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A mild and efficient synthesis of 3-hetarylamino-*s*-tetrazines

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3,6-Bis(3,5-dimethylpyrazol-1-yl)-*s*-tetrazine reacts with weakly based hetarylamines such as aminofurazans, aminoimidazoles, aminotriazoles, aminotetrazoles, or aminotetrazines on heating in MeCN in the presence of M_2CO_3 (M = K, Cs) to afford 3-hetarylamino-*s*-tetrazines, the products of 3,5-dimethylpyrazolyl group displacement.

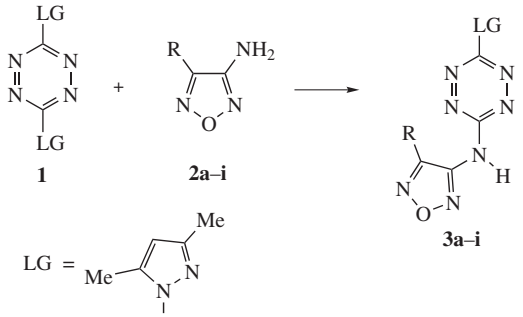
The design and synthesis of new high nitrogen energetic compounds with high density and improved performance have been the focus of recent studies in several research laboratories. For this purpose, azoles (pyrazoles,[1] triazoles,[2] tetrazoles,[2(c),(d),3] furazans[4]) and azines (triazines[5] and tetrazines[6]) are mostly considered as the core moiety. Energetic compounds constructed from such heterocycles are attractive not only owing to their higher heats of formation, density, thermal stability, and oxygen balance, but also due to their greater environmental acceptability, since they produce a high percentage of nitrogen gas upon explosion or burning.

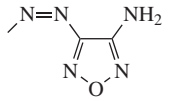
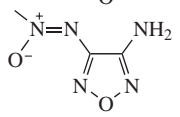
Combination in a molecule of few the same[7] or different[8] heterocyclic subunits is an approach to control properties of the target compounds. Hybrids in which furazan (1,2,5-oxadiazole) and 1,2,4,5-tetrazine (*s*-tetrazine) rings are bridged through the NH-spacer make only a fleeting appearance in energetic material synthesis.[9] Their first preparation from 3,6-bis(3,5-dimethylpyrazol-1-yl)-*s*-tetrazine **1** and 3,4-diaminofurazan **2a** was reported in 2009.[9(a)] Using sodium hydride at room temperature in DMF, 6-(3-aminofurazan-4-ylamino)-1,2,4,5-tetrazines were prepared from **1** and **2a** in good yields. However, this protocol is limited to substituents resistant to NaH. Thus, our attempts to use 3-amino-4-nitrofurazan and 3-amino-4-azidofurazan were unsuccessful due to the undesired reduction of the functional groups by NaH. Recently, we developed an alternative synthesis of 6-(3-R-furazan-4-ylamino)-*s*-tetrazines *via* copper catalyzed cross-coupling of *s*-tetrazinylamines with iodofurazans.[9(c)] While this method displays good functional group tolerance, starting iodofurazans[10] are not easily accessible. Furthermore, the yields were moderate (42–58%).

In our effort toward the construction of high nitrogen energetic compounds based on the furazan ring, we hoped to develop a more simple protocol for the efficient synthesis of 6-(3-R-furazan-4-ylamino)-*s*-tetrazines *via* nucleophilic substitution chemistry. Herein, we present our progress toward that goal.

Although the displacement of dimethylpyrazolyl moiety in compound **1** by N-nucleophiles has been known for many years,[11] this reaction was limited to amines of high nucleophilicity. We recently reported an efficient procedure for the displacement of dimethylpyrazolyl moiety (LG) at *s*-tetrazine ring by furazancarboxylic acid hydrazides in refluxing MeCN, using K_2CO_3 as the base.[12] We were pleased to discover that this procedure can be extended to some other poor N-nucleophiles, *e.g.* to 3,4-diaminofurazan[13] **2a** (Scheme 1).

