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A Novel Method for the Synthesis of Imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-ones

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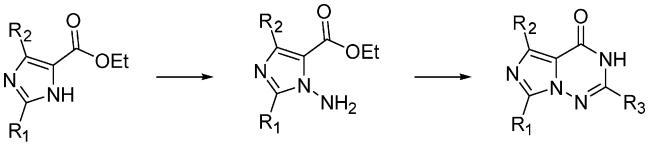
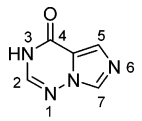


Imidazo[5,1-*f*][1,2,4]triazinones, as isosteres of purine, are of interest for pharmaceutical research. The syntheses reported in the literature generally require several steps. We report a novel method to access a broad range of diversely substituted derivatives. The key step is the electrophilic *N*-amination of 3*H*-imidazoles containing a 4-carbonyl group. Several different substituted imidazoles have been *N*-aminated in this manner. The resulting *N*-aminoimidazoles were cyclized under different conditions to the corresponding imidazotriazinones, which allowed for additional diversification. This novel method was applied in a formal synthesis of vardenafil, a well-known representative of this class of compounds. Furthermore, we report the first synthesis of a 7-aryl-imidazotriazinone via bromination of an unsubstituted imidazotriazinone followed by a Suzuki coupling.

Introduction

The imidazo[5,1-*f*][1,2,4]triazinone scaffold **1** has recently received attention as the core structure of vardenafil (Levitra) (**2**), a potent and effective PDE5 inhibitor for the treatment of erectile dysfunction.[1]



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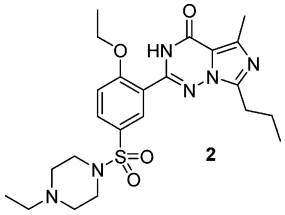

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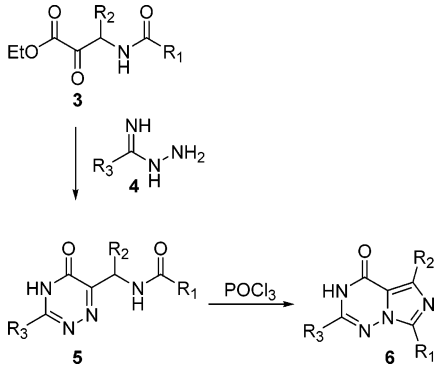
Analogues of this interesting heterocycle containing nitrogen in the ring junction have also been described as muscle relaxants, bronchodilators,[2] as *C*-nucleoside isosteres,[3] and purine analogues.[4] Imidazo[5,1-*f*][1,2,4]-triazinones have been synthesized generally by a previously reported method (Scheme 1).[5] The sequence begins with a Dakin−West reaction of acylated α-amino acids and ethyl oxalyl chloride to afford acylamino-α-ketoester **3**. Ketoester **3** is typically used without isolation to react with amidrazones **4**, which are prepared in situ from the corresponding amidine and hydrazine. This condensation results in the triazinone-core **5** in moderately low yields

SCHEME 1. Classic Imidazotriazinone Synthesis



(1) (a) Haning, H.; Niewöhner, U.; Schenke, T.; Es-Sayed, M.; Schmidt, G.; Lampe, T.; Bischoff, E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 865. (b) Niewohner, U.; Es-Sayed, M.; Haning, H.; Schenke, T.; Schlemmer, K.-H.; Keldenich, J.; Bischoff, E.; Perzborn, E.; Dembowsky, K.; Serno, P.; Nowakowski, M. U.S. Patent 6,362,178. (c) Nowakowski, M.; Gehring, R.; Heilman, W.; Wahl, K.-H. World Patent, WO 02/50076. (d) Review on PDE5 inhibitors: Dunn, P. J. *Org. Process Res. Dev.* **2005**, *9*, 88.

(2) (a) Garside, S. C.; Hartley, D.; Lunts, L. H. C.; Oxford, A. W. Deutsche Offenlegungsschrift 2255172, 1974; *Chem. Abstr.* **1973**, *79*, 53376. (b) Hartley, D.; Clarke, R. W.; Oxford, A. W. Deutsche Offenlegungsschrift 2364076, 1974; *Chem. Abstr.* **1974**, *81*, 120704. (c) Hartley, D.; Oxford, A. W. Deutsche Offenlegungsschrift 2811780, 1978; *Chem. Abstr.* **1978**, *89*, 215442. (d) Dansey, R.; Oxford, A. W.; Ellis, F.; Hartley, D. European Patent EP0009384, 1980; *Chem. Abstr.* **1980**, *93*, 204694. (e) Marshall, D. R. *Chem. Ind.* **1983**, 331.

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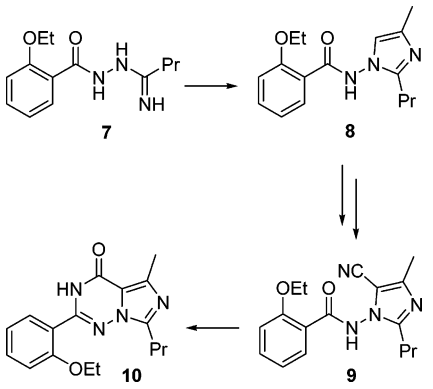
SCHEME 2. Bayer's Alternative Route to Vardenafil



of 13−26% over two steps. Triazinone **5** can then be cyclized to the imidazo[5,1-*f*][1,2,4]triazinone **6** in the presence of phosphoryl chloride.

This sequence was used not only for the medicinal chemistry synthesis but also in the chemical development of vardenafil (**2**).[1] In both cases, reactive intermediates such as ketoester **3** (R_1 = *n*-propyl, R_2 = Me) complicate the synthesis. The overall yield of the vardenafil intermediate **10** over five steps is 30% for the medicinal chemistry and 50% for the chemical development route.

An alternative route to **10** avoiding the most reactive intermediate **3** has been reported (Scheme 2).[6] This approach differs from the classical sequence with respect to the order of ring construction. The key steps of this synthesis were the formation of imidazole **8** followed by the cyclization of nitrile **9** to imidazotriazinone **10**. An overall yield of 19% over five steps was reported.

