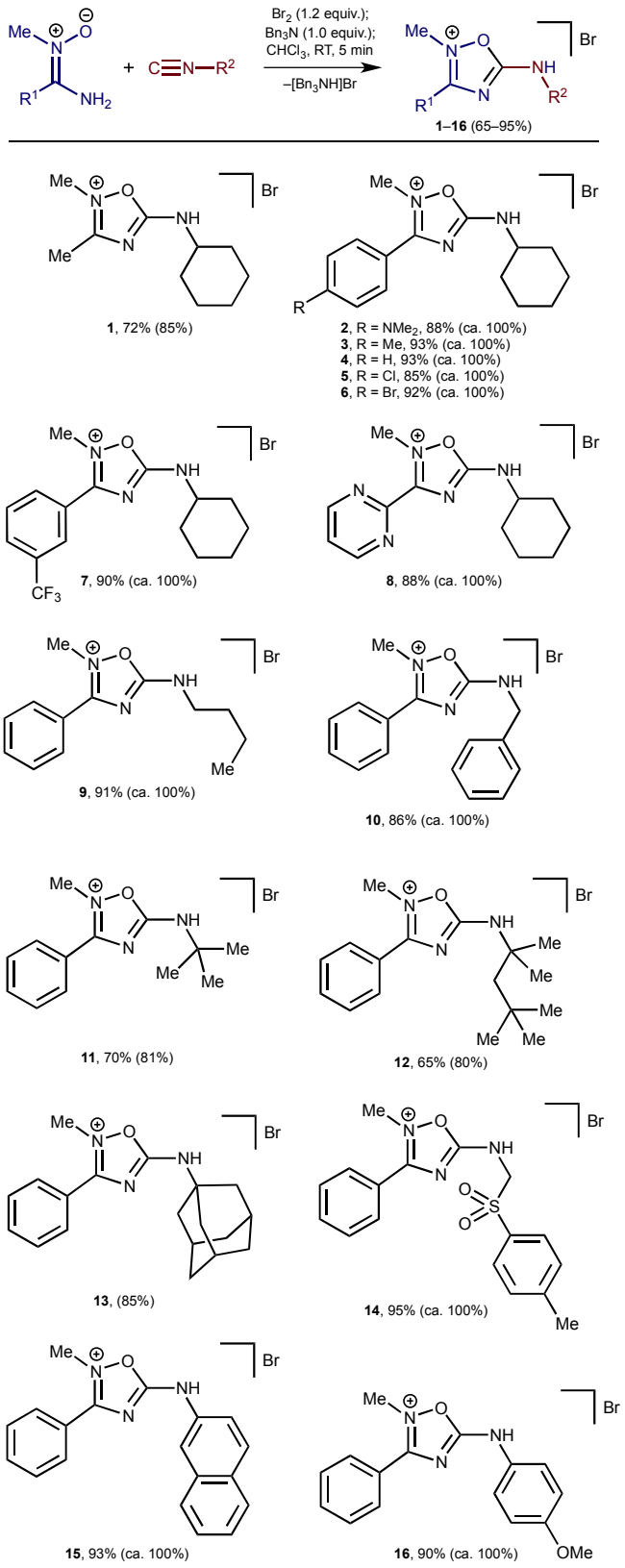


Entry	Equivs. of CyNC	Base	Duration (min)	Yield of heterocycle (%)
1	1.5	Et_3N	15	ca. 100
2	1.5	Bn_3N	15	ca. 100
3	1.5	Bn_3N	5	ca. 100
4	1.5	Bn_3N	2	91
5	**1.2**	**Bn_3N**	**5**	**ca. 100**
6	1.0	Bn_3N	5	89

