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A One-Pot, Three-Component Synthesis of 3-(1*H*-Pyrazol-1-yl)-4*H*,7*H*-[1,2,4,5]tetraazino[6,1-*b*][1,3]benzoxazin-7-ones under Solvent-Free Conditions

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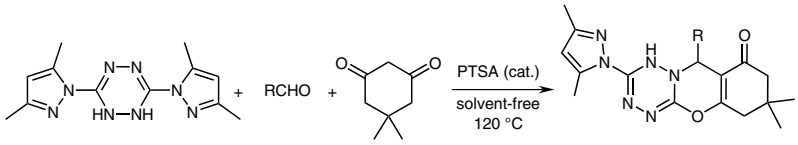

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Abstract A one-pot, three-component synthesis of 3-(1*H*-pyrazol-1-yl)-4*H*,7*H*-[1,2,4,5]tetraazino[6,1-*b*][1,3]benzoxazin-7-ones is described which involves heating a mixture of 1,2-dihydro-3,6-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-1,2,4,5-tetrazine, aldehydes, and dimedone in the presence of a catalytic amount of *p*-toluenesulfonic acid under solvent-free conditions. The bridgehead-fused 6:6:6 systems with one ring-junction nitrogen atom were obtained in excellent yields.

Key words [1,2,4,5]tetraazino[6,1-*b*][1,3]benzoxazin-7-ones, 1,2-dihydro-3,6-bis(1*H*-pyrazol-1-yl)-1,2,4,5-tetrazine, solvent-free reaction, multicomponent reactions, cyclizations, heterocycles

Multicomponent reactions (MCR) have been proved to be a powerful tool in organic and medicinal chemistry and are widely used for the synthesis of chemically and biologically important compounds. They enable multistep syntheses to be conducted in a one-pot operation to obtain a variety of valuable products from readily available starting materials. These reactions hold the possibility for convenient, safe, short, selective, high-yielding, and environmentally benign procedures and to reduce generation of chemical waste.[1]

A major challenge for synthetic chemists is to develop environment-friendly synthetic procedures. One of the most promising approaches is the solvent-free organic synthesis. These reactions may provide greater selectivity, proceed with enhanced reaction rates, give cleaner products, and involve simple manipulation.[2]

Tetrazines, an important class of high-nitrogen organic compounds, have received much synthetic attention because of their inherent biological potential.[3] These heterocyclic compounds can readily be implemented in various functional molecular systems, such as polymers in which tetrazine derivatives are coupled to electron-rich thiophene groups.[4] They have also been frequently used as building blocks in organic transformations or bridging ligands in metal complexes.[5] 1,2,4,5-Tetrazines[6] are the most important class of tetrazines that, due to the four electronegative nitrogen atoms in the tetrazine ring, have great synthetic utility and are capable of participating in inverse electron-demand Diels–Alder cycloadditions,[7] providing access to a wide range of other heterocycles such as dihydropyridazine and pyridazine systems.[8] 1,2,4,5-Tetrazines, containing heterocyclic azole fragments at 3- and 6 positions, are capable of substituting these fragments with nucleophiles such as amines and alcohols.[9] Among these, 1,2-dihydro-3,6-dipyrazolyl-1,2,4,5-tetrazines are heterocycles of particular importance because they are including two pyrazole groups at C-3 and C-6 that can be used as good leaving groups for nucleophilic substitution reactions. In addition, they possess two active NH groups in the tetrazine ring that can act as a good N-nucleophilic heterocycle.

Three-component reaction between aldehydes, 4-phenylurazole, and dimedone has been shown to give bridgehead-fused 5:5:6 systems with two ring-junction nitrogen atoms, 1*H*,6*H*-[1,2,4]triazolo[1,2-*a*]indazole-1,3,8-triones (**1**, Figure 1).[10] Fused 6:5:6 systems, 1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-triones (**2**, Figure 1), were obtained by use of phthalhydrazide as the hydrazide component in a similar reaction.[11]