Our interest in developing a novel method for the synthesis of the imidazo[5,1-*f*][1,2,4]triazinone scaffold was based on the need to access derivatives with diversely substituted imidazole rings. In our hands, certain imidazotriazinones were difficult to obtain through the classical sequence, notably where R_1 is aryl. Difficulties include the formation of ketoester **3** or the deacylation of triazinone **5** to access the free amine as a synthon for subsequent acylation with aromatic carboxylic acids. These limitations led us to investigate a novel route for the construction of the imidazo[5,1-*f*][1,2,4]triazin-4(3*H*)-one scaffold. Consequently, instead of forming the triazinone first, we envisioned a synthesis starting with the imidazole.

Results and Discussion

Our strategy was based on the electrophilic amination of imidazoles containing a carboxyl function ortho- to one of the imidazole nitrogens. Besides hydroxylamine-*O*-sulfonic acid, which has been widely used for *N*-aminations of NH-acidic heterocycles,[7] *O*-(diphenylphosphinyl)-hydroxylamine has been applied to aminate nitroimidazoles.[8] Both reagents have been employed to aminate 2-substituted pyrroles, and these *N*-aminopyrroles were cyclized to pyrrolo[2,1-*f*][1,2,4]triazines and pyrrolo[2,1-*f*][1,2,4]triazinones, respectively, by using formamidine, formic acid, or formamide.[9] However, when we used hydroxylamine-*O*-sulfonic acid in anhydrous DMF for the *N*-amination of imidazole **11**, we observed 20% conversion to the desired *N*-aminoimidazole **12** regardless of variable reaction conditions including a large excess of reagent. By switching to *O*-(diphenylphosphinyl)hydroxylamine in combination with LHMDS as the base in NMP, conditions used for the amination of electron-deficient indoles,[10] we were delighted to see that ethyl 3-amino-3*H*-imidazole **12** was formed as the major isomer in reproducibly good yields of greater than 70% (Scheme 3).

The other isomer **12a** can also be isolated in yields around 20%. Because only isomer **12** may undergo cyclization, in principle, the mixture could be treated with formamide to provide imidazotriazinone **13**. However, the cyclization was carried out on isolated **12** and led to **13** in excellent yields of around 90%. It should be noted that all our attempts to synthesize **13** through the established route did not provide the product. To demonstrate that triazinone **13** can be further functionalized, we treated it with phosphoryl chloride and obtained the useful synthon **14** as a stable, isolable product.

Because our goal was to access a variety of differently substituted imidazoles, we applied the *N*-amination conditions to imidazoles **15**, **17**, and **20** and obtained all three aminoimidazoles in good yields (Table 1). Using DMF instead of NMP as the solvent did not influence the yield but facilitated product isolation. NMP requires extensive extraction with an organic solvent (EtOAc, Et_2O, CH_2Cl_2) after the reaction is quenched with water. Running the reaction in DMF allows evaporation of the solvent in vacuo. The remaining solid can be efficiently extracted with dichloromethane to give the product in greater than 90% purity. In case of compounds with poor solubility in organic solvents such as *N*-aminoimidazole **18**, filtration of the reaction mixture to remove the formed $LiOP(Ph)_2O$ was carried out without quenching the reaction with water. Upon concentration of the filtrate in vacuo, the product precipitated and was obtained by filtration in greater than 95% purity.

The cyclization of the differently substituted *N*-aminoimidazoles **16**, **18**, and **21** with formamide led to the corresponding imidazotriazinones **1**, **19**, and **22**. Next, we investigated the accessibility of substituents on the triazinone ring. Based on the formation of bicyclic pyrimidinones,[11] we envisioned the acid-catalyzed reaction

(3) (a) Mitchell, W. L.; Hill, M. L.; Newton, R. F.; Ravenscroft, P.; Scopes, D. I. C. *J. Heterocycl. Chem.* **1984**, *21*, 697. (b) Knutsen, L. J. S.; Judkins, B. D.; Mitchell, W. L.; Newton, R. F.; Scopes, D. I. C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 229. (c) Knutsen, L. J. S.; Judkins, B. D.; Newton, R. F.; Scopes, D. I. C.; Klinkert, G. *J. Chem. Soc., Perkin Trans. 1* **1985**, 621. (d) Bhattacharya, B. K.; Rao, T. S.; Lewis, A. F.; Revankar, G. R.; Sangvhi, Y. S.; Robins, R. K. *J. Heterocycl. Chem.* **1993**, *30*, 1341.

(4) Clarke, R. W.; Garside, S. C.; Lunts, L. H. C.; Hartley, D.; Hornby, R.; Oxford, A. W. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1120.

(5) Charles, I.; Latham, D. W. S.; Hartley, D.; Oxford, A. W.; Scopes, D. I. C. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1139.

(6) Nowakowsky, M.; Vetter, A. World Patent, WO 02/50075; *Chem. Abstr.* **2002**, *137*, 47232.

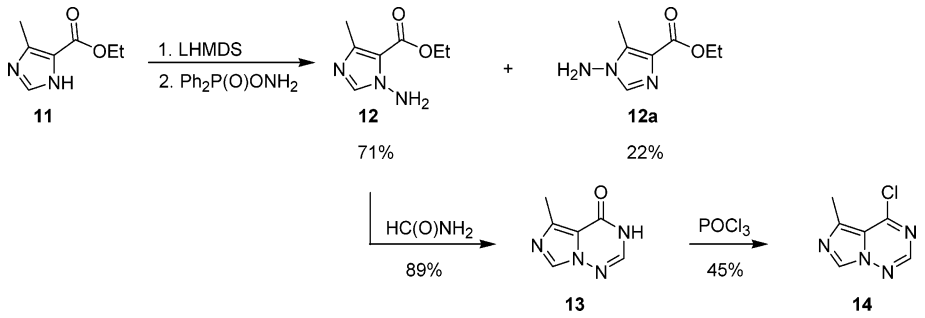
(7) (a) Somei, M.; Matsubara, M.; Kanda, Y.; Natsume, M. *Chem. Pharm. Bull.* **1978**, *26*, 2522. (b) Wallace, R. G. *Aldrichimica Acta* **1980**, *13*, 3.

(8) Klötzer, W.; Baldinger, H.; Karpitschka, E. M.; Knoflach, J. *Synthesis* **1982**, 592.

