Three Novel Sequential Reactions for the Facile Synthesis of a Library of Bisheterocycles Possessing the 3-Aminoimidazo[1,2-*a*]pyridine Core Catalyzed by Bismuth(III) Chloride

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Abstract: Novel, one-pot, two-step, sequential protocols for the synthesis of 1,4-phenylene bisheterocyclic compounds have been developed. Successive sequencing of the Groebke–Blackburn–Bienaymé reaction with Ugi-azide, Hantzsch and Biginelli reactions results in rapid and efficient formation of bisheterocyclic compounds. A simple, fast and high yielding method for the synthesis of 3-aminoimidazo[1,2-*a*]pyridines catalyzed by bismuth(III) chloride under solvent-free conditions is reported. Bismuth(III) chloride is also an efficient catalyst for the Ugi-azide reaction under solvent free conditions.

Keywords: sequential reactions, Groebke–Blackburn–Bienaymé reaction, 1,4-phenylene bisheterocyclic compounds, Ugi-azide reaction, bismuth(III) chloride, solvent-free reactions

In recent years, many multicomponent reactions (MCRs) have been applied in the synthesis of different heterocycles.[1] Imidazo[1,2-*a*]pyridines, tetrazoles, 1,4-dihydropyridines and 3,4-dihydropyrimidines have attracted growing interest from both organic and medicinal chemists owing to their diverse range of biological and pharmacological activities.[2]

For example, zolpidem is an effective hypnotic agent indicated for the short-term treatment of insomnia,[3] candesartan and olmesartan are AT_1 receptor antagonists,[4] nifedipine and azelnidipine are calcium channel antagonists[5] and SQ 32.926 is an antihypertensive drug (Figure 1).[6]

One of the MCRs that is well suited for the construction of imidazo[1,2-*a*]azines derivatives is the Groebke–Blackburn–Bienaymé multicomponent reaction (GBB MCR)[7] that is the three-component condensation of an aldehyde, an isocyanide and a 2-aminoazine (Scheme 1). Compounds containing the imidazo[1,2-*a*]azine ring system have been shown to possess a broad range of useful pharmacological and biological properties, including antibacterial,[8] antifungal,[9] anthelmintic,[10] antiviral,[11] antiprotozoal,[12] anticonvulsant,[13] anxiolytic, hypnotic,[14] HIV-1 reverse transcriptase inhibition[15] and anticancer.[16] GBB MCR has been carried out using different Brønsted or Lewis acid catalysts such as acetic acid,[7a] perchloric acid,[7c] *para*-toluenesulfonic acid,[17] cellulose sulfuric acid,[18] silica sulfuric acid,[19] scandium(III) triflate,[7b] $ZnBr_2$,[20] $ZnCl_2$,[21] montmorillonite K10,[22] ammonium chloride,[23]

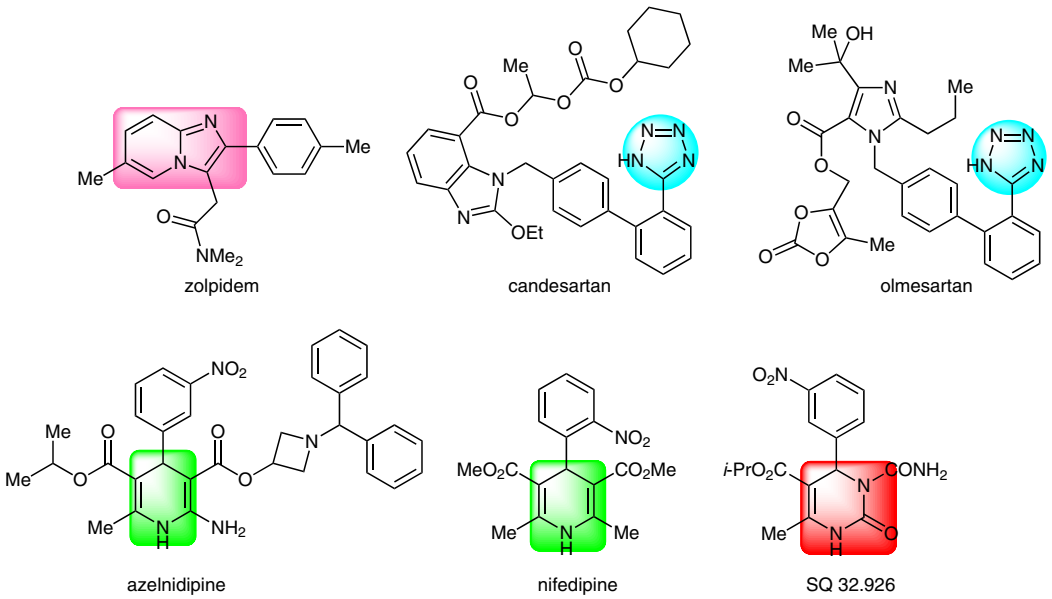

Figure 1 Examples of imidazo[1,2-*a*]pyridine-, tetrazole 1,4-dihydropyridine- and 3,4-dihydropyrimidone-containing drugs

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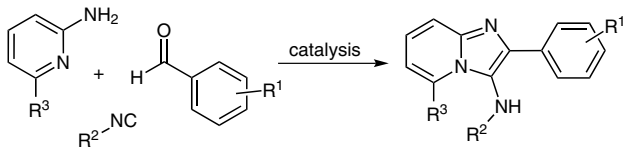
tin(II) chloride dehydrate,[24] zeolite HY,[25] and ionic liquids.[26] However, some of the reported methods suffer from disadvantages such as long reaction times, low yields of products, the use of large amounts of catalyst and strongly acidic conditions. Therefore, to avoid these limitations, the discovery of a new, inexpensive, nontoxic, easily available catalyst with high catalytic activity and short reaction time for the synthesis of imidazo[1,2-*a*]azines continues to attract interest.