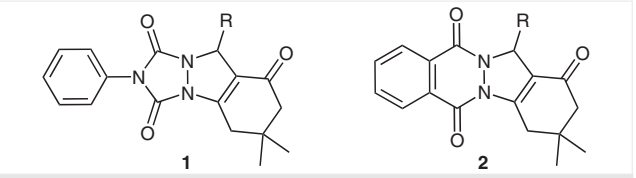
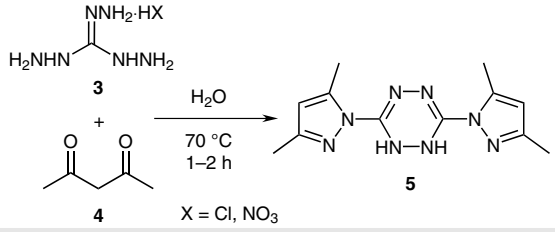


Figure 1 Fused bridgehead polycyclic systems synthesized from aldehydes, dimedone, and cyclic hydrazides

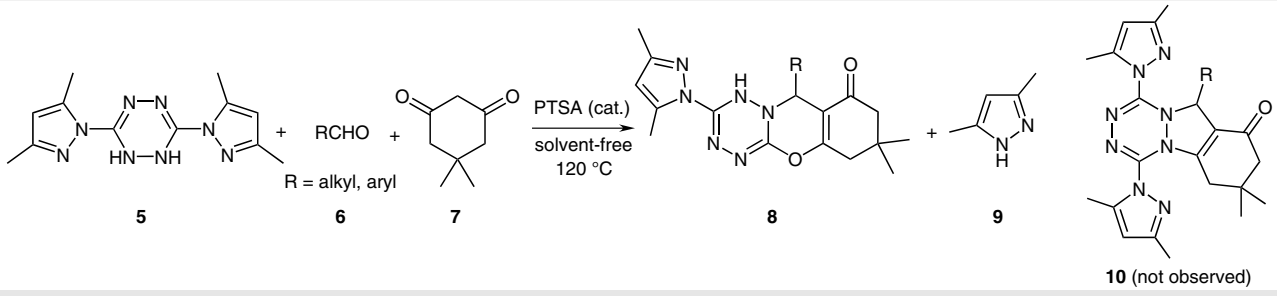
To the best of our knowledge, there has been no report concerning the use of 1,2-dihydro-3,6-dipyrazolyl-1,2,4,5-tetrazine as a starting material for the preparation of complex heterocyclic compounds. Hence, in this study we proposed using this heterocycle in MCR. 1,2-Dihydro-3,6-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-1,2,4,5-tetrazine (DHBPTz; **5**) was first introduced by Scott in 1957.[12] As shown in Scheme 1, this heterocycle is readily prepared via condensation reaction of a triaminoguanidinum salt (**3**) and acetylacetone (**4**) in water.[13]



Scheme 1 Synthesis of 1,2-dihydro-3,6-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-1,2,4,5-tetrazine (DHBPTz)

As part of our continuing efforts on the development of new routes for the preparation of biologically active heterocyclic compounds and pursuing our studies on MCR,[14] we describe herein a novel, one-pot approach to the synthesis of 4*H*,7*H*-[1,2,4,5]tetraazino[6,1-*b*][1,3]benzoxazin-7-ones. Thus, a mixture of DHBPTz (**5**), an aldehyde **6**, and 5,5-dimethyl-1,3-cyclohexanedione (dimedone, **7**), in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA) was heated at 120 °C under solvent-free conditions. TLC monitoring of the reaction mixture indicated formation of a new product, which was isolated and purified. Identification of its structure by NMR spectroscopy and mass spectrometry revealed it to be the fused tricyclic 6:6:6 system, 4*H*,7*H*-[1,2,4,5]tetraazino[6,1-*b*][1,3]benzox- azin-7-one **8**, not the expected product **10** as has been previously reported with similar cyclic hydrazides.[10,11] No product other than **8** and 3,5-dimethyl-1*H*-pyrazole (**9**) could be detected by NMR spectroscopy.[15] The scope of the procedure was assessed with a range of representative aldehydes. The present procedure is quite general as a wide range of aromatic, aliphatic, and heterocyclic aldehydes **6** reacted readily with DHBPTz (**5**) and dimedone (**7**) to produce the corresponding 4*H*,7*H*-[1,2,4,5]tetraazino[6,1-*b*][1,3]benzoxazin-7-ones **8** in excellent yields under the reaction conditions indicated in Scheme 2 and Table 1.