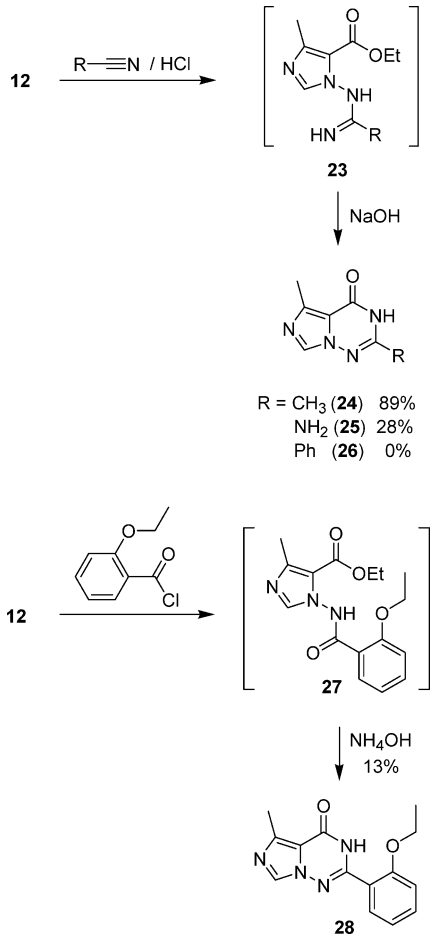
(9) (a) Patil, S. A.; Otter, B. A.; Klein, R. S. *J. Heterocycl. Chem.* **1994**, *31*, 781. (b) Hunt, J. T.; Mitt, T.; Borzilleri, R.; Gullo-Brown, J.; Fargnoli, J.; Fink, B.; Han, W.-C.; Mortillo, S.; Vite, G.; Wautlet, B.; Wong, T.; Yu, C.; Zheng, X.; Bhide, R. *J. Med. Chem.* **2004**, *47*, 4054.

(10) Belley, M.; Scheigetz, J.; Dubé, P.; Dolman, S. *Synlett* **2001**, 222.

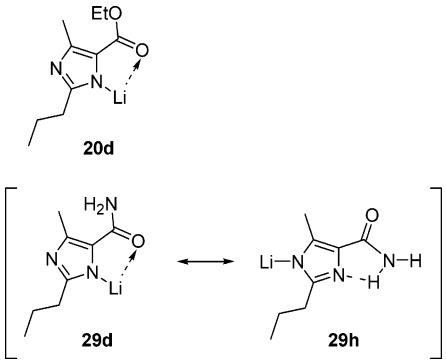
SCHEME 3. *N*-Amination of Imidazole Followed by Cyclization to Imidazotriazinone



SCHEME 4. Synthesis of 2-Substituted Triazinones



SCHEME 5. Ester versus Amide



of *N*-aminoimidazole **12** with nitriles to form amidine intermediate **23**, which under subsequent treatment with base cyclizes to 2-substituted triazinones (Scheme 4). Alkyl-, heteroatom-, and aryl-substituents were selected to cover three important classes of substituents. Treatment of *N*-aminoimidazole **12** with acetonitrile or cyanamide led to 2,5-dimethyl-imidazotriazinone **24** in 89% yield and 2-amino-5-methyl-imidazotriazinone **25** in 28% yield, respectively (Scheme 4). However, cyclization with benzonitrile to triazinone **26** could not be carried out successfully. Monitoring the reaction by LC−MS clearly showed the formation of the expected amidine intermediate **23** but no cyclization to the desired product. In an effort toward a formal synthesis of vardenafil (**2**), reaction of **12** with the sterically more demanding 2-ethoxybenzonitrile was also unsuccessful.

As an alternative, we generated an amide instead of an amidine intermediate to explore the influence of the linkage between the *N*-aminoimidazole and the aryl group on the cyclization. We followed the one-pot procedure, which has been applied to the synthesis of a pyrido-[3′,2′:4,5]thieno[2,3-*e*]pyrimidine.[12] In this case, after acylation of 3-amino-thiophene with benzoyl chloride, the cyclization to the pyrimidine ring was achieved by simply stirring for several days with concentrated ammonium hydroxide at room temperature. Applying this method to *N*-aminoimidazole **12**, we observed the (2-ethoxybenzoylamino)-imidazole intermediate **27**, but the cyclization to the imidazotriazinone-ring **28** required high temperatures and pressure. The obtained yield was usually below 15%, probably due to the competing amide bond cleavage at higher temperatures in concentrated ammonium hydroxide.

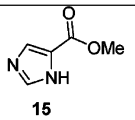
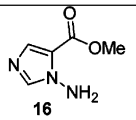
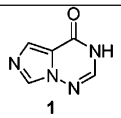
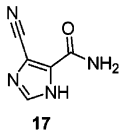
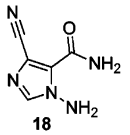
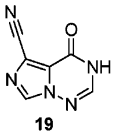
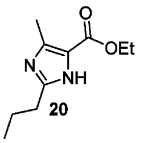
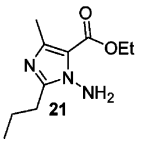
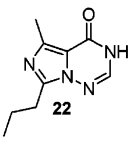
Recognizing the difficulties with ring formation using ammonium hydroxide, a better source of nitrogen was needed. In Bayer's alternative synthesis, precursor **9** was cyclized in sulfuric acid to give a 50% yield of the vardenafil intermediate **10**. In comparison, the final cyclization step in the synthesis of the pyrazolo[4,3-*d*]-pyrimidinone sildenafil was base catalyzed under anhydrous conditions in yields greater than 95%.[13] The common feature in both syntheses is the primary amide functionality of the five-membered heterocycle, which seems to facilitate the cyclization.

(11) (a) Melik-Ogandzhanyan, R. G.; Khachatryan, V. E.; Gapoyan, A. S. *Russ. Chem. Rev.* **1985**, *54*, 262. (b) Dave, K. G.; Shishoo, C. J.; Devani, M. B.; Kalyanaraman, R.; Ananthan, S.; Ullas, G. V.; Bhadti, V. S. *J. Heterocycl. Chem.* **1980**, *17*, 1497. (c) Venugopalan, B.; Desai, P. D.; de Souza, N. J. *J. Heterocycl. Chem.* **1988**, *25*, 1633.