Scheme 1 GBB three-component coupling reaction for the synthesis of imidazo[1,2-*a*]pyridines

Another MCR that has been used in the synthesis of nitrogen-containing heterocycles is the Ugi-azide MCR. The Ugi reaction, involving a four-component condensation of an aldehyde, an amine, an isocyanide, and a carboxylic acid, is known to produce highly diverse molecules containing a dipeptide-like backbone.[27] Various compounds can be used as the acid component in this reaction. The Ugi reaction with trimethylsilyl azide ($TMSN_3$) affords 1,5-disubstituted tetrazoles and is known as the Ugi-azide reaction.[28] The Hantzsch[29] and Biginelli reactions[30] are two other well-known synthetic sequences that afford 1,4-dihydropyridines and 3,4-dihydropyrimidin-2(1*H*)-ones, respectively, but improving the conditions of these reactions remains desirable.[31] In recent years, applications of bismuth(III) salts as catalysts in organic synthesis have been increased considerably,[32] as they are air-stable, nontoxic, inexpensive, mild Lewis acids, even less toxic than sodium chloride.[33] To the best of our knowledge, the generality and applicability of $BiCl_3$ as a catalyst in the GBB and Ugi-azide reactions has not been reported. As a part of our ongoing interest in the study of MCRs involving combinations of reactions,[34,35] herein we describe three novel sequential reactions that combine the GBB MCR with Ugi-azide MCR, Hantzsch and Biginelli reactions, with a library of new bisheterocyclic compounds being synthesized using them. The retrosynthetic pathways for these sequential reactions are shown in Scheme 2.

In this work, for the modification of GBB MCR, we surveyed the catalytic activities of a number of catalysts using 4-nitrobenzaldehyde (1 mmol), 2-aminopyridine (1 mmol) and cyclohexyl isocyanide (1.1 mmol) without solvent. We found that $BiCl_3$ was the most effective catalyst producing 3-aminoimidazo[1,2-*a*]pyridine in highest yield and shortest reaction time. In the absence of catalyst, the yield of product was found to be very low (Table 1, entries 1–5). This combination was studied at different temperatures (Table 1, entries 6–9) and 110 °C was found to be the optimal reaction temperature (Table 1, entry 6). The optimal quantity of catalyst was found to be 5 mol% (Table 1, entry 6).

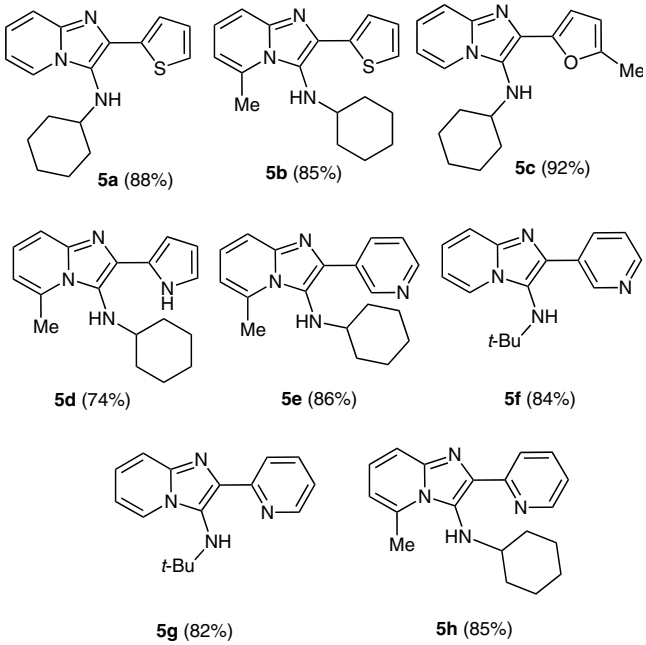
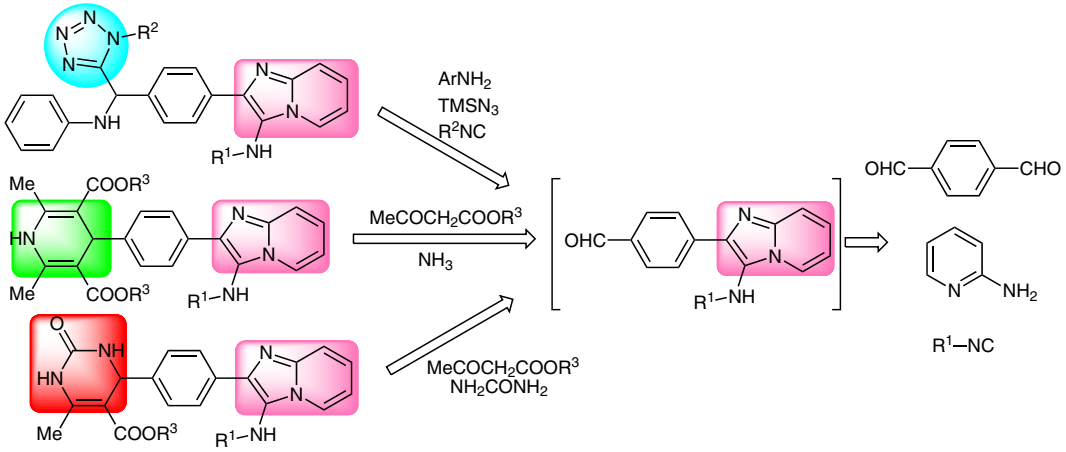
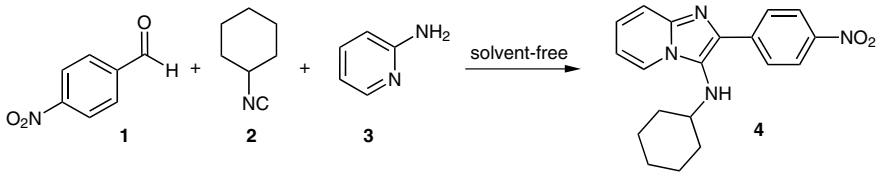