We screened a set of twelve bases (pyridine, NEt_3, Li_2CO_3, Na_2CO_3, $Na_2CO_3{\cdot}10H_2O$, NaF, Na_3PO_4, K_2CO_3, KF, K_3PO_4, Cs_2CO_3, CsF) for the preparation of **3a**[†] in refluxing acetonitrile



	R	*t*/h	Isolated product yield (%)
a	NH_2	1	85
b	Me	4	73
c	OMe	2.2	82
d	Ph	2	91
e	N_3	1.1	81
f	CO_2Me	1	92
g		1.5	79
h		1.5	80
i	NO_2	0.8	90

Scheme 1 *Reagents and conditions*: aminofurazan **2a–i** (1.1 mmol), tetrazine **1** (1 mmol), K_2CO_3 (1 mmol), acetonitrile (10 ml), 80 °C; full consumption of starting materials was achieved at specified time.

(80 °C) (Table S1, see Online Supplementary Materials). Cesium cabonate was most effective, however, less expensive K_2CO_3 was of similar efficiency at longer reaction time. Notably, no reaction of the second amino group at the furazan ring or displacement of both dimethylpyrazole moieties at the tetrazine ring did occur.

Then, we conducted a small solvent screen at synthesis of compound **3a** (K_2CO_3 as the base) (see Online Supplementary Materials). Of the solvents studied (MeCN, DME, THF, diglyme, dioxane, DMSO, DMF), acetonitrile and DME provided the best

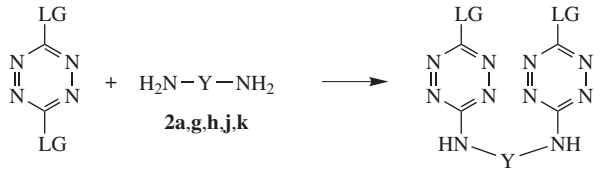
† The identity of products **3a**,[9(c)] **3b**,[9(c)] **3c**,[9(c)] **3d**,[9(c)] **3e**,[9(c)] **3i**,[9(b)] **4a**,[9(a)] **4b**,[9(b)] **4c**,[9(b)] and **6e**[8(a)] was confirmed by NMR spectra, CHN analysis, mp, MS, and comparison with the literature data. For characteristics of compounds **3f–h**, **4d**, **6a–d** and **6f**, see Online Supplementary Materials.

results, whilst DMF afforded the worst. Although the majority of the solvents provided complete conversion after 1 h at 80 °C, we chose to proceed with MeCN because it provided better solubility for many substrates of interest.

With K_2CO_3 as the base, the nucleophilic substitution of dimethylpyrazole moiety (LG) in compound **1** with 1 equiv. of various aminofurazans **2a–i** was explored (Scheme 1).† Excellent isolated yields were achieved with amines bearing either electron-donating or electron-withdrawing substituents. Furthermore, excellent tolerance was observed in the presence of azido group and even with nitro compound. Moreover, the reaction rate was much higher for the substrates with electron-withdrawing groups. Thus, nitrofurazan **2i** showed complete reaction in less than 1 h, while methoxyfurazan **2c** required over 2 h to react completely (TLC control, $CHCl_3$–MeCN, 3:1).

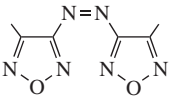
It is important to note that diamino derivative **2h** gave product **3h** arising from regioselective reaction of the amino group located at the proximate position to the *N*-oxide of the azoxy group. The structure of **3h** was confirmed by ^{13}C and ^{14}N NMR using selective ^{13}C-{^{14}N} double heteronuclear resonance.

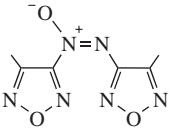
To our delight, we were able to promote the double coupling of diamines (Scheme 2)† in high yields using 2.2 equiv. of tetrazine **1a** and Cs_2CO_3 as the base. The use of weaker base such as K_2CO_3 was not effective. In the presence of Cs_2CO_3, diamine **2g** fully reacted in ~1 h, whereas K_2CO_3 required longer time (8–10 h) to react completely to give an inseparable mixture (~2:1) of **4b** and **3g**, as well as *ca.* 11% of 3-hyrdoxy-6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine. In the case of diamine **2a**, even at longer time the yield of product **4a** remained moderate. Apparently, NHR substituent in the monosubstituted intermediate **3a** had the most influence at the second step when it was located too close to the reacting amino group. In contrast, more remote diamines **2g**, **2h**, **2j**, and **2k** turned out to be good bi-nucleophiles.