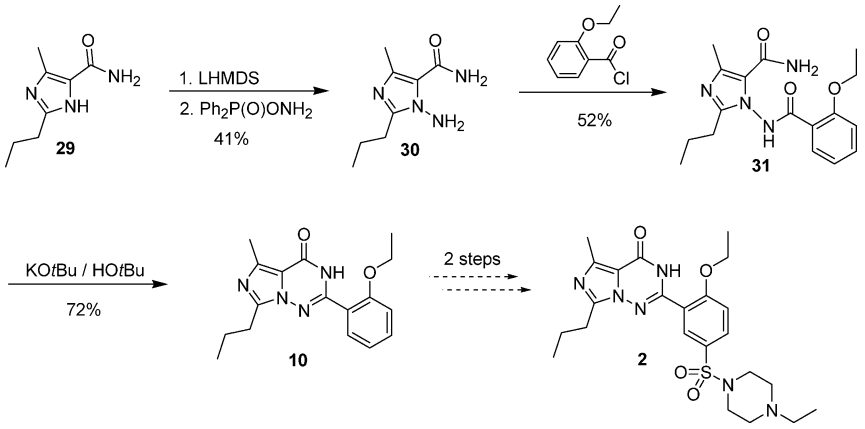
(12) Vieweg, H.; Böhm, N.; Krasselt, U.; Leistner, S.; Wagner, G. *Pharmazie* **1992**, *47*, 751.

(13) Dale, D. J.; Dunn, P. J.; Golightly, C.; Hughes, M. L.; Levett, P. C.; Pearce, A. K.; Searle, P. M.; Ward, G.; Wood, A. S. *Org. Process Res. Dev.* **2000**, *4*, 17.

TABLE 1. *N*-Amination of Different Imidazoles Followed by Cyclization to Imidazotriazinones

Entry	Imidazole	*N*-Aminoimidazole	Yield	Imidazotriazinone	Yield
1	 **15**	 **16**	64%	 **1**	52%
2	 **17**	 **18**	65%	 **19**	83%
3	 **20**	 **21**	75%	 **22**	68%

SCHEME 6. Formal Synthesis of Vardenafil



To test the significance of the amide functionality, we prepared imidazole **20** according to the published procedure[14] and subjected it to the *N*-amination conditions. Aminolysis of aminoimidazole carboxylic ester **21** in concentrated ammonium hydroxide led to the required aminoimidazole carboxamide **30** (Scheme 6). This reaction proceeded with low yields (~20%), and the major product is the hydrolyzed *N*-aminoimidazole carboxylic acid. Therefore, **30** was also synthesized through *N*-amination of imidazole carboxamide **29**, which again can be accessed through aminolysis of imidazole **20** in greater than 50% yield. Interestingly, the isomer ratio for this *N*-amination was approximately 1:1 as compared to the 3:1 ratio observed for carboxylic ester **20**.

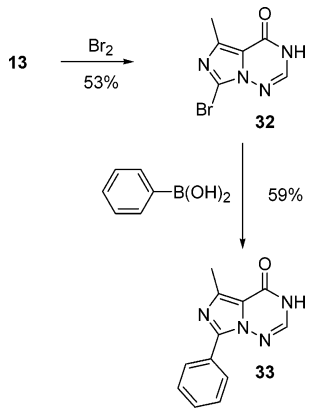
We believe that the main reason for the regioselectivity in favor of the desired isomer is due to the chelating effect as shown in the lithiated species **20d** and **29d**, respectively (Scheme 5). One possible cause for the decrease in regioselectivity in the carboxamide case could be the stabilization of the imidazole anion **29h** through an intramolecular hydrogen bond. This could make the other imidazole nitrogen more nucleophilic and thus more reactive. Because in the case of the aminoimidazole carboxamide **18** the desired regioisomer can be obtained in 65% yield, the different nature of the substituents on the imidazole seems to influence the reaction as well.

With *N*-aminoimidazole **30** in hand, acylation with 2-ethoxybenzoyl chloride provided the 3-(2-ethoxy-benzoylamino)-imidazole **31** in 52% yield (Scheme 6). Compound **31** was subjected to a modified protocol[13] using 10 equiv of potassium *tert*-butoxide in *tert*-butyl alcohol in a sealed tube at 160 °C. Cyclization to imidazotriazinone **10** proceeded in 72% yield and successfully completed the formal synthesis of vardenafil (**2**). None of the conditions have been optimized, and therefore the lower overall yield of 15% as compared to the published syntheses[1,6] could be improved. However, this synthesis demonstrates the potential of this method to access a variety of diversely substituted imidazotriazinones.

After successfully incorporating an aryl substituent in the 2-position of the imidazotriazinone, we also wanted to access imidazotriazinones with an aryl group at the 7-position. Few 2-aryl-imidazoles as starting materials are commercially available and would have to be synthesized. Therefore, we investigated the introduction of this substituent after the imidazotriazinone formation.

(14) Ross, B. C.; Middlemiss, D.; Scopes, D. I. C.; Jack, T. I. M.; Cardwell, K. S.; Dowle, M. D.; Judd, D. B. European Patent EP0514216A1, 1992; *Chem. Abstr.* **1993**, *118*, 169107. See also: Judd, D. B.; Dowle, M. D.; Middlemiss, D.; Scopes, D. I. C.; Ross, B. C.; Jack, T. I.; Pass, M.; Tranquillini, E.; Hobson, J. E.; Panchal, T. A.; Stuart, P. G.; Paton, J. M. S.; Hubbard, T.; Hilditch, A.; Drew, G. M.; Robertson, M. J.; Clark, K. L.; Travers, A.; Hunt, A. A. E.; Polley, J.; Eddershaw, P. J.; Bayliss, M. K.; Manchee, G. R.; Donnelly, M. D.; Walker, D. G.; Richards, S. A. *J. Med. Chem.* **1994**, *37*, 3108.

SCHEME 7. Synthesis of 7-Aryl-imidazotriazinones



Starting with unsubstituted imidazotriazinone **13**, bromination led selectively to the 7-bromo-imidazotriazinone **32**, which constituted a useful synthon for C−C-coupling conditions. In this case, standard Suzuki coupling[15] provided 7-phenyl-imidazotriazinone **33** in 59% yield (Scheme 7).