The structures of the isolated products were deduced on the base of IR, ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The IR spectrum of **8e** showed the stretching bands for N–H, C=O, and C=N bonds at 3220, 3124, 1695, and 1648 cm^{-1}. The mass spectrum of **8e** displayed the molecular ion [M$^+$] peaks at *m/z* = 440 [M$^+$, ^{37}Cl] and 438 [M$^+$, ^{35}Cl], which was consistent with the 1:1:1 adduct of DHBPTz, 4-chlorobenzaldehyde, and dimedone, with the loss of H_2O and a 3,5-dimethyl-1*H*-pyrazole molecule (**9**). The ^{1}H NMR spectrum of **8e** exhibited four single lines readily recognized as arising from the two methyl groups of the cyclohexenone ring (at δ = 0.99 and 1.00 ppm) and the two methyl groups of the pyrazole ring (δ = 2.28 and 2.35 ppm), as well as two AB quartet systems (CH_AH_B and CH_CCH_D) for the diastereotopic H atoms of the two methylene moieties in the cyclohexenone ring (at δ_A = 1.79 ppm, δ_B = 1.80 ppm, ^2J = 17.3 Hz; and at δ_C = 2.18 ppm, δ_D = 2.23 ppm, ^2J = 16.4 Hz). Two single sharp lines were observed at δ = 6.05 and 6.36 ppm due to the CH moieties of pyrazole and oxazine rings, respectively. Finally, two apparent doublets were seen at δ = 7.31 and 7.45 ppm for the four protons of the 4-chlorophenyl substituent, along with a fairly sharp singlet at δ = 8.51 ppm for the NH group of tetrazine ring. The ^{1}H-decoupled ^{13}C NMR spectrum of **8e** showed characteristic signals at δ = 11.9, 13.6, 28.2, and 28.6 ppm due to the four methyl substituents, a deshielded signal at δ = 191.6 ppm arising from the carbonyl group, as well as 13 other distinct resonances (2 CH_2, 4 CH, and 9 C) in agreement with the proposed structure.[15]



Scheme 2 Three-component reaction between DHBPTz, aldehydes, and dimedone – synthesis of 4*H*,7*H*-[1,2,4,5]tetraazino[6,1-*b*][1,3]benzoxazin-7-ones **8**

Table 1 Synthesis of 4*H*,7*H*-[1,2,4,5]Tetraazino[6,1-*b*][1,3]benzoxazin-7-ones **8a**–**k**

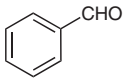
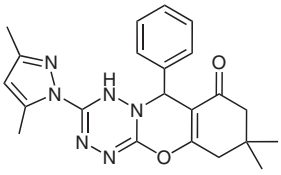
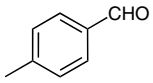
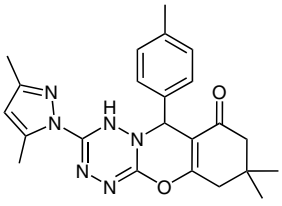
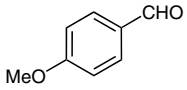
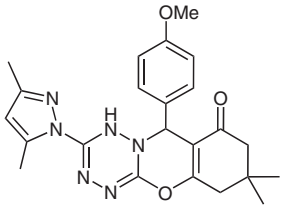
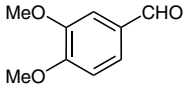
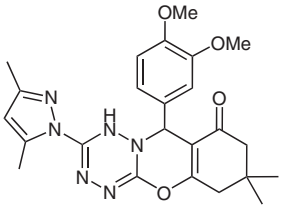
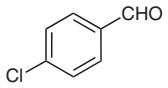
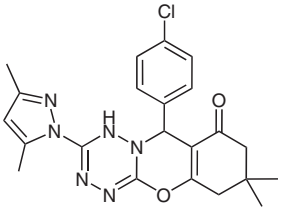
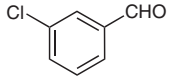
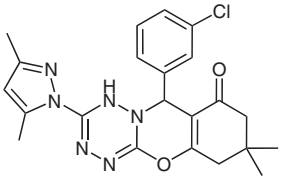
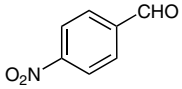
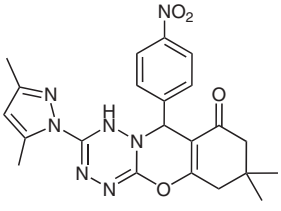
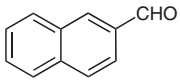
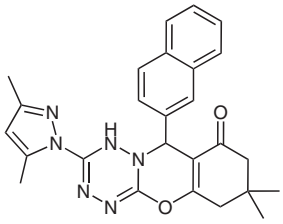
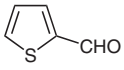
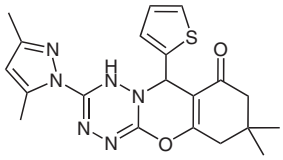
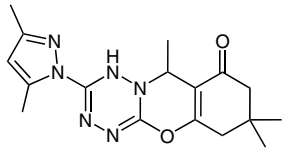
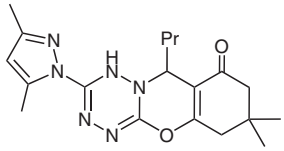
Entry	Product	Aldehyde	Structure of **8**	Time (min)	Yield of **8** (%)[a]
1	**8a**			10	92
2	**8b**			8	94
3	**8c**			8	94
4	**8d**			10	95
5	**8e**			10	92
6	**8f**			12	90
7	**8g**			12	90