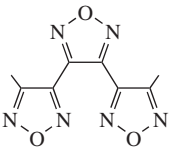


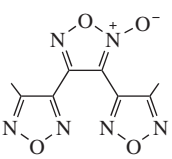
1 **4a–e**

4a Y =  (from **2a**, 8 h, 42%, 53% of **3a**)

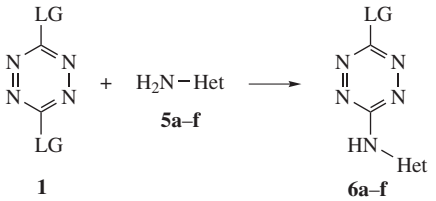
4b Y =  (from **2g**, 1 h, 92%)

4c Y =  (from **2h**, 1 h, 97%)

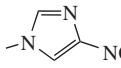
4d Y =  (from **2j**, 2 h, 94%)

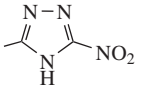
4e Y =  (from **2k**, 2 h, 85%)

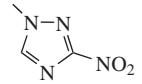
Scheme 2 *Reagents and conditions*: diamine **2** (0.5 mmol), tetrazine **1** (1.1 mmol), Cs_2CO_3 (1 mmol), MeCN (15 ml), 80 °C; TLC control (CCl_4–MeCN, 1:1) of full conversion; the yields are given for isolated products.

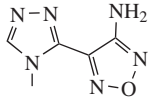


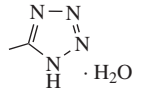
1 **6a–f**

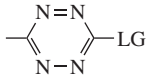
a Het =  (1.5 h, 85%)

b Het =  (2 h, 77%)

c Het =  (2 h, 67%)

d Het =  (2 h, 67%)

e Het =  (4 h, 50%, K_2CO_3) (2.5 h, 70%, Cs_2CO_3)

f Het =  (1 h, 87%)

Scheme 3 *Reagents and conditions*: amine **5** (1.1 mmol), tetrazine **1** (1 mmol), K_2CO_3 (1 mmol), acetonitrile (15 ml), 80 °C; TLC control (CCl_4–MeCN, 1:1) of full conversion; the yields are given for isolated products.

Finally, in order to further extend the scope of the chemistry studied, a diversity of secondary di(hetaryl)amines (Scheme 3) were prepared under similar conditions. Gratifyingly, the procedure (K_2CO_3 as the base) was applicable to the weakly based *C*- and *N*-amino hetarenes. As can be seen in Scheme 3, desired secondary tetrazinylamines **6a–e**† derived from imidazole, triazole, and tetrazole amines were consistently prepared in good to excellent yields.‡ Bis(*s*-tetrazinyl)amine **6f** was also prepared in high yield. Diamine **5d** reacted in high yields and with excellent chemoselectivity: *N*-amino group was more nucleophilic than *C*-amino one.

The structure of compound **6c** was determined by single crystal X-ray crystallography. An asymmetric unit cell of the compound contains one molecule incorporating three heteroaromatic moieties (Figure 1).§

‡ In reaction of compound **1** with amine **5e** (K_2CO_3, MeCN, 4 h), in addition to product **6e** (50%), 3-hydroxy-6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine was isolated (43%).