Conclusion

We have developed a method for the synthesis of imidazo[5,1-*f*][1,2,4]triazinones allowing access to a broad variety of substituents around the bicyclic heterocycle in only two to three steps and generally good yields. This method was applied to a formal synthesis of vardenafil. As compared to the published syntheses, our method provides a straightforward sequence with stable intermediates and can lead to more structurally diverse derivatives. Furthermore, we report for the first time the synthesis of unsubstituted imidazotriazinones, which can be later modified and serve as important synthons for more complex derivatives of this class of compounds.

Experimental Section

Ethyl 5-Methyl-2-propyl-3*H*-imidazole-4-carboxylate (20).[14] To a stirred suspension of ethyl butaneimidate hydrochloride (24.0 g, 0.16 mol) and triethylamine (32 mL, 0.23 mol) in absolute EtOH (200 mL) was added a solution of ethyl 2-amino-3-oxobutanoate hydrochloride (11.6 g, 0.06 mol) in absolute EtOH (100 mL) dropwise over 1 h. After being stirred overnight under an atmosphere of N_2, the orange reaction mixture was concentrated in vacuo to ~50 mL. The TEA hydrochloride, which had precipitated, was filtered off, and the remaining solution was concentrated in vacuo to afford an orange oil. Purification by chromatography eluting with 40% increasing to 75% ethyl acetate in hexane gave the title compound as a white solid (7.65 g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.27 (q, J = 6.85 Hz, 2H), 2.65 (t, J = 6.95 Hz, 2H), 2.46 (s, 3H), 1.69 (sextet, J = 6.95 Hz, 2H), 1.24 (t, J = 6.95 Hz, 3H), 0.89 (t, J = 6.95 Hz, 3H).

5-Methyl-2-propyl-3*H*-imidazole-4-carboxamide (29). In a sealed tube, ethyl ester (**20**) (1.49 g, 7.59 mmol) in concentrated ammonium hydroxide (20 mL) was stirred at 130 °C for 24 h. The solvent was removed in vacuo, and the remaining solid was purified by flash chromatography on silica gel eluting with 2% increasing to 10% methanol in dichloromethane. The product was obtained as a white solid (671 mg, 53%). R_f = 0.44 (10% MeOH in DCM). ^{1}H NMR (300 MHz, [d_6]-DMSO): δ 11.86 (s_{br}, 1H), 6.99 (s_{br}, 1H), 6.80 (s_{br}, 1H), 2.50 (t, J = 7.53 Hz, 2H), 2.38 (s, 3H), 1.63 (sextet, J = 7.40 Hz, 2H), 0.88 (t, J = 7.34 Hz, 3H). ^{13}C NMR (75 MHz, [d_6]-DMSO): δ 166.1, 145.6, 130.5, 129.6, 30.1, 21.6, 13.9, 10.9. MS, *m/z* (%) 168.0 (100) [M^+ + 1].

General Procedure for *N*-Amination of Imidazoles. Lithium hexamethyldisilazane (1.10 mL of a 1 M solution in THF, 1.1 mmol) was slowly added to the imidazole (1.0 mmol) in anhydrous DMF (10 mL) at −10 °C. After the mixture was stirred for 10 min, *O*-(diphenylphosphinyl)hydroxylamine[16] (280 mg, 1.2 mmol) was added at 0 °C, followed by stirring at room temperature for 4−6 h (in cases where the reaction mixture became too viscous, additional DMF was added). The reaction was quenched with water until a clear solution was formed and concentrated to dryness under reduced pressure. The residue was washed several times with ethyl acetate or dichloromethane. The combined organic fractions were concentrated in vacuo and purified by flash chromatography on silica gel.

Ethyl 3-Amino-5-methyl-3*H*-imidazole-4-carboxylate (12) and Ethyl 1-Amino-5-methyl-1*H*-imidazole-4-carboxylate (12a). *N*-Amination of **11** (5.39 g, 34.96 mmol) followed the general procedure. Purification by flash chromatography on silica gel eluting with 0% increasing to 4% methanol in dichloromethane gave **12** as a yellow-white solid (4.23 g, 71%) and **12a** as a yellow-waxy solid (1.29 g, 22%). **12**: R_f 0.53 (7% MeOH in DCM). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (s, 1H), 5.33 (s, 2H), 4.27 (q, J = 6.9 Hz, 2H), 2.35 (s, 3H), 1.31 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.9 (CO_2Et), 146.6, 140.4 (CH), 118.4, 60.8, 16.4, 14.7. MS, *m/z* (%) 170 (100) [M^+ + 1]. Anal. Calcd for $C_7H_{11}N_3O_2$ (169.18): C, 49.70; H, 6.55; N, 24.84. Found: C, 49.85; H, 6.45; N, 24.74. **12a**: R_f 0.18 (7% MeOH in DCM). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (s, 1H), 4.79 (s_{br}, 2H), 4.25 (q, J = 7.2 Hz, 2H), 2.44 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.1 (CO_2Et), 137.6 (CH), 137.2, 127.3, 60.6, 14.8, 9.5.

Methyl 3-Amino-3*H*-imidazole-4-carboxylate (16). *N*-Amination of **15** (1.0 g, 7.93 mmol) followed the general procedure. Purification by flash chromatography on silica gel eluting with 50% increasing to 100% ethyl acetate in hexane gave a white solid (0.72 g, 64%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.59 (s, 1H), 5.42 (s, 2H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.5 (CO_2Et), 142.1 (CH), 135.9 (CH), 122.0, 52.0. MS, *m/z* (%) 142 (100) [M^+ + 1]. Anal. Calcd for $C_5H_7N_3O_2$ (141.13): C, 42.55; H, 5.00; N, 29.77. Found: C, 42.59; H, 4.89; N, 29.88.

3-Amino-5-cyano-3*H*-imidazole-4-carboxamide (18). *N*-Amination of **17** (200 mg, 1.469 mmol) followed the general procedure. After 6 h, the reaction mixture was filtered to remove the formed lithium salt of *O*-diphenylphosphinic acid without quenching the reaction. Evaporation of the solvent in vacuo led to precipitation of product. The product was collected by filtration and washed with MeOH to give a pale yellow solid (145 mg, 65%). ^{1}H NMR (300 MHz, [d_6]-DMSO): δ 8.35 (s_{br}, 1H), 8.07 (s_{br}, 1H), 7.92 (s, 1H), 6.72 (s, 2H). ^{13}C NMR (75 MHz, [d_6]-DMSO): δ 158.3 ($CONH_2$), 142.1 (CH), 133.4, 115.2, 113.9. MS, *m/z* (%) 152 (100) [M^+ + 1]. Anal. Calcd for $C_5H_5N_5O$ (151.13): C, 39.74; H, 3.33; N, 46.34. Found: C, 39.82; H, 3.12; N, 46.56.