View Article Online
DOI: 10.1039/C8NJ01682H

Having optimized the conditions, we studied the substrate scope of the reaction (**Scheme 4**). In general, it proceeded smoothly and furnished **1**–**16** in good to excellent yields (65–95%). The nature of R^1 substituents in the tested aminonitrones did not significantly affect the yield of the product. The ^{1}H NMR yield of **1** (prepared from the aliphatic aminonitrone) was 85%, whereas adducts **2**–**8** (prepared from aromatic aminonitrones) were formed in nearly quantitative ^{1}H NMR yields. The nature of R^2 group in R^2NC displayed a greater influence on the product yield. For the bulky R^2 substituents (**11**–**13**), the yields were 80–85% (full conversion). Aryl isocyanides reacted with the aminonitrones in the presence of Br_2 and gave oxadiazolium salts **15**–**16** in quantitative yields. Compound **13** appear to be inseparable from adamantyl ammonium bromide, generated as by-product, by column chromatography due to similar retention times and by recrystallization and therefore **13** was characterized in the reaction mixture.

View Article Online
DOI: 10.1039/C8NJ01682H

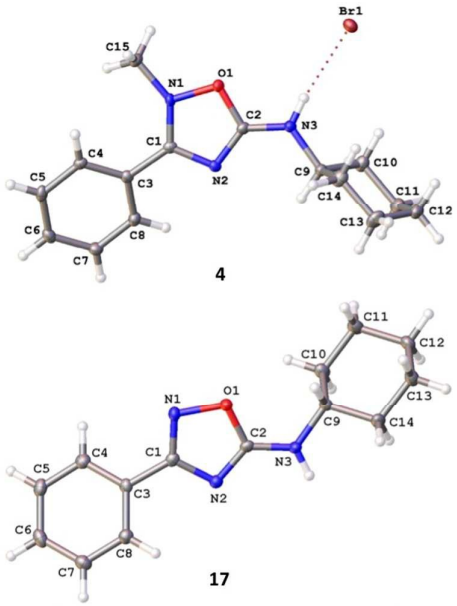


Isolated yields are given. ^{1}H NMR yields are given in parentheses.

Scheme 4. Substrate scope for aminonitrones and isocyanides.

View Article Online
DOI: 10.1039/C8NJ01682H

Compounds **1**–**16** were unknown before this work and characterized by HRESI$^+$-MS, IR, ^{1}H and ^{13}C{^{1}H} NMR spectroscopies (see **Supporting Information**). In addition, **4** and **6** were studied by single-crystal X-ray diffraction (**Figure 1**). These are the first examples of molecular structures of 2-substituted-5-amino-1,2,4-oxadiazolium salts and comparison of bond distances in them and corresponding neutral 5-amino-1,2,4-oxadiazoles is of interest. Comparison of bond lengths in **4** and **17** (**Figure 1**; see next section for generation of **17**) indicates the shortening of the O(1)–N(1), C(1)–N(2), and C(2)–N(3) distances in **4** (other bond lengths overlap within 3σ) as compared to **17** most likely because of significant charge delocalization in the 1,2,4-oxadiazole ring and the N atom of the NHCy moiety of **4**.



Bond	**4**	**17**
O(1)–N(1)	**1.402(3)**	**1.4457(14)**
N(1)–C(1)	1.322(4)	1.3129(17)
C(1)–N(2)	**1.342(4)**	**1.3702(17)**
N(2)–C(2)	1.331(4)	1.3174(17)
C(2)–O(1)	1.366(4)	1.3522(16)
C(2)–N(3)	**1.304(4)**	**1.3303(17)**