Figure 2 Synthesis of 3-aminoimidazo[1,2-*a*]pyridines using heteroaromatic aldehydes

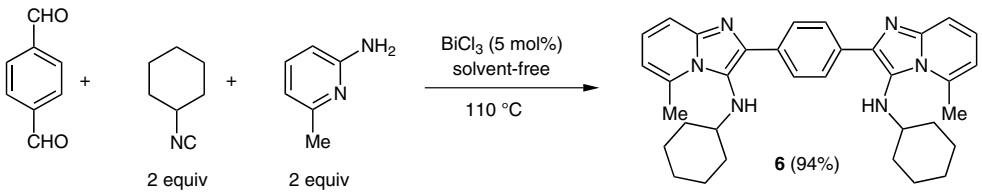


Scheme 2 Retrosynthetic pathways for sequential GBB/Ugi-azide, GBB/Hantzsch and GBB/Biginelli reactions

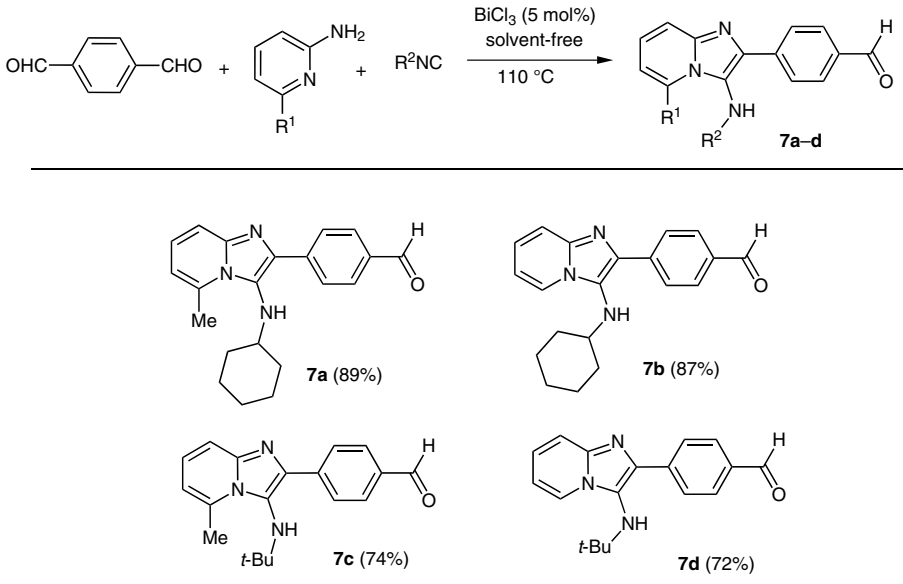
Table 1 Catalytic Activities of Various Catalysts and Optimization of Temperature and Amount of $BiCl_3$ under Solvent-Free Conditions



Entry	Catalyst (mol%)	Temperature (°C)	Time (min)	Yield (%)
1	none (–)	110	20	trace
2	$ZrOCl_2 \cdot 8H_2O$ (10)	110	10	<10
3	L-proline (10)	110	10	15
4	P_2O_5 (10)	110	7	47
5	H_3BO_3 (10)	110	7	68
6	$BiCl_3$ (5)	110	2	98
7	$BiCl_3$ (5)	80	4	84
8	$BiCl_3$ (5)	100	3	92
9	$BiCl_3$ (5)	120	2	94
10	$BiCl_3$ (3)	110	3	86
11	$BiCl_3$ (8)	110	2	96
12	$BiCl_3$ (10)	110	3	90



Scheme 3 Reaction of terephthalaldehyde, 2-amino-6-methylpyridine and cyclohexyl isocyanide for the synthesis of bisimidazo[1, 2-*a*]pyridine



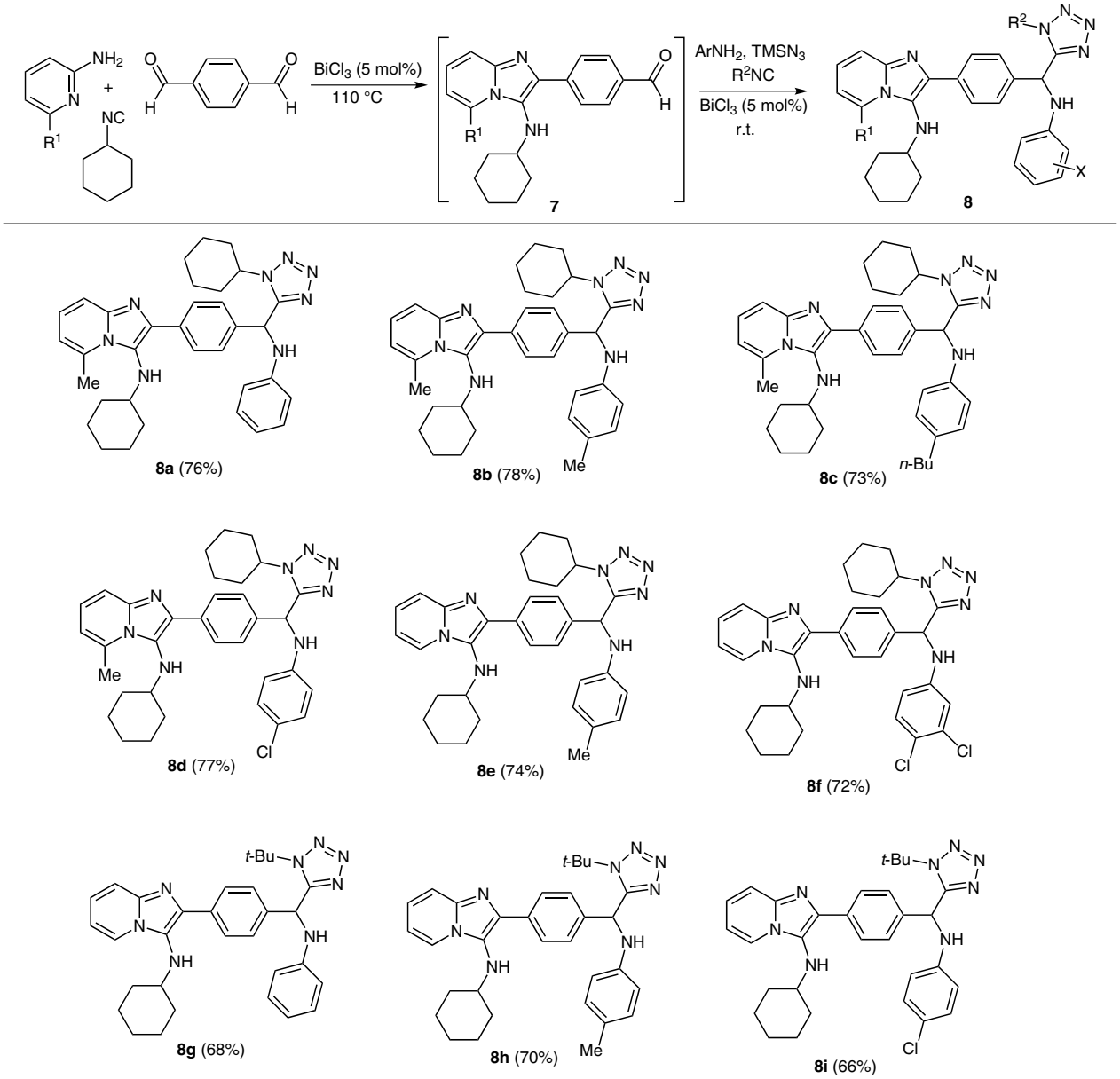
Scheme 4 Synthesis of aldehyde-containing imidazo[1,2-*a*]pyridines **7a–d**