Ethyl 3-Amino-5-methyl-2-propyl-3*H*-imidazole-4-carboxylate (21). *N*-Amination of **20** (2.0 g, 10.19 mmol) followed the general procedure. Purification by flash chromatography on silica gel eluting with 50% increasing to 75% ethyl acetate in hexane gave a yellow-white solid (1.63 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.95 (s, 2H), 4.01 (q, J = 7.0 Hz, 2H), 2.43 (t, J = 7.5 Hz, 2H), 2.10 (s, 3H), 1.42 (sextet, J = 7.5 Hz, 2H), 1.07 (t, J = 7.0 Hz, 3H), 0.66 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2, 152.4, 145.2, 117.6, 60.4, 28.3, 21.5, 16.2, 14.7, 14.2. MS, *m/z* (%) 212 (100) [M^+ + 1]. Anal.

(15) Gong, Y.; He, W. *Org. Lett.* **2002**, *4*, 3803.

(16) Colvin, E. W.; Kirby, G. W.; Wilson, A. C. *Tetrahedron Lett.* **1982**, *23*, 3835.

Calcd for $C_{10}H_{17}N_3O_2$ (211.25): C, 56.85; H, 8.11; N, 19.89. Found: C, 56.62; H, 7.85; N, 19.97.

3-Amino-5-methyl-2-propyl-3*H*-imidazole-4-carboxamide (30) and 1-Amino-5-methyl-2-propyl-1*H*-imidazole-4-carboxamide (30a). *N*-Amination of **29** (583 mg, 3.48 mmol) followed the general procedure. Purification by flash chromatography on silica gel eluting with 4% increasing to 10% methanol in dichloromethane gave **30** as a pale yellow waxy solid (259 mg, 41%) and **30a** as a white solid (350 mg, 55%). **30**: R_f 0.32 (10% MeOH in DCM). ^{1}H NMR (300 MHz, CD_3-OD): δ 2.72 (t, J = 7.5 Hz, 2H), 2.41 (s, 3H), 1.76 (sextet, J = 7.5 Hz, 2H), 1.01 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, CD_3-OD): δ 165.1, 151.9, 141.9, 121.5, 28.4, 21.8, 15.1, 14.2. MS, *m/z* (%) 183.2 (100) [M^+ + 1]. Anal. Calcd for $C_8H_{14}N_4O$ (182.23): C, 52.73; H, 7.53; N, 30.75. Found: C, 52.72; H, 7.53; N, 31.00. **30a**: R_f 0.44 (10% MeOH in DCM). ^{1}H NMR (300 MHz, CD_3OD): δ 2.75 (t, J = 7.3 Hz, 2H), 2.50 (s, 3H), 1.75 (sextet, J = 7.3 Hz, 2H), 1.00 (t, J = 7.3 Hz, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 168.5, 149.8, 136.4, 126.9, 28.9, 22.3, 14.1, 9.4.

General Procedure for the Preparation of Imidazo-[5,1-*f*][1,2,4]triazin-4(3*H*)-ones. In a sealed tube, amino-imidazole (1.00 mmol) in formamide (1−2 mL) was heated at 180 °C for 2−8 h. Upon cooling to rt, most imidazo[5,1-*f*][1,2,4]-triazin-4(3*H*)-ones precipitated out and could be isolated by filtration. The precipitate was washed with ethyl acetate. The same solvent was used to precipitate out the products if necessary. The products were obtained as white/beige solids (52−89% yield).

5-Methyl-3*H*-imidazo[5,1-*f*][1,2,4]triazin-4-one (13). According to the general procedure, amino-imidazole **12** (2.50 g, 14.77 mmol) gave beige crystals (1.96 g, 89%). ^{1}H NMR (300 MHz, [d_6]-DMSO): δ 11.32 (s_{br}, 1H), 8.28 (s, 1H), 7.79 (s, 1H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, [d_6]-DMSO): δ 155.2, 140.8 (CH), 139.0, 133.1 (CH), 115.7, 14.7. MS, *m/z* (%) 150.9 (100) [M^+ + 1]. Anal. Calcd for $C_6H_6N_4O$ (150.14): C, 48.00; H, 4.03; N, 37.32. Found: C, 48.25; H, 4.03; N, 37.29.

3*H*-Imidazo[5,1-*f*][1,2,4]triazin-4-one (1). According to the general procedure, amino-imidazole **16** (110 mg, 0.779 mmol) gave white crystals (55 mg, 52%). ^{1}H NMR (300 MHz, [d_6]-DMSO): δ 11.87 (s_{br}, 1H), 8.47 (s, 1H), 7.93 (s, 1H), 7.78 (s, 1H). ^{13}C NMR (75 MHz, [d_6]-DMSO): δ 154.2, 140.9 (CH), 135.0, 128.0 (CH), 120.4. MS, *m/z* (%) 137.0 (100) [M^+ + 1]. Anal. Calcd for $C_5H_4N_4O$ (136.11): C, 44.12; H, 2.96; N, 41.16. Found: C, 43.91; H, 2.70; N, 41.26.

5-Cyano-3*H*-imidazo[5,1-*f*][1,2,4]triazin-4-one (19). According to the general procedure, amino-imidazole **18** (96 mg, 0.653 mmol) gave the product (90% pure), which was purified by reversed phase HPLC, eluted with 0.1% TFA H_2O/MeOH gradient, to give the product as a beige-white solid (87 mg, 83%). ^{1}H NMR (300 MHz, [d_6]-DMSO): δ 12.56 (s_{br}, 1H), 8.72 (s, 1H), 8.14 (s, 1H). ^{13}C NMR (75 MHz, [d_6]-DMSO): δ 152.7, 142.8 (CH), 136.4 (CH), 126.9, 114.2, 109.2. MS, *m/z* (%) 160.1 (100) [M^+ − 1]. HPLC-Purity: 100% at 0.30 min (A = 10 μM $CH_3CO_2NH_4$, B=CH_3CN, Grad. 10−95% B in 2 min, 4.5 mL/min, Col: Luna phenylhexyl (Phenomenex) 50 mm × 4.6 mm (3 μm) @ 45 °C, detection 220/250 nm).