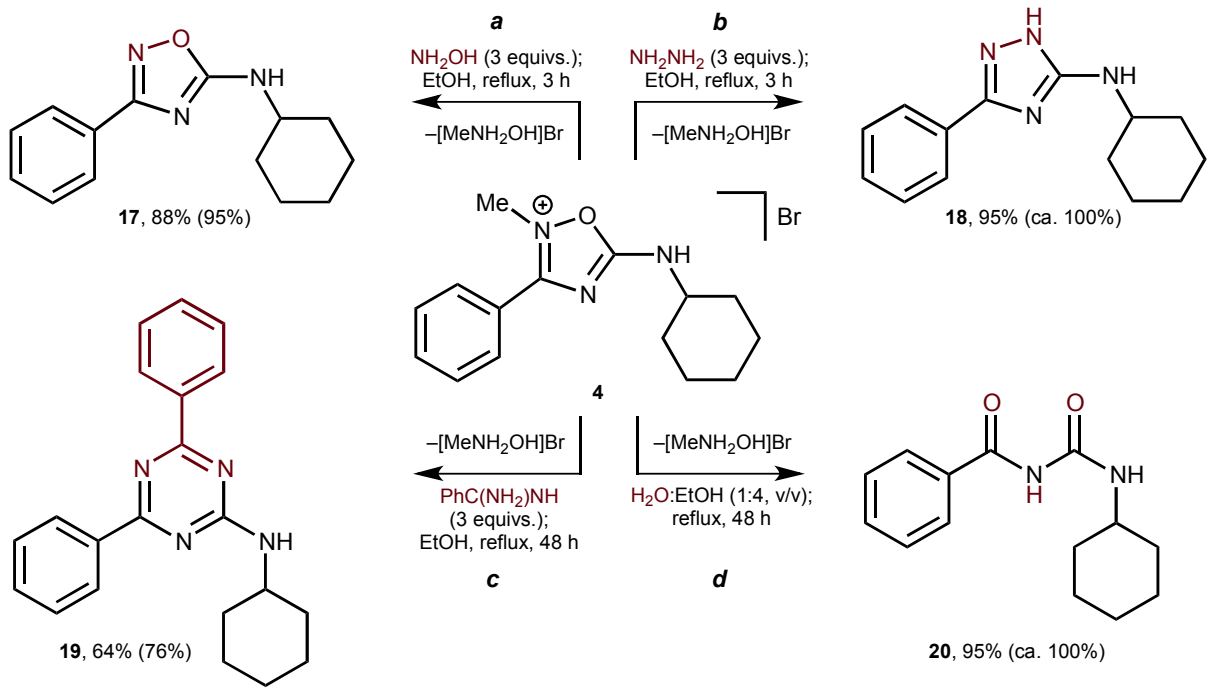
Figure 1. Molecular structures of **4** (top) and **17** (bottom) showing the atomic numbering scheme. Thermal ellipsoids are given at the 50% level. In the table, selected bond lengths are given.

View Article Online
DOI: 10.1039/C8NJ01682H

The charged character of these heterocyclic systems makes them suitable substrates for reactions with nucleophiles, which are likely to proceed in this case faster compared to non-charged congeners.[1g] In some instances, reaction with nucleophiles can lead to the formation of new heterocycles via ANRORC rearrangement.[5] Azaheterocyclic cations can also react with radical species, though the radical reactions are substantially less common.[6]

For neutral 1,2,4-oxadiazoles, ANRORC rearrangements were observed only for ring systems bearing strong electron-withdrawing groups such as perfluoroalkyl.[7] Because of the positive charge on 2-methyl-5-amino-1,2,4-oxadiazolium core, these species—by contrast to uncharged 1,2,4-oxadiazoles—can be expected to be more reactive toward nucleophiles. We found that **4** was easily transformed to corresponding 5-amino-1,2,4-oxadiazole (**17**) and 2-amino-1,2,4-triazole (**18**) in high yields via [2 + 3]-ANRORC reaction (**Scheme 5**, ***a*** and ***b***, respectively). Generation of **17** proceeded regioselectively and the isomeric 3-amino-1,2,4-oxadiazole was not detected in the reaction mixture. Direct reactions of benzamidoxime and benzamidrazone with CyNC and Br_2 gave complex mixtures of unidentified products at temperature range from –18 to 60 °C in $CHCl_3$, MeCN, or MeOH and corresponding **17** and **18** were not detected in these mixtures even by HRESI-MS. This experiment indicates that **17** and **18** cannot be prepared by this method starting from amidoximes or amidrazones.