§ *Crystal data for compound* **6c**. Crystals of $C_9H_9N_{11}O_2$ are monoclinic, space group $P2_1/c$: a = 9.5677(5), b = 9.9155(6) and c = 14.0602(8) Å, β = = 104.4010(10)°, V = 1291.96(13) Å^3, Z = 4, M = 303.27, d_{calc} = 1.559 g cm^{-3}, μ = 0.121 mm^{-1}. 15758 reflections were collected at SMART APEX II CCD diffractometer [λ(MoKα) = 0.71073 Å, graphite monochromator, ω-scans, $2\theta < 64°$] at 100 K. The structure was solved by the direct methods and refined by the full-matrix least-squares procedure in anisotropic approximation. 4440 independent reflections (R_{int} = 0.0283) were used in the refinement procedure that was converged to wR_2 = 0.1307 calculated on F^2_{hkl} [GOF = 1.050, R_1 = 0.0456 calculated on F_{hkl} using 3464 reflections with $I > 2\sigma(I)$].

CCDC 907789 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2012.

For more details of the crystal packing, see Online Supplementary Materials.

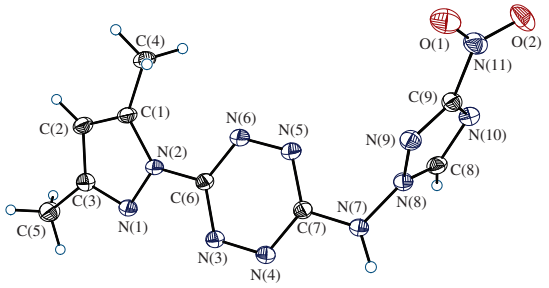


Figure 1 ORTEP view (thermal ellipsoids are shown with 50% probability) of the molecule of **6c**.

The pyrazole and the tetrazine rings are practically coplanar that imply conjugation between them. This is supported by the length [1.393(2) Å] of N(2)–C(6) bond which is shorter than the standard X-ray value (1.431 Å).[14] Coplanarity of these rings leads to short [2.849(2) Å] intramolecular contact between N(6) and C(4) atoms. The N(7)–H(7) fragment is in the plane of the tetrazine ring while 1,2,4-triazole ring is oriented nearly perpendicular to the conjugated part of the molecule of **6c**, what can be explained by sterical hindrance.

In conclusion, we have developed a very mild, efficient and scalable protocol for the synthesis of secondary polynitrogen dihetarylamines using an inexpensive commercially available reagent. Future work will look at extending the conditions employed in this study to the construction of other tetrazine derivatives.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2012.11.007.

References

1 (*a*) S. A. Shevelev and I. L. Dalinger, *Zh. Org. Khim.*, 1998, **34**, 1127 (*Russ. J. Org. Chem.*, 1998, **34**, 1071); (*b*) A. A. Zaitsev, I. L. Dalinger and S. A. Shevelev, *Usp. Khim.*, 2009, **78**, 643 (*Russ. Chem. Rev.*, 2009, **78**, 589).

2 (*a*) Y. Ou, B. Chen, J. Li, S. Dong, J. Li and H. Jia, *Heterocycles*, 1994, **38**, 1651; (*b*) M. S. Pevzner, *Ross. Khim. Zh. (Zh. Ross. Khim. Ob-va im. D. I. Mendeleeva)*, 1997, **41** (2), 73 [*Mendeleev Chem. J.* (*Engl. Transl.*), 1997, **41** (2), 113]; (*c*) V. A. Ostrovskii, M. S. Pevzner, T. P. Kofman, M. B. Shcherbinin and I. V. Tselinskii, *Targets Heterocycl. Syst.*, 1999, **3**, 467; (*d*) T. P. Kofman, *Zh. Org. Khim.*, 2002, **38**, 1289 (*Russ. J. Org. Chem.*, 2002, **38**, 1231); (*e*) H. Gao and J. M. Shreeve, *Chem. Rev.*, 2011, **111**, 7377.

3 (*a*) V. A. Ostrovskii and G. I. Koldobskii, *Ross. Khim. Zh. (Zh. Ross. Khim. Ob-va im. D. I. Mendeleeva)*, 1997, **41** (2), 84 [*Mendeleev Chem. J.* (*Engl. Transl.*), 1997, **41** (2), 133]; (*b*) T. M. Klapotke, in *High Energy Density Materials*, ed. T. M. Klapotke, Springer, Berlin, 2007, p. 85; (*c*) V. A. Ostrovskii, G. I. Koldobskii and R. E. Trifonov, in *Comprehensive Heterocyclic Chemistry III*, 2008, vol. 6, p. 257.