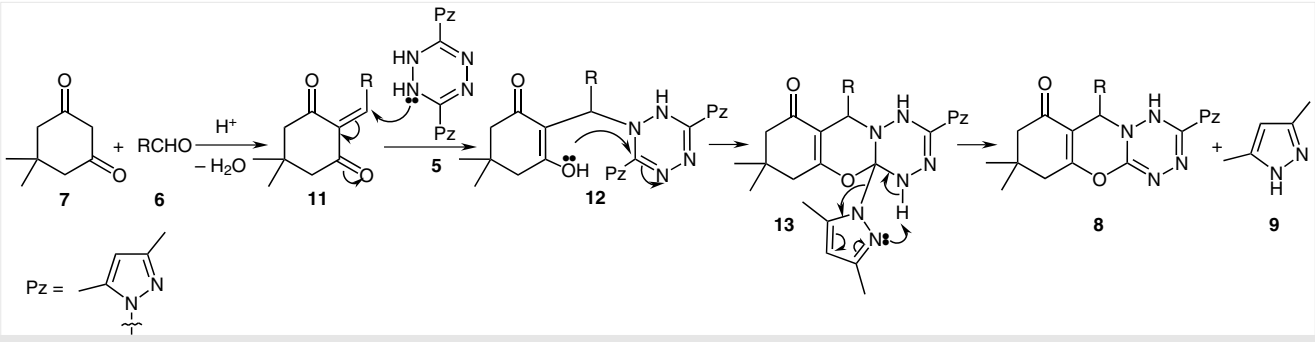
Table 1 (continued)

Entry	Product	Aldehyde	Structure of **8**	Time (min)	Yield of **8** (%)[a]
8	**8h**			10	91
9	**8i**			12	90
10	**8j**	MeCHO		15	85
11	**8k**	$MeCH_2CH_2CHO$		15	87

[a] Isolated yields.

A plausible mechanism for the formation of the 4*H*,7*H*-[1,2,4,5]tetraazino[6,1-*b*][1,3]benzoxazin-7-ones **8** is provided in Scheme 3. It is reasonable to assume that the enedione **11**, formed by Knoevenagel condensation of the aldehyde **6** and dimedone (**7**), may undergo Michael addition of DHBPTz (**5**) to give the adduct **12**. This adduct may cyclize via nucleophilic attack of the enol onto the active imine bond of the tetrazine moiety to give intermediate **13**. This intermediate may undergo elimination of 3,5-dimethyl-1*H*-pyrazole (**9**) to afford the corresponding 4*H*,7*H*-[1,2,4,5]tetraazino[6,1-*b*][1,3]benzoxazin-7-one **8**.