View Article Online
DOI: 10.1039/C8NJ01682H



Scheme 5. Utilization of **4** for synthesis of aminoheterocycles and ureides.

The reaction of **4** with benzamidine required longer time (48 h vs. 3 h for **17**–**18**; **Scheme 5**, ***c***) and led to 2-amino-1,3,5-triazine **19** (64%; full conversion of **4**). This provides an attractive alternative to generation of 2-aminotriazines (like **19**) from cyanuric chloride as it involves only two chemical operations and does not require the use of reactive organometallic species under inert and dry atmosphere.[8]

In addition to generation of the five- and six-membered heterocycles, we found that **4** can be utilized for preparation of acyclic ureides. Compound **4** reacted with excess of H_2O (H_2O:EtOH mixture 1:4, v/v, reflux, 48 h) giving ureide **20** in quantitative ^1H NMR yield (**Scheme 5**, ***d***).

Compounds **17**–**20** were unknown before this work and characterized by HRESI$^+$-MS, IR, ^1H and $^{13}C\{^1H\}$ NMR spectroscopies, and also by single-crystal X-ray diffraction (see **Figure 1** and **Supporting Information**).

Condensation of aminonitrones with isocyanide dibromides in presence of an organic base leads to selective formation of 2-substituted 5-amino-1,2,4-oxadiazolium salts. This is the first

View Article Online
DOI: 10.1039/C8NJ01682H

example of employing isocyanide dihalides for constructions of positively charged heterocyclic systems. Unlike aldonitrones,[9] 5-amino-1,2,4-oxadiazolium salts thus obtained are poorly represented in current literature and aminonitrones have not been employed in preparation of charged heterocyclic systems (a handful of literature reports describes redox transformations into acyclic compounds[10] and syntheses of neutral heterocyclic species where aminonitrones act as nucleophiles[10d, 11]).

We established that 2-methyl-1,2,4-oxadiazolium salts are substrates for addition of various nucleophiles (such as hydroxylamine, hydrazine, benzamidine, and water) giving rise to diverse heterocyclic cores, such as 5-amino-1,2,4-oxadiazoles, 2-amino-1,2,4-triazoles, 2-amino-1,3,5-triazines featured in many biologically active compounds.[12]

Acknowledgements

This work was supported by Russian Science Foundation (grant 17-73-20004). Physicochemical studies were performed at the Center for Magnetic Resonance, Center for X-ray Diffraction Studies, and Center for Chemical Analysis and Materials Research (all belonging to Saint Petersburg State University). Prof. Dr. Mikhail Krasavin is thanked for valuable suggestions.

View Article Online
DOI: 10.1039/C8NJ01682H

References

1. (a) B. D. Krane, M. O. Fagbule and M. Shamma, *J. Nat. Prod.*, 1984, **47**, 1–43; (b) A. Schmidt, *Adv. Heterocycl. Chem.*, 2003, **85**, 67–171; (c) I. Mancini, A. Sicurelli, G. Guella, T. Turk, P. Macek and K. Sepcic, *Org. Biomol. Chem.*, 2004, **2**, 1368–1375; (d) N. J. Martin, S. Prado, G. Lecellier, O. P. Thomas and P. Raharivelomanana, *Molecules*, 2012, **17**, 12015–12022; (e) D. Sucunza, A. M. Cuadro, J. Alvarez-Builla and J. J. Vaquero, *J. Org. Chem.*, 2016, **81**, 10126–10135; (f) P. Gandeepan and C. H. Cheng, *Chem. Asian J.*, 2016, **11**, 448–460; (g) S. Sowmiah, J. M. S. S. Esperança, L. P. N. Rebelo and C. A. M. Afonso, *Org. Chem. Front.*, 2018, **5**, 453–493.