4 (*a*) A. B. Sheremetev, *Ross. Khim. Zh. (Zh. Ross. Khim. Ob-va im. D. I. Mendeleeva)*, 1997, **41** (2), 43 [*Mendeleev Chem. J.* (*Engl. Transl.*), 1997, **41** (2), 62]; (*b*) A. B. Sheremetev, *Usp. Khim.*, 1999, **68**, 154 (*Russ. Chem. Rev.*, 1999, **68**, 137); (*c*) A. B. Sheremetev, N. N. Makhova and W. Friedrichsen, *Adv. Heterocycl. Chem.*, 2001, **78**, 65; (*d*) A. B. Sheremetev and I. L. Yudin, *Usp. Khim.*, 2003, **72**, 93 (*Russ. Chem. Rev.*, 2003, **72**, 87); (*e*) G. N. Nikonov and S. Bobrov, in *Comprehensive Heterocyclic Chemistry III*, 2008, vol. 5, p. 315.

5 A. V. Shastin, T. I. Godovikova and B. L. Korsunskii, *Usp. Khim.*, 2003, **72**, 311 (*Russ. Chem. Rev.*, 2003, **72**, 279).

6 (*a*) D. E. Chavez, M. A. Hiskey and D. L. Naud, *Propellants Explos. Pyrotech.*, 2004, **29**, 209; (*b*) G. Clavier and P. Audebert, *Chem. Rev.*, 2010, **110**, 3299; (*c*) J. Wang, S. Liang, C. Tian and Y. Wang, *Chem. Propellants Polym. Mater.*, 2011, **9** (4), 91.

7 (*a*) D. B. Lempert, G. N. Nechiporenko and S. I. Soglasnova, *Fiz. Goren. Vzryva*, 2009, **45** (2), 58 (*Combust. Explos. Shock Waves*, 2009, **45**, 160); (*b*) V. V. Semenov, S. A. Shevelev, A. B. Bruskin, M. I. Kanishchev and A. T. Baryshnikov, *Izv. Akad. Nauk, Ser. Khim.*, 2009, 2014 (*Russ. Chem. Bull., Int. Ed.*, 2009, **58**, 2077); (*c*) T. V. Romanova, M. P. Zelenov, S. F. Mel'nikova and I. V. Tselinsky, *Izv. Akad. Nauk, Ser. Khim.*, 2009, 2123 (*Russ. Chem. Bull., Int. Ed.*, 2009, **58**, 2188); (*d*) K. Yu. Suponitsky, K. A. Lyssenko, M. Yu. Antipin, N. S. Aleksandrova, A. B. Sheremetev and T. S. Novikova, *Izv. Akad. Nauk, Ser. Khim.*, 2009, 2065 (*Russ. Chem. Bull., Int. Ed.*, 2009, **58**, 2129); (*e*) O. P. Shitov, V. L. Korolev and V. A. Tartakovsky, *Izv. Akad. Nauk, Ser. Khim.*, 2009, 2275 (*Russ. Chem. Bull., Int. Ed.*, 2009, **58**, 2347); (*f*) I. V. Tselinskii, V. V. Tolstyakov, S. M. Putis and S. F. Mel'nikova, *Izv. Akad. Nauk, Ser. Khim.*, 2009, 2283 (*Russ. Chem. Bull., Int. Ed.*, 2009, **58**, 2356).