5-Methyl-2-propyl-3*H*-imidazo[5,1-*f*][1,2,4]triazin-4-one (22). According to the general procedure, amino-imidazole **21** (100 mg, 0.509 mmol) gave a white solid (67 mg, 68%). ^{1}H NMR (300 MHz, [d_6]-DMSO): δ 11.51 (s_{br}, 1H), 7.76 (s, 1H), 2.79 (t, J = 7.2 Hz, 2H), 2.43 (s, 3H), 1.69 (sextet, J = 7.2 Hz, 2H), 0.90 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, [d_6]-DMSO): δ 155.3, 144.4, 139.9, 137.9, 115.2, 27.4, 20.6, 14.6, 14.0. MS, *m/z* (%) 193.2 (100) [M^+ + 1]. Anal. Calcd for $C_9H_{12}N_4O$ (192.22): C, 56.24; H, 6.29; N, 29.15. Found: C, 55.94; H, 6.42; N, 29.13.

4-Chloro-5-methyl-imidazo[5,1-*f*][1,2,4]triazine (14). Imidazotriazinone **13** (500 mg, 3.33 mmol) was heated under reflux in phosphoryl chloride (10 mL) for 5 h. The reaction mixture was cooled to room temperature and poured on ice followed by extraction with dichloromethane (3 × 20 mL). The organic layer was washed with saturated Na_2CO_3-solution, brine, and dried over $MgSO_4$. The solvent was removed in vacuo, and the remaining solid was purified by flash chromatography on silica gel eluting with 75% ethyl acetate in hexane. Chloride **14** was obtained as a beige-white solid (309 mg, 45%). R_f 0.51 (50% EtOAc in hexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 8.06 (s, 1H), 2.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.69, 146.9 (CH), 137.3, 131.3 (CH), 116.9, 15.6. MS, *m/z* (%) 168.9 (100) [M^+ + 1]. Anal. Calcd for $C_6H_5ClN_4$ (168.59): C, 42.75; H, 2.99; Cl, 21.03; N, 33.23. Found: C, 42.98; H, 3.09; Cl, 20.87; N, 33.09.

2,5-Dimethyl-3*H*-imidazo[5,1-*f*][1,2,4]triazin-4-one (24). To a solution of amino-imidazole **12** (200 mg, 1.18 mmol) in acetonitrile (10 mL) was passed dry hydrogen chloride gas at room temperature for 30 min. The reaction mixture was stirred for 18 h. Upon concentration, a white solid precipitated and was filtered off. The solid was taken up in absolute ethanol (20 mL) and 5% aqueous sodium hydroxide (5 mL) and heated under reflux for 6 h. The solvent was evaporated, and the reaction mixture was dissolved in water and acidified with 6 N HCl. The precipitate was filtrated and washed with water. After drying in vacuo, the product was obtained as a white solid (172 mg, 89%). ^{1}H NMR (300 MHz, [d_6]-DMSO): δ 11.61 (s_{br}, 1H), 8.21 (s, 1H), 2.45 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (75 MHz, [d_6]-DMSO): δ 155.5, 149.5, 138.7, 132.6, 114.3, 18.4, 14.6. MS, *m/z* (%) 165.0 (100) [M^+ + 1]. Anal. Calcd for $C_7H_8N_4O$ (164.17): C, 51.21; H, 4.91; N, 34.13. Found: C, 51.21; H, 4.73; N, 34.08.

2-Amino-5-methyl-3*H*-imidazo[5,1-*f*][1,2,4]triazin-4-one (25). To a solution of amino-imidazole **12** (145 mg, 0.857 mmol) and cyanamide (42 mg, 1.028 mmol) in dioxane (8 mL) was added concentrated hydrochloric acid (0.5 mL). The reaction mixture was heated under reflux under nitrogen atmosphere for 24 h. The formed brown oil was separated from the reaction mixture, and after the addition of a solution of sodium hydroxide (41 mg, 1.028 mmol) in water (10 mL) it was heated at 100 °C for 3 h. The cooled mixture was acidified with hydrochloric acid (6 N) and was purified by reversed phase HPLC, eluted with 0.1% TFA H_2O/MeOH gradient, to give the product as a white solid (40 mg, 28%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.84 (s, 1H), 2.52 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 155.7, 153.9, 134.2, 127.9, 116.5, 11.1. MS, *m/z* (%) 166.1 (100) [M^+ + 1]. HPLC-Purity: 100% at 0.31 min (A = 10 μM $CH_3CO_2NH_4$, B=CH_3CN, Grad. 10−95% B in 2 min, 4.5 mL/min, Col: Luna phenylhexyl (Phenomenex) 50 mm × 4.6 mm (3 μm) @ 45 °C, detection 220/250 nm).

2-(2-Ethoxy-phenyl)-5-methyl-3*H*-imidazo[5,1-*f*][1,2,4]-triazin-4-one (28). To a solution of aminoimidazole **12** (100 mg, 0.591 mmol) in anhydrous pyridine (2 mL) was added 2-ethoxy-benzoyl chloride (130 mg, 0.709 mmol). The reaction mixture was stirred under nitrogen for 2 h at 100 °C before it was transferred into a sealed tube. After addition of concentrated ammonium hydroxide (5 mL), the mixture was stirred at 110 °C for 24 h. To the cooled reaction mixture was added ethyl acetate, and the organic layer was extracted with water, brine, and dried over $MgSO_4$. After the solvent was removed in vacuo, the crude product was purified by flash chromatography on silica gel eluting with 0% increasing to 5% methanol in dichloromethane. The product was obtained as a white solid (20 mg, 13%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.97 (s_{br}, 1H), 8.08 (dd, ^3J = 8.0 Hz, ^4J = 1.8 Hz, 1H), 7.99 (s, 1H), 7.43 (t, J = 7.8 Hz, 1H), 7.05 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 8.0 Hz, 1H), 4.19 (q, J = 6.9 Hz, 2H), 2.58 (s, 3H), 1.49 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4, 154.9, 147.5, 141.4, 133.8, 133.5, 130.4, 122.2, 117.4, 113.5, 65.7, 15.1, 15.0. MS, *m/z* (%) 271.1 (100) [M^+ + 1]. Anal. Calcd for $C_{14}H_{14}N_4O_2$ (270.29): C, 62.21; H, 5.22; N, 20.73. Found: C, 62.03; H, 4.99; N, 20.47.