2. R. Abu-El-Halawa, P. B. Shrestha-Dawadi and J. C. Jochims, *Chem. Ber.*, 1993, **126**, 109–116.

3. M. R. Dobler, *Org. Biomol. Chem.*, 2004, **2**, 963–964.

4. (a) T. Soeta, A. Matsumoto, Y. Sakata and Y. Ukaji, *J. Org. Chem.*, 2017, **82**, 4930–4935; (b) L. El Kaim, L. Grimaud and P. Patil, *Org. Lett.*, 2011, **13**, 1261–1263; (c) H. Yu, Y. Z. Li, Q. Liu, M. S. Zhang and W. L. Sun, *Chin. Chem. Lett.*, 2012, **23**, 130–132; (d) B. Mirza, *Tetrahedron Lett.*, 2016, **57**, 146–147.

5. (a) H. C. Van der Plas, *Adv. Heterocycl. Chem.*, 1999, **74**, 1–253; (b) H. C. Van der Plas, *Acc. Chem. Res.*, 1978, **11**, 462–468.

6. J. Tauber, D. Imbri and T. Opatz, *Molecules*, 2014, **19**, 16190–16222.

7. A. P. Piccionello, A. Pace and S. Buscemi, *Chem. Heterocycl. Comp.*, 2017, **53**, 936–947.

8. E. Weerapana, R. Banerjee and D. R. Brown, *Synlett*, 2013, **24**, 1599–1605.

9. (a) I. A. Grigor'ev, *Nitrones: novel strategies in synthesis*, John Wiley & Sons, Inc., 2008; (b) L. L. Anderson, *Asian J. Org. Chem.*, 2016, **5**, 9–30; (c) N. A. Bokach, M. L. Kuznetsov and V. Y. Kukushkin, *Coord. Chem. Rev.*, 2011, **255**, 2946–2967; (d) A. Brandi, F. Cardona, S. Cicchi, F. M. Cordero and A. Goti, *Chem.–Eur. J.*, 2009, **15**, 7808–7821; (e) C. Najera and J. M. Sansano, *Org. Biomol. Chem.*, 2009, **7**, 4567–4581.

View Article Online
DOI: 10.1039/C8NJ01682H

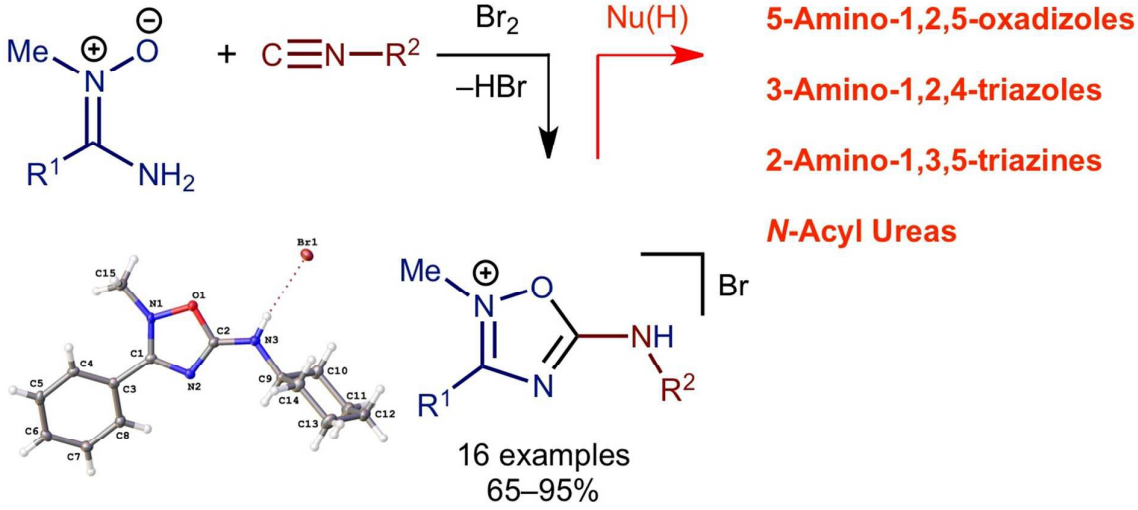
10. (a) H. G. Aurich and J. Trosken, *Chem. Ber.*, 1972, **105**, 1216–1223; (b) A. R. Forrester and R. H. Thomson, *J. Chem. Soc.*, 1965, 1224–1231; (c) B. Trzewik, D. Cież, M. Hodorowicz and K. Stadnicka, *Synthesis*, 2008, **2008**, 2977–2985; (d) B. Trzewik, T. Seidler, E. Brocławik and K. Stadnicka, *New J. Chem.*, 2010, **34**, 2220–2228.