8 (*a*) A. Saikia, R. Sivabalan, B. G. Polke, G. M. Gore, A. Singh, A. S. Rao and A. K. Sikder, *J. Hazard. Mater.*, 2009, **170**, 306; (*b*) V. N. Kizhnyaev, F. A. Pokatilov, L. I. Vereshchagin, O. N. Verkhozina, T. L. Petrova, A. G. Prodaikov, G. V. Ratovskii and O. V. Tyukalova, *Zh. Prikl. Khim.*, 2009, **82**, 1616 (*Russ. J. Appl. Chem.*, 2009, **82**, 1769); (*c*) P. W. Leonard, C. J. Pollard, D. E. Chavez, B. M. Rice and D. A. Parrish, *Synlett*, 2011, 2097; (*d*) T. K. Kim, B. W. Lee and K.-H. Chung, *Bull. Korean Chem. Soc.*, 2011, **32**, 3802; (*e*) A. B. Sheremetev, I. L. Yudin, N. V. Palysaeva and K. Yu. Suponitsky, *J. Heterocycl. Chem.*, 2012, **49**, 394; (*f*) Z. Fu, C. He and F.-X. Chen, *J. Mater. Chem.*, 2012, **22**, 60.

9 (*a*) D. E. Chavez and D. A. Parrish, *J. Heterocycl. Chem.*, 2009, **46**, 88; (*b*) A. B. Sheremetev, N. V. Palysaeva and M. I. Struchkova, *Mendeleev Commun.*, 2010, **20**, 350; (*c*) A. B. Sheremetev, N. V. Palysaeva, M. I. Struchkova, K. Yu. Suponitsky and M. Yu. Antipin, *Eur. J. Org. Chem.*, 2012, 2266.

10 (*a*) A. B. Sheremetev, Yu. L. Shamshina, D. E. Dmitriev, D. V. Lyubetskii and M. Yu. Antipin, *Heteroatom Chem.*, 2004, **15**, 199; (*b*) T. S. Novikova, T. M. Mel'nikova, O. V. Kharitonova, V. O. Kulagina, N. S. Aleksandrova, A. B. Sheremetev, T. S. Pivina, L. I. Khmel'nitskii and S. S. Novikov, *Mendeleev Commun.*, 1994, 138.

11 (*a*) M. D. Coburn, G. A. Buntain, B. W. Harris, M. A. Hiskey, K.-Y. Lee and D. G. Ott, *J. Heterocycl. Chem.*, 1991, **28**, 2049; (*b*) D. E. Chavez and M. A. Hiskey, *J. Heterocycl. Chem.*, 1998, **35**, 1329; (*c*) N. I. Latosh, G. L. Rusinov, I. N. Ganebnykh and O. N. Chupakhin, *Zh. Org. Khim.*, 1999, **35**, 1392 (*Russ. J. Org. Chem.*, 1999, **35**, 1363); (*d*) G. L. Rusinov, I. N. Ganebnykh and O. N. Chupakhin, *Zh. Org. Khim.*, 1999, **35**, 1379 (*Russ. J. Org. Chem.*, 1999, **35**, 1350); (*e*) Z. Novak, B. Bostai, M. Csekei, K. Lorincz and A. Kotschy, *Heterocycles*, 2003, **60**, 2653; (*f*) S. G. Tolshchina, A. G. Vyakhireva, N. K. Ignatenko, R. I. Ishmetova, I. N. Ganebnykh, P. A. Slepukhin and G. L. Rusinov, *Izv. Akad. Nauk, Ser. Khim.*, 2009, 1245 (*Russ. Chem. Bull., Int. Ed.*, 2009, **58**, 1281); (*g*) S. G. Tolshchina, N. K. Ignatenko, P. A. Slepukhin, R. I. Ishmetova and G. L. Rusinov, *Khim. Geterotsikl. Soedin.*, 2010, 860 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 2010, **46**, 691].

12 A. B. Sheremetev, N. V. Palysaeva, M. I. Struchkova and K. Yu. Suponitsky, *Izv. Akad. Nauk, Ser. Khim.*, 2012, 119 (*Russ. Chem. Bull., Int. Ed.*, 2012, **61**, 121).

13 I. V. Tselinskii, S. F. Mel'nikova and S. N. Vergizov, *Khim. Geterotsikl. Soedin.*, 1981, 321 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1981, **17**, 228].

14 F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1987, S1.

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