In summary, we have developed a novel and efficient approach for the preparation of 4*H*,7*H*-[1,2,4,5]tetraazino[6,1-*b*][1,3]benzoxazin-7-ones via a cyclocondensation reaction of 1,2-dihydro-3,6-bis(3,5-dimethyl-1*H*-pyrazol-1-yl)-1,2,4,5-tetrazine, aldehydes, and 5,5-dimethyl-1,3-cyclohexanedione under solvent-free conditions. The simplicity of the starting materials, short reaction times, one-pot procedure, as well as solvent-free conditions and excellent yields of the products are the main advantages of the reported reaction.



Scheme 3 Suggested reaction mechanism for the formation of 4*H*,7*H*-[1,2,4,5]tetraazino[6,1-*b*][1,3]benzoxazin-7-ones **8**

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378928.

References and Notes

(1) (a) *Multicomponent Reactions*; Zhu, J.; Bienaymé, H., Eds.; Wiley-VCH: Weinheim, **2005**. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (c) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3169. (d) Ramón, D. J.; Yus, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602. (e) Ma, C.; Yang, Y. *Org. Lett.* **2005**, *7*, 1343. (f) Cheng, Y.; Meth-Cohn, O. *Chem. Rev.* **2004**, *104*, 2507. (g) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 6234.

(2) (a) *Solvent-Free Organic Synthesis*; Tanaka, K., Ed.; Wiley-VCH: Weinheim, **2004**, 1st print. (b) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025. (c) Singh, M. S.; Chowdhury, S. *RSC Adv.* **2012**, *2*, 4547. (d) Zhao, Y. N.; Li, J.; Li, C. J.; Yin, K.; Ye, D. Y.; Jia, X. S. *Green Chem.* **2010**, *12*, 1370. (e) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. *Chem. Rev.* **2009**, *109*, 4140.

(3) (a) Bleehen, N. M.; Newlands, E. S.; Lee, S. M.; Thatcher, N.; Selby, P.; Calvert, A. H.; Rustin, G. J. S.; Brampton, M.; Stevens, M. F. G. *J. Clin. Oncol.* **1995**, *13*, 910. (b) Newlands, E. S.; Blackledge, G. R. P.; Slack, J. A.; Rustin, G. J. S.; Smith, D. B.; Stuart, N. S. A.; Quarterman, C. P.; Hoffman, R.; Stevens, M. F. G.; Brampton, M. H.; Gibson, A. C. *Br. J. Cancer* **1992**, *65*, 287.

(4) (a) Audebert, P.; Sadki, S.; Miomandre, F.; Clavier, G. *Electrochem. Commun.* **2004**, *6*, 144. (b) Li, Z.; Ding, J. F.; Song, N. H.; Du, X. M.; Zhou, J. Y.; Lu, J. P.; Tao, Y. *Chem. Mater.* **2011**, *23*, 1977. (c) Ding, J.; Song, N.; Li, Z. *Chem. Commun.* **2010**, *46*, 8668. (d) Li, Z.; Ding, J.; Song, N.; Lu, J.; Tao, Y. *J. Am. Chem. Soc.* **2010**, *132*, 13160.

(5) (a) Kaim, W. *Coord. Chem. Rev.* **2002**, *230*, 127. (b) Kaim, W.; Berger, S.; Greulich, S.; Reinhardt, R.; Fiedler, J. *J. Organomet. Chem.* **1999**, *582*, 153. (c) Parimal, K.; Witlicki, E. H.; Flood, A. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 4628.

(6) (a) Benson, F. R. *The High Nitrogen Compounds*; Wiley-Interscience: New York, **1984**. (b) Neunhoeffer, H. In *Comprehensive Heterocyclic Chemistry I*; Vol. 3; Katritzky, A. R.; Rees, C. W., Eds.; Chapt. 2.21; Pergamon Press: Oxford, **1984**, 531–572. (c) Hurst, D. T. In *Comprehensive Heterocyclic Chemistry II*; Vol. 6; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Chapt. 6.22; Pergamon Press: London, **1996**, 957–965. (d) Churakov, A. M.; Tartakovsky, V. A. *Chem. Rev.* **2004**, *104*, 2601. (e) Saracoglu, N. *Tetrahedron* **2007**, *63*, 4199.