11. (a) P. S. Branco, S. Prabhakar, A. M. Lobof and D. J. Williams, *Tetrahedron*, 1992, **48**, 6335–6360; (b) C. Z. Dong, A. Ahamada-Himidi, S. Plocki, D. Aoun, M. Touaibia, N. Meddad-Bel Habich, J. Huet, C. Redeuilh, J. E. Ombetta, J. J. Godfroid, F. Massicot and F. Heymans, *Bioorg. Med. Chem.*, 2005, **13**, 1989–2007; (c) B. N. Naidu and M. E. Sorenson, *Org. Lett.*, 2005, **7**, 1391–1393; dP. W. Seale and W. K. Warburton, *J. Chem. Soc.*, 1974, **1**, 85–88.

12. (a) A. Pace and P. P., *Org. Biomol. Chem.*, 2009, **7**, 4337–4348; (b) M. Ispikoudi, M. Amvrazis, C. Kontogiorgis, A. E. Koumbis, K. E. Litinas, D. Hadjipavlou-Litina and K. C. Fylaktakidou, *Eur. J. Inorg. Chem.*, 2010, **45**, 5635-5645 ; (c) J. V. dos Anjos, R. A. W. Neves, S. C. do Nascimento, R. M. Srivastava, S. J. de Melo and D. Sinou, *Eur. J. Med. Chem.*, 2009, **44**, 3571–3576; (d) W. Kemnitzer, J. Kuemmerle, H. Z. Zhang, S. Kasibhatla, B. Tseng, J. Drewe and X. Cai Sui, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 4410-4415; (e) L. E. Kiss, H. S. Ferreira, L. Torrao, M. J. Bonifacio, P. N. Palma, P. Soares-da-Silva and D. A. Learmonth, *J. Med. Chem.*, 2010, **53**, 3396–3411; (f) R. A. W. Neves Filho, C. Aguiar da Silva, C. S. Borges da Silva, V. P. Brustein, D. M. A. F. Navarro, F. A. Brayner dos Santos, L. C. Alves, M. G. S. Cavalcanti, R. M. Srivastava and M. G. Carneiro-Da-Cunha, *Chem. Pharm. Bull.*, 2009, **57**, 819-825; (g) C.-H. Zhou and Y. Wang, *Curr. Med. Chem.*, 2012, **19**, 239–280; (h) R. S. Keri, S. A. Patil, S. Budagumpi and B. M. Nagaraja, *Chem. Biol. Drug Des.*, 2015, **86**, 410–423; (i) R. Kharb, P. C. Sharma and M. S. Yar, *J. Enzyme Inhib. Med. Chem.*, 2011, **26**, 1–21; (j) R. Kharb, M. S. Yar and P. C. Sharma, *Curr. Med. Chem.*, 2011, **18**, 3265–3297; (k) P. Singla, V. Luxami and K. Paul, *Eur. J. Med. Chem.*, 2015, **102**, 39–57; (l) S. Batra, Z. Tusi and S. Madapa, *Antiinfect. Agents Med. Chem.* , 2006, **5**, 135–160.

View Article Online
DOI: 10.1039/C8NJ01682H

Table of contents



Reaction of aminonitrones with isocyanides and Br_2 gives 2-methyl-5-amino-1,2,4-oxadiazolium bromides, which are convenient precursors for other heterocycles and ureides.