3-(2-Ethoxy-benzoylamino)-5-methyl-2-propyl-3*H*-imidazole-4-carboxamide (31). To a solution of aminoimidazole **30** (160 mg, 0.878 mmol) in anhydrous pyridine (10 mL) was added 2-ethoxy-benzoyl chloride (194 mg, 1.054 mmol). The

reaction mixture was stirred under nitrogen for 2 h at 60 °C before the solvent was removed in vacuo. Ethyl acetate was added followed by extraction with saturated sodium carbonate solution, brine, and drying over $MgSO_4$. After the solvent was removed in vacuo, the crude product was purified by flash chromatography on silica gel eluting with 2% increasing to 7% methanol in dichloromethane. The product was obtained as a white solid (150 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.64 (s_{br}, 1H), 8.10 (dd, ^3J = 8.2 Hz, ^4J = 1.8 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 5.63 (s_{br}, 2H), 4.24 (q, J = 6.9 Hz, 2H), 2.53 (t, J = 7.6 Hz, 2H), 2.36 (s, 3H), 1.68 (sextet, J = 7.6 Hz, 2H), 1.52 (t, J = 6.9 Hz, 3H), 0.89 (t, J = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 162.6, 157.9, 152.4, 139.9, 134.9, 133.1, 121.8, 121.0, 119.0, 113.0, 65.7, 28.4, 21.1, 15.7, 15.1, 14.3. MS, *m/z* (%) 331.1 (100) [M^+ + 1]. Anal. Calcd for $C_{17}H_{22}N_4O_3$ (330.39): C, 61.80; H, 6.71; N, 16.96. Found: C, 61.39; H, 6.78; N, 16.95.

2-(2-Ethoxy-phenyl)-5-methyl-2-propyl-3*H*-imidazo[5,1-*f*][1,2,4]triazin-4-one (10). A solution of carboxamide **31** (70 mg, 0.213 mmol) and potassium *tert*-butoxide (239 mg, 2.13 mmol) in anhydrous *tert*-butyl alcohol (5 mL) was stirred at 160 °C in a sealed tube for 30 h. The cooled reaction mixture was neutralized with 1 N HCl before ethyl acetate was added. The organic layer was extracted with water, brine, and dried over $MgSO_4$. After the solvent was removed in vacuo, the crude product was purified by flash chromatography on silica gel eluting with 0% increasing to 5% methanol in dichloromethane. The product was obtained as a white solid (48 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.96 (s_{br}, 1H), 8.18 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1H), 7.51 (t, J = 7.6 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.06 (d, J = 8.1 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.02 (t, J = 7.6 Hz, 2H), 2.66 (s, 3H), 1.89 (sextet, J = 7.6 Hz, 2H), 1.58 (t, J = 7.1 Hz, 3H), 1.05 (t, J = 7.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4, 155.3, 146.4, 146.3, 140.2, 133.5, 130.5, 122.1, 117.9, 114.3, 113.5, 65.7, 28.4, 21.4, 15.1, 14.9, 14.4. MS, *m/z* (%) 313.1 (100) [M^+ + 1]. Anal. Calcd for $C_{17}H_{20}N_4O_2$ (312.38): C, 65.37; H, 6.45; N, 17.94. Found: C, 64.99; H, 6.67; N, 17.76.

7-Bromo-5-methyl-3*H*-imidazo[5,1-*f*][1,2,4]triazin-4-one (32). To a solution of imidazotriazinone **13** (250 mg, 1.66 mmol) in DMF (20 mL) was added bromine (530 mg, 3.32 mmol) at 0 °C. The reaction was monitored by TLC, and after completion saturated Na_2CO_3-solution (1 mL) was added. The reaction mixture was dried down in vacuo and purified by flash chromatography on silica gel eluting with 2% increasing to 7% methanol in dichloromethane. The product was obtained as a pale yellow solid (203 mg, 53%). ^{1}H NMR (400 MHz, [d_6]-DMSO): δ 11.82 (s_{br}, 1H), 7.88 (s, 1H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, [d_6]-DMSO): δ 154.6, 141.4, 139.9, 118.8, 116.1, 14.7. MS, *m/z* (%) 230.8 (100) [M^+ + 1]. Anal. Calcd for $C_6H_5BrN_4O$ (229.04): C, 31.46; H, 2.20; N, 24.46. Found: C, 31.70; H, 2.13; N, 24.27.

5-Methyl-7-phenyl-3*H*-imidazo[5,1-*f*][1,2,4]triazin-4-one (33). A microwave vial was charged with 7-bromo-imidazotriazinone **31** (50 mg, 0.218 mmol), phenylboronic acid (26 mg, 0.218 mmol), $Pd(dppf)_2Cl_2$ (8 mg, 0.010 mmol), 1 N Na_2CO_3 (0.436 mL, 0.436 mmol), and acetonitrile (1 mL). After sealing, the vial was degassed and flushed with nitrogen. The suspension was heated to 150 °C for 10 min. The conversion was followed by LC−MS, and another equivalent of boronic acid and catalyst was added before the same microwave conditions were applied. Ethyl acetate (10 mL) was added to the clear reaction mixture followed by extraction with water (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo. Purification by flash chromatography on silica gel eluting with 75% ethyl acetate in hexane gave the product as a beige-white solid (29 mg, 59%). R_f 0.23 (75% EtOAc in hexane). ^{1}H NMR (300 MHz, [d_6]-DMSO): δ 11.79 (s_{br}, 1H), 8.26 (d, J = 7.5 Hz, 2H), 7.92 (s, 1H), 7.48 (m, 3H), 2.54 (s, 3H). ^{13}C NMR (75 MHz, [d_6]-DMSO): δ 155.2, 140.7, 139.3, 129.6, 128.9, 128.8, 128.2, 116.9, 14.7. MS, *m/z* (%) 227.0 (100) [M^+ + 1]. Anal. Calcd for $C_{12}H_{10}N_4O$ (226.24): C, 63.71; H, 4.46; N, 24.77. Found: C, 63.50; H, 4.26; N, 25.00.

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