(7) (a) Cioslowski, J.; Sauer, J.; Hetzenegger, J.; Karcher, T.; Hierstetter, T. *J. Am. Chem. Soc.* **1993**, *115*, 1353. (b) Panek, J. S.; Zhu, B. *Tetrahedron Lett.* **1996**, *37*, 8151. (c) Müller, K.; Sauer, J. *Tetrahedron Lett.* **1984**, *25*, 2541. (d) Burg, B.; Dittmar, W.; Reim, H.; Steigel, A.; Sauer, J. *Tetrahedron Lett.* **1975**, *16*, 2897.

(8) (a) Kovalev, E. G.; Postovskii, I. Y.; Rusinov, G. L.; Shegal, I. L. *Chem. Heterocycl. Compd.* **1981**, *17*, 1063. (b) Tolshchina, S. G.; Ishmetova, R. I.; Ignatenko, N. K. *Chem. Heterocycl. Compd.* **2013**, *49*, 604.

(9) (a) Latosh, N. I.; Rusinov, G. L.; Ganebnykh, I. N.; Chupakhin, O. N. *Russ. J. Org. Chem.* **1999**, *35*, 1363. (b) Rusinov, G. L.; Latosh, N. I.; Ganebnykh, I. N.; Ishmetova, R. I.; Ignatenko, N. K.; Chupakhin, O. N. *Russ. J. Org. Chem.* **2006**, *42*, 757. (c) Chavez, D. E.; Hiskey, M. A. *J. Heterocycl. Chem.* **1998**, *35*, 1329.

(10) (a) Chari, M. A.; Karthikeyan, G.; Pandurangan, A.; Naidu, T. S.; Sathyaseelan, B.; Zaidi, S. M. J.; Vinu, A. *Tetrahedron Lett.* **2010**, *51*, 2629. (b) Hasaninejad, A.; Zare, A.; Shekouhy, M. *Tetrahedron* **2011**, *67*, 390. (c) Subba Reddy, B. V.; Umadevi, N.; Narasimhulu, G.; Yadav, J. S. *Chem. Lett.* **2013**, *42*, 927. (d) Bazgir, A.; Seyyedhamzeh, M.; Yasaei, Z.; Mirzaei, P. *Tetrahedron Lett.* **2007**, *48*, 8790. (e) Azarifar, D.; Nejat-Yami, R.; Akrami, Z.; Sameri, F.; Samadi, S. *Lett. Org. Chem.* **2012**, *9*, 128. (f) Tavakoli, H. R.; Moosavi, S. M.; Bazgir, A. *J. Korean Chem. Soc.* **2013**, *57*, 472.

(11) (a) Sayyafi, M.; Seyyedhamzeh, M.; Khavasi, H. R.; Bazgir, A. *Tetrahedron* **2008**, *64*, 2375. (b) Ghorbani-Vaghei, R.; Karimi-Nami, R.; Toghraei-Semiromi, Z.; Amiri, M.; Ghavidel, M. *Tetrahedron* **2011**, *67*, 1930.

(12) Scott, F. L. *Angew. Chem.* **1957**, *69*, 506.

(13) (a) Coburn, M. D.; Buntain, G. A.; Harris, B. W.; Hiskey, M. A.; Lee, K. Y.; Ott, D. G. *J. Heterocycl. Chem.* **1991**, *28*, 2049. (b) Gong, Y. H.; Miomandre, F.; Méallet-Renault, R.; Badré, S.; Galmiche, L.; Tang, J.; Audebert, P.; Clavier, G. *Eur. J. Org. Chem.* **2009**, *35*, 6121. (c) Li, Y.; Asadi, A.; Perrin, D. M. *J. Fluorine Chem.* **2009**, *130*, 377.