To explore the scope and generality of this procedure, the reaction of different aldehydes, 2-aminopyridines and isocyanides was examined in the presence of bismuth chloride (5 mol%) at 110 °C under solvent-free conditions. In all cases, the requisite 3-aminoimidazo[1,2-*a*]pyridines were obtained within two to five minutes in excellent yields. Aromatic aldehydes bearing either electron-donating or electron-withdrawing groups reacted successfully and gave the corresponding products in high yields (Table 1 in supporting information). Heteroaromatic aldehydes such as thiophene-2-carbaldehyde, 5-methylfuran-2-carbaldehyde, pyrrole-2-carbaldehyde, 2-pyridine carbaldehyde and 3-pyridine carbaldehyde were also catalyzed successfully with $BiCl_3$ to afford the corresponding imidazo[1,2-*a*]pyridines in good yields (Figure 2).[36]

Rousseau and co-workers reported that reaction with nicotinaldehyde did not go to completion when zinc chloride was used as catalyst, requiring montmorillonite clay K10 to afford the desired imidazo[1,2-*a*]pyridines.[21a] However, this also proceeded successfully with bismuth chloride and the corresponding products were synthesized in good yields after short reaction times (**5e**,**f**, Figure 2).

Furthermore, this reaction was explored for the synthesis of bisimidazo[1,2-*a*]pyridine **6** by the reaction of terephthalaldehyde, 2-aminopyridine (2 equiv) and cyclohexyl isocyanide (2 equiv) under similar conditions (Scheme 3). This demonstrated the generality and efficiency of this rapid synthesis of 3-aminoimidazo[1,2-*a*]pyridines.

When equimolar amounts of terephthalaldehyde, 2-aminopyridines and cyclohexyl isocyanide were used, we unexpectedly observed that monoimidazo[1,2-*a*]pyridines **7a**–**d** with a free aldehyde group were obtained in good yields (Scheme 4).[37] The survival of this aldehyde group without need for protection inspired us to design sequen-