(14) (a) Adib, M.; Sheikhi, E.; Bagheri, M.; Bijanzadeh, H. R.; Amanlou, M. *Tetrahedron* **2012**, *68*, 3237. (b) Adib, M.; Sheikhi, E.; Rezaei, N. *Tetrahedron Lett.* **2011**, *52*, 3191. (c) Adib, M.; Ansari, S.; Bijanzadeh, H. R. *Synlett* **2011**, 619. (d) Adib, M.; Karimzadeh, M.; Mahdavi, M.; Sheikhi, E.; Mirzaei, P. *Synlett* **2011**, 834. (e) Adib, M.; Sheikhi, E.; Kavoosi, A.; Bijanzadeh, H. R. *Tetrahedron* **2010**, *66*, 9263. (f) Adib, M.; Sheikhi, E.; Kavoosi, A.; Bijanzadeh, H. R. *Synthesis* **2010**, 4082. (g) Adib, M.; Mohamadi, A.; Sheikhi, E.; Ansari, S.; Bijanzadeh, H. R. *Synlett* **2010**, 1606.

(15) **Typical Procedure for the Preparation of Compounds 8a–k**

A mixture of DHBPTz (0.272 g, 1.0 mmol), benzaldehyde (0.127 g, 1.2 mmol), dimedone (0.140 g, 1.0 mmol) and PTSA (0.052 g, 0.3 mmol) was heated at 120 °C for the time indicated in Table 1. After completion of the reaction as indicated by TLC monitoring, the reaction mixture was cooled to r.t., and the residue was purified by column chromatography using *n*-hexane–EtOAc (5:1) as eluent. The solvent was removed and the pure product **8a** was obtained.

3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-9,9-dimethyl-6-phenyl-6,8,9,10-tetrahydro-4*H*,7*H*-[1,2,4,5]tetraazino[6,1-*b*][1,3]-benzoxazin-7-one (8a)

Yield 0.372 g (92%); yellow powder; mp 167 °C. IR (KBr): 3255 and 3144 (NH), 1709 (C=O), 1642 (C=N), 1601, 1491, 1370, 1318, 1270, 1219, 1113, 1028, 971, 911, 773, 744 cm^{-1}. ^1H NMR (500.1 MHz, $CDCl_3$): δ = 1.04 and 1.05 (2 × s, 6 H, 2 × CH_3), 1.83 (s, 2 H, CH_2), 2.21 (d, ^2J = 16.5 Hz, 1 H, CH_CCH_D), 2.28 (d, ^2J = 16.5 Hz, 1 H, CH_CCH_D), 2.31 and 2.40 (2 × s, 6 H, 2 × CH_3), 6.08 (s, 1 H, pyrazole CH), 6.42 (s, 1 H, NCH), 7.31 (t, *J* = 7.5 Hz, 1 H, CH), 7.39 (t, *J* = 7.5 Hz, 2 H, 2 × CH), 7.53 (d, *J* = 7.5 Hz, 2 H, 2 × CH), 7.95 (s, 1 H, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 11.9 and 13.7 (2 × pyrazole CH_3), 28.4 and 28.6 [$C(CH_3)_2$], 34.6 (CH_2C=C), 34.7 [$C(CH_3)_2$], 50.8 (CH_2C=O), 64.0 (NCH), 109.7 (pyrazole CH), 114.0 (C), 127.1, 128.2 and 128.7 (3 × CH), 135.8, 139.2, 143.0, 150.2, 152.5 and 157.8 (6 × C), 191.5 (C=O). MS: *m/z* (%) = 404 (58) [M^+], 368 (6), 339 (6), 327 (100), 243 (25), 227 (36), 202 (10), 179 (23), 163 (22), 149 (36), 122 (20), 95 (32), 77 (32). Anal. Calcd (%)for $C_{22}H_{24}N_6O_2$ (404.47): C, 65.33; H, 5.98; N, 20.78. Found: C, 65.30; H, 6.05; N, 20.72.

6-(4-Chlorophenyl)-3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-9,9-dimethyl-6,8,9,10-tetrahydro-4*H*,7*H*-[1,2,4,5]tetraazino-[6,1-*b*][1,3]benzoxazin-7-one (8e)