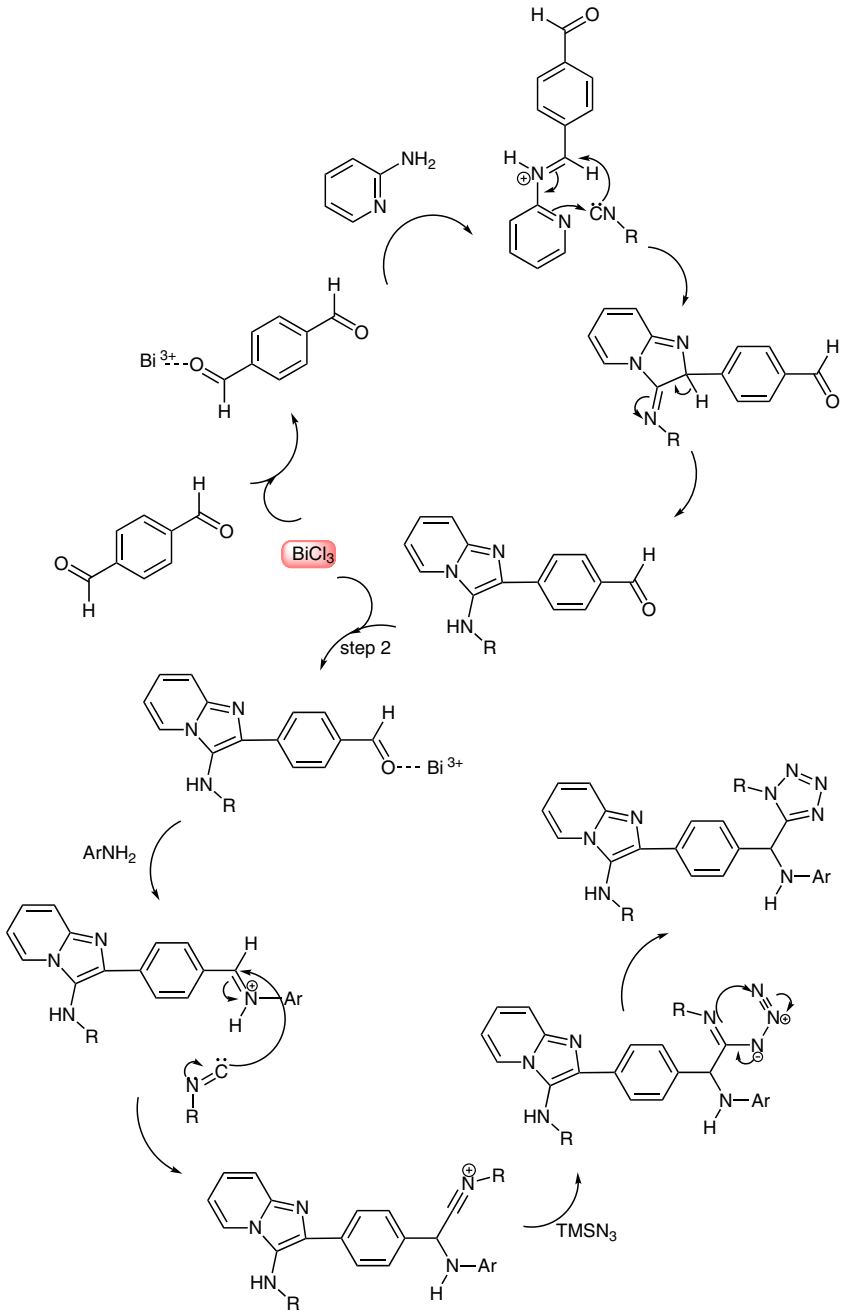


Scheme 5 Products obtained from GBB/Ugi-azide sequential reaction

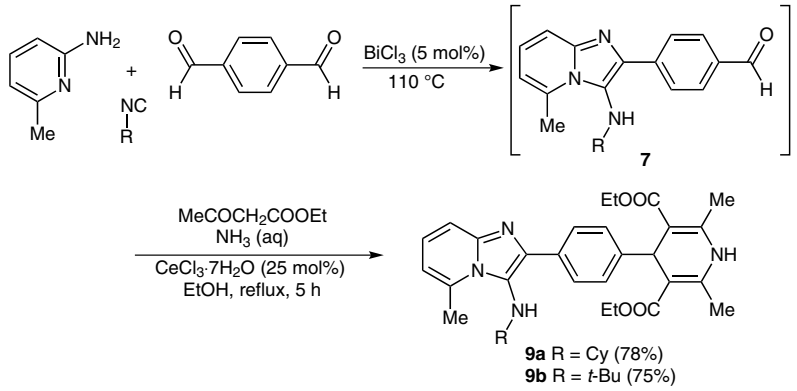
tial reactions for the synthesis of novel bisheterocyclic compounds.

Thus, we began by investigating conditions for the tandem combination of the GBB MCR with the Ugi-azide MCR. The first stage of the process involves formation of compounds **7a**,**b** which were synthesized under solvent-free conditions according to Scheme 5 and the crude products were then directly used in the next Ugi-azide step; wherein condensation of **7a**,**b** with an aldehyde, an amine, $TMSN_3$ and isocyanide in the presence of catalytic amount of $BiCl_3$ (5 mol%) at room temperature under solvent-free conditions afforded the desired bisheterocyclic compounds **8a**–**i** within 10 minutes. The applicability and generality of this six-component sequential GBB/Ugi-azide reaction were also tested by synthesis of a variety of these types of compounds (Scheme 5).[38] The proposed mechanism for the $BiCl_3$-catalyzed GBB/Ugi-azide reaction is shown in Scheme 6. Bismuth(III) chloride is a mild Lewis acid that activates the carbaldehyde to generate an imine intermediate, which undergoes [4+1] cycloaddition with the isonitrile to give the bicyclic adduct followed by rearomatization via 1,3-H shift to give the GBB product. In the Ugi-azide reaction, $BiCl_3$ again catalyzes the imine formation which reacts with isocyanide and $TMSN_3$, respectively, to give the final product.

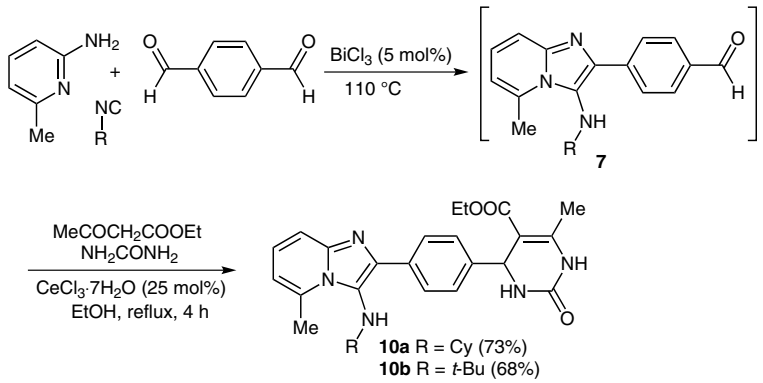
To combine the GBB with a Hantzsch reaction, the aldehyde-containing GBB MCR product was reacted with two equivalents a β-keto ester and ammonia in the presence of



Scheme 6 Proposed mechanism for the synthesis of GBB/Ugi-azide products



Scheme 7 Sequential GBB/Hantzsch reaction



Scheme 8 Sequential GBB/Biginelli reaction

$CeCl_3 \cdot 7H_2O$ (25 mol%) at reflux in ethanol for five hours to afford the bisheterocyclic structures **9a**,**b** in good yields (Scheme 7).[39] When the Hantzsch reaction was carried out under solvent-free condition using $BiCl_3$, the Knoevenagel product was obtained in good yield and only trace amounts of desired dihydropyridine compound were obtained.

In another approach, a GBB/Biginelli five-component protocol was investigated. As shown in Scheme 8, three-component condensation of terephthalaldehyde, 2-amino-6-methylpyridine and isocyanide using $BiCl_3$ produced the aldehyde-containing key intermediate **7**, that was subjected to sequential three-component Biginelli reaction to produce the dihydropyrimidone [cerium(III) chloride was used successfully as the catalyst for the Biginelli reaction].[40] To the crude GBB product, the β-keto ester, urea, a catalytic amount of $CeCl_3 \cdot 7H_2O$ (25 mol%) and EtOH were added and reaction mixture was refluxed for four hours to produce compounds **10a**,**b** in 73% and 68% yield, respectively.[41]

In summary, we have developed three new sequential reactions including GBB/Ugi-azide, GBB/Hantzsch and GBB/Biginelli reactions. The approach described herein allows the construction of bisheterocycles in a one-pot, economic, and facile operation. We have also introduced a novel, rapid and highly efficient method for the synthesis of 3-aminoimidazo[1,2-*a*]pyridines by three-component condensation of aromatic and heteroaromatic aldehydes, 2-aminopyridines and isocyanides in the presence of a catalytic amount of $BiCl_3$ under solvent-free conditions. We have found that $BiCl_3$ is also an efficient catalyst for the Ugi-azide MCR. These two-step, one-pot sequential reactions will provide new alternatives in the synthesis of novel heterocyclic scaffolds.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are experimental details, ^{1}H NMR, ^{13}C NMR, FT-IR and elemental analysis of new compounds.

References and Notes

(1) Orru, R. V. A.; Ruijter, E. *Synthesis of Heterocycles via Multicomponent Reactions*; Springer Verlag: Berlin, **2010**.
(2) (a) Lygin, A. V.; de Meijere, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 9094. (b) Sadjadi, S.; Heravi, M. M. *Tetrahedron* **2011**, *67*, 2707. (c) Eckert, H. *Molecules* **2012**, *17*, 1074. (d) Zou, Y.; Hu, Y.; Liu, H.; Shi, D. *ACS Comb. Sci.* **2011**, *14*, 38. (e) Pellegatti, L.; Vedrenne, E.; Hiebel, M. A.; Buron, F.; Massip, S.; Leger, J. M.; Jarry, C.; Routier, S. *Tetrahedron Lett.* **2011**, *52*, 5224. (f) Akritopoulou-Zanze, I.; Wakefield, B. D.; Gasiecki, A.; Kalvin, D.; Johnson, E. F.; Kovar, P.; Djuric, S. W. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1480.