Yield 0.404 g (92%); yellow powder; mp 207 °C. IR (KBr): 3220 and 3124 (NH), 1695 (C=O), 1648 (C=N), 1593, 1492, 1458, 1370, 1321, 1272, 1220, 1115, 1087, 1018, 970, 909, 831, 791, 743, 680 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$): δ = 0.99 and 1.00 (2 × s, 6 H, 2 × CH_3), 1.79 (d, ^2J = 17.3 Hz, 1 H, CH_ACH$_B$), 1.80 (d, ^2J = 17.3 Hz, 1 H, CH$_A$CH_B), 2.18 (d, ^2J = 16.4 Hz, 1 H, CH_CCH$_D$), 2.23 (d, ^2J = 16.4 Hz, 1 H, CH$_C$CH_D), 2.28 and 2.35 (2 × s, 6 H, 2 × CH_3), 6.05 (s, 1 H, pyrazole CH), 6.36 (s, 1 H, NCH), 7.31 (d, *J* = 8.8 Hz, 2 H, 2 × CH), 7.45 (d, *J* = 8.8 Hz, 2 H, 2 × CH), 8.51 (s, 1 H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 11.9 and 13.6 (2 × pyrazole CH_3), 28.2 and 28.6 [C(*C*H$_3$)$_2$], 34.6 (*C*H$_2$C=C), 34.7 [*C*(CH$_3$)$_2$], 50.7 (*C*H$_2$C=O), 63.3 (NCH), 109.7 (pyrazole CH), 113.5 (C), 128.5 and 128.8 (4 × CH), 133.9, 135.6, 137.9, 143.1, 150.5, 152.6 and 157.8 (7 × C), 191.6 (C=O). MS: *m/z* (%) = 440 (20) [M^+, ^{37}Cl], 438 (65) [M^+, ^{35}Cl], 353 (2), 342 (4), 327 (100), 271 (5), 243 (42), 179 (30), 163 (45), 95 (28), 67 (18), 55 (17). Anal. Calcd (%) for $C_{22}H_{23}ClN_6O_2$ (438.92): C, 60.20; H, 5.28; N, 19.15. Found: C, 60.18; H, 5.32; N, 19.11.

3-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-9,9-dimethyl-6-propyl-6,8,9,10-tetrahydro-4*H*,7*H*-[1,2,4,5]tetraazino[6,1-*b*][1,3]benzoxazin-7-one (8k)

Yield 0.322 g (87%); yellow powder; mp 189 °C. IR (KBr): 3237 (NH), 1713 (C=O), 1670 (C=N), 1628, 1593, 1493, 1439, 1382, 1323, 1279, 1223, 1134, 1110, 1085, 1028, 970, 934, 904, 850, 814, 773, 716, 670 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.3 Hz, 3 H, CH$_2$CH_3), 0.98 and 1.01 (2 × s, 6 H, 2 × CH_3), 1.40–1.51 (m, 2 H, CH_2), 1.62 (d, *J* = 17.4 Hz, 1 H, CH_ACH$_B$), 1.63–1.71 (m, 1 H, CH), 1.72 (d, *J* = 17.4 Hz, 1 H, CH$_A$CH_B), 1.81–1.88 (m, 1 H, CH), 2.18 (d, *J* = 16.3 Hz, 1 H, CH_CCH$_D$), 2.24 (d, *J* = 16.3 Hz, 1 H, CH$_C$CH_D), 2.27 and 2.36 (2 × s, 6 H, 2 × CH_3), 5.37 (br d, *J* = 6.3 Hz, 1 H, NC*H*CH$_2$), 6.04 (s, 1 H, pyrazole CH), 7.55 (s, 1 H, NH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 11.8, 13.6 and 13.8 (2 × pyrazole CH_3 and CH$_2$*C*H$_3$), 18.3 (*C*H$_2$CH$_3$), 28.1 and 28.7 [C(*C*H$_3$)$_2$], 34.4 (*C*H$_2$C=C), 34.5 [*C*(CH$_3$)$_2$], 36.2 (CH*C*H$_2$), 50.8 (*C*H$_2$C=O), 62.3 (NCH), 109.6 (pyrazole CH), 113.9, 135.8, 142.9, 150.5, 152.4 and 158.6 (6 × C), 191.7 (C=O). MS: *m/z* (%) = 370 (5) [M^+], 327 (100), 273 (3), 243 (22), 163 (20), 95 (12), 67 (8), 55 (7). Anal. Calcd (%) for $C_{19}H_{26}N_6O_2$ (370.45): C, 61.60; H, 7.07; N, 22.69. Found: C, 61.51; H, 6.93; N, 22.57.