(g) Guntreddi, T.; Allam, B. K.; Singh, K. N. *Synlett* **2012**, *23*, 2635.
(3) Sanger, D. J.; Depoortere, H. *CNS Drug Rev.* **1998**, *4*, 323.
(4) Warner, G. T.; Jarvis, B. *Drugs* **2002**, *62*, 1345.
(5) Wellington, K.; Scott, L. J. *Drugs* **2003**, *63*, 2613.
(6) (a) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806. (b) Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reilly, B. C.; Schwartz, J.; Malley, M. F. *J. Med. Chem.* **1992**, *35*, 3254.
(7) (a) Groebke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, 661. (b) Blackburn, C. A. *Tetrahedron Lett.* **1998**, *39*, 5469. (c) Bienayme, H.; Bouzid, K. *Angew. Chem. Int. Ed.* **1998**, *37*, 2234.
(8) Rival, Y.; Grassy, G.; Michel, G. *Chem. Pharm. Bull.* **1992**, *40*, 1170.
(9) Rival, Y.; Grassy, G.; Taudou, A.; Ecalle, R. *Eur. J. Med. Chem.* **1991**, *26*, 13.
(10) Fisher, M. H.; Lusi, A. *J. Med. Chem.* **1972**, *15*, 982.
(11) Gueiffier, A.; Mavel, S.; Lhassani, M.; Elhakmaoui, A.; Snoeck, R.; Andrei, G.; Chavignon, O.; Teulade, J. C.; Witvrouw, M.; Balzarini, J. *J. Med. Chem.* **1998**, *41*, 5108.
(12) Ismail, M. A.; Brun, R.; Wenzler, T.; Tanious, F. A.; Wilson, W. D.; Boykin, D. W. *J. Med. Chem.* **2004**, *47*, 3658.
(13) Almirante, L.; Polo, L.; Mugnaini, A.; Provinciali, E.; Rugarli, P.; Biancotti, A.; Gamba, A.; Murmann, W. *J. Med. Chem.* **1965**, *8*, 305.
(14) Langer, S. Z.; Arbilla, S.; Benavides, J.; Scatton, B. *Adv. Biochem. Psychopharmacol.* **1990**, *46*, 61.
(15) Bode, M. L.; Gravestock, D.; Moleele, S. S.; van der Westhuyzen, C. W.; Pelly, S. C.; Steenkamp, P. A.; Hoppe, H. C.; Khan, T.; Nkabinde, L. A. *Bioorg. Med. Chem.* **2011**, *19*, 4227.
(16) Dahan-Farkas, N.; Langley, C.; Rousseau, A. L.; Yadav, D. B.; Davids, H.; de Koning, C. B. *Eur. J. Med. Chem.* **2011**, *46*, 4573.
(17) (a) Chen, J. J.; Golebiowski, A.; McClenaghan, J.; Klopfenstein, S. R.; West, L. *Tetrahedron Lett.* **2001**, *42*, 2269. (b) Shaabani, A.; Soleimani, E.; Maleki, A.; Moghimi-Rad, J. *Synth. Commun.* **2008**, *38*, 1090.
(18) Shaabani, A.; Maleki, A.; Moghimi Rad, J.; Soleimani, E. *Chem. Pharm. Bull.* **2007**, *55*, 957.
(19) Shaabani, A.; Soleimani, E.; Maleki, A. *Monatsh. Chem.* **2007**, *138*, 73.
(20) Katritzky, A. R.; Xu, Y. J.; Tu, H. *J. Org. Chem.* **2003**, *68*, 4935.
(21) (a) Rousseau, A. L.; Matlaba, P.; Parkinson, C. J. *Tetrahedron Lett.* **2007**, *48*, 4079. (b) Guchhait, S. K.; Madaan, C. *Synlett* **2009**, 628.
(22) Varma, R. S.; Kumar, D. *Tetrahedron Lett.* **1999**, *40*, 7665.
(23) Parchinsky, V. Z.; Shuvalova, O.; Ushakova, O.; Kravchenko, D. V.; Krasavin, M. *Tetrahedron Lett.* **2006**, *47*, 947.
(24) Shaabani, A.; Soleimani, E.; Sarvary, A.; Rezayan, A. H.; Maleki, A. *Chin. J. Chem.* **2009**, *27*, 369.
(25) Thompson, M. J.; Hurst, J. M.; Chen, B. *Synlett* **2008**, 3183.
(26) Shaabani, A.; Soleimani, E.; Malek, A. *Tetrahedron Lett.* **2006**, *47*, 3031.
(27) (a) Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386. (b) Ugi, I.; Steinbrückner, C. *Angew. Chem.* **1960**, *72*, 267.
(28) (a) Bienaymé, H.; Bouzid, K. *Tetrahedron Lett.* **1998**, *39*, 2735. (b) Nixey, T.; Kelly, M.; Semin, D.; Hulme, C. *Tetrahedron Lett.* **2002**, *43*, 3681.
(29) Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1.
(30) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360.
(31) (a) Gunawan, S.; Nichol, G.; Hulme, C. *Tetrahedron Lett.* **2012**, *53*, 1664. (b) Schaffert, E. S.; Höfner, G.; Wanner, K. T. *Bioorg. Med. Chem.* **2011**, *19*, 6492. (c) Gunawan, S.; Keck, K.; Laetsch, A.; Hulme, C. *Mol. Divers.* **2012**, *16*, 601. (d) Marcos, C. F.; Marcaccini, S.; Menchi, G.; Pepino, R.; Torroba, T. *Tetrahedron Lett.* **2008**, *49*, 149. (e) Evans, C. G.; Gestwicki, J. E. *Org. Lett.* **2009**, *11*, 2957. (f) Wang, R.; Liu, Z. Q. *J. Org. Chem.* **2012**, *77*, 3952. (g) Mistry, S. R.; Joshi, R. S.; Sahoo, S. K.; Maheria, K. C. *Catal. Lett.* **2011**, *141*, 1541. (h) Reddy, M. V.; Jeong, Y. T. *Synlett* **2012**, *23*, 2985.
(32) (a) Bothwell, J. M.; Krabbe, S. W.; Mohan, R. S. *Chem. Soc. Rev.* **2011**, *40*, 4649. (b) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373. (c) Kouznetsov, V. V.; Gómez, C. M. M.; Parada, L. K. L.; Bermudez, J. H.; Méndez, L. Y. V.; Acevedo, A. M. *Mol. Divers.* **2011**, *15*, 1007.
(33) Suzuki, H.; Matano, Y. *Organobismuth Chemistry*; Elsevier: Amsterdam, **2001**.
(34) (a) Attanasi, O. A.; Bartoccini, S.; Favi, G.; Giorgi, G.; Perrulli, F. R.; Santeusanio, S. *J. Org. Chem.* **2012**, *77*, 1161. (b) Alizadeh, A.; Rezvanian, A.; Zhu, L. G. *J. Org. Chem.* **2012**, *77*, 4385. (c) Balalaie, S.; Bararjanian, M.; Hosseinzadeh, S.; Rominger, F.; Bijanzadeh, H. R.; Wolf, E. *Tetrahedron* **2011**, *67*, 7294. (d) Sreejalekshmi, K. G.; Rajasekharan, K. N. *Tetrahedron Lett.* **2012**, *53*, 3627. (e) Al-Tel, T. H.; Al-Qawasmeh, R. A.; Voelter, W. *Eur. J. Org. Chem.* **2010**, *29*, 5586. (f) Kalinski, C.; Umkehrer, M.; Gonnard, S.; Jäger, N.; Ross, G.; Hiller, W. *Tetrahedron Lett.* **2006**, *47*, 2041.
(35) (a) Shahrisa, A.; Miri, R.; Esmati, S.; Saraei, M.; Mehdipour, A. R.; Sharifi, M. *Med. Chem. Res.* **2012**, *21*, 284. (b) Shahrisa, A.; Esmati, S.; Gholamhosseini Nazari, M. *J. Chem. Sci.* **2012**, *124*, 927.
(36) **General Procedure for the Synthesis of 3-Amino-imidazo[1,2-*a*]pyridines 5a–h**: To a mixture of aldehyde (0.5 mmol), 2-aminopyridine or 2-amino-6-methylpyridine (0.5 mmol) and isocyanide (0.5 mmol) was added $BiCl_3$ (5 mol%) and the reaction mixture was stirred on a preheated oil bath at 110 °C. After completion of the reaction (monitored by TLC, within 2–5 min), the crude residue was either treated with EtOAc–*n*-hexane to afford the product as a precipitate, or was subjected to silica gel preparative layer chromatography (EtOAc–*n*-hexane, 1:3) to give the desired product. Compound **5a**: cream solid; mp 168–170 °C. FT-IR (KBr): 3276, 3078, 2924, 2848, 1630, 1577 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.11–1.36 (m, 5 H, CH_2 of cyclohexyl), 1.61–1.88 (m, 5 H, CH_2 of cyclohexyl), 3.04–3.07 (m, 2 H, CHN of cyclohexyl and NH), 6.74 (t, *J* = 6.6 Hz, 1 H, ArH), 7.08–7.13 (m, 2 H, ArH), 7.31 (d, *J* = 4.8 Hz, 1 H, ArH), 7.50 (d, *J* = 8.9 Hz, 1 H, ArH), 7.59 (d, *J* = 2.9 Hz, 1 H, ArH), 8.06 (d, *J* = 6.6 Hz, 1 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.8, 24.7, 33.2, 55.9, 110.5, 116.1, 121.6, 122.7, 122.9, 123.0, 123.5, 126.5, 131.8, 136.3, 140.7. Anal. Calcd for $C_{17}H_{19}N_3S$: C, 68.65; H, 6.44; N, 14.13. Found: C, 68.37; H, 6.46; N, 14.02.
(37) **General Procedure for the Synthesis of Imidazo[1,2-*a*]pyridin-2-yl Benzaldehydes 7a–d**: To a mixture of terephthalaldehyde (0.55 mmol), 2-aminopyridine or 2-amino-6-methylpyridine (0.5 mmol) and isocyanide (0.5 mmol) was added $BiCl_3$ (5 mol%) and the reaction mixture was stirred on a preheated oil bath at 110 °C. After completion of the reaction (monitored by TLC, within 5 min), the crude residue was subjected to silica gel preparative layer chromatography (EtOAc–*n*-hexane, 1:3) to give the desired product. Compound **7a**: yellow solid; mp 126–128 °C. FT-IR (KBr): 3298, 3050, 2926, 2849, 2721,

1695, 1598 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.99–1.06 (m, 5 H, CH_2 of cyclohexyl), 1.53–1.68 (m, 5 H, CH_2 of cyclohexyl), 2.77 (m, 1 H, CHN of cyclohexyl), 2.93 (s, 3 H, CH_3), 3.13 (br s, 1 H, NH), 6.46 (d, *J* = 6.6 Hz, 1 H, ArH), 7.04 (dd, *J* = 8.9, 6.6 Hz, 1 H, ArH), 7.42 (d, *J* = 8.9 Hz, 1 H, ArH), 7.94 (d, *J* = 8.0 Hz, 2 H, ArH), 8.21 (d, *J* = 8.0 Hz, 2 H, ArH), 10.04 (s, 1 H, aldehyde). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1, 23.8, 24.7, 32.2, 58.1, 112.9, 115.1, 123.8, 126.9, 128.8, 133.9, 135.2, 136.5, 140.3, 142.6, 191.1. Anal. Calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60. Found: C, 75.42; H, 6.89; N, 12.37.

(38) **General Procedure for the Synthesis of GBB/Ugi Azide Products 8a–i**: A mixture of terephthalaldehyde (0.55 mmol), 2-aminopyridine or 2-amino-6-methylpyridine (0.5 mmol) and isocyanide (0.5 mmol) containing $BiCl_3$ (5 mol%) was stirred on a preheated oil bath at 110 °C for 5 min. Without workup, to the resulting mixture containing imidazo[1,2-*a*]pyridin-2-yl benzaldehyde **7** (after being cooled to r.t.) were added the desired amine (0.5 mmol), $TMSN_3$ (0.5 mmol), isocyanide (0.5 mmol) and $BiCl_3$ (5 mol%) and the reaction mixture was stirred at r.t. for 10 min (completion of the reaction monitored by TLC). The crude product was purified by silica gel preparative layer chromatography (EtOAc–$CHCl_3$–*n*-hexane, 1:1:3) to give the desired product. Compound **8h**: yellow solid; mp 204–206 °C. FT-IR (KBr): 3320, 2924, 2852, 1616, 1517 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.06–1.73 (m, 19 H, 5 × CH_2 of cyclohexyl, *t*-Bu), 2.14 (s, 3 H, CH_3), 2.85–2.89 (m, 2 H, CHN of cyclohexyl and NH), 4.66 (d, *J* = 6.7 Hz, 1 H, NH), 6.06 (d, *J* = 6.7 Hz, 1 H, benzylic), 6.56 (d, *J* = 8.2 Hz, 2 H, ArH), 6.72 (t, *J* = 6.7 Hz, 1 H, ArH), 6.90 (d, *J* = 8.2 Hz, 2 H, ArH), 7.05–7.08 (m, 1 H, ArH), 7.31 (d, *J* = 8.3 Hz, 2 H, ArH), 7.46 (d, *J* = 8.9 Hz, 1 H, ArH), 7.97 (d, *J* = 8.3 Hz, 2 H, ArH), 8.02 (d, *J* = 6.7 Hz, 1 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.4, 23.8, 24.7, 29.1, 33.2, 54.2, 55.9, 60.5, 110.7, 113.9, 116.4, 121.7, 123.2, 124.2, 126.6, 127.1, 127.7, 128.9, 133.8, 134.5, 135.9, 142.6, 154.3. Anal. Calcd for $C_{32}H_{38}N_8$: C, 71.88; H, 7.16; N, 20.96. Found: C, 71.56; H, 7.22; N, 20.64.

(39) **General Procedure for the Synthesis of GBB/Hantzsch Products 9a,b**: A mixture of terephthalaldehyde (0.55 mmol), 2-amino-6-methylpyridine (0.5 mmol) and isocyanide (0.5 mmol) containing $BiCl_3$ (5 mol%) was stirred on a preheated oil bath at 110 °C for 5 min. Without workup, to the resulting imidazo[1,2-*a*]pyridin-2-yl benzaldehyde **7** were added ethyl acetoacetate (1 mmol), NH_3 (0.5 mL) and $CeCl_3·7H_2O$ (25 mol%) and the mixture was refluxed in EtOH for 5 h. The mixture was concentrated under reduced pressure and the crude product was purified by silica gel preparative layer chromatography (EtOAc–$CHCl_3$–*n*-hexane, 1:1:2) to give the desired product. Compound **9b**: yellow solid; mp 252 °C (dec.). FT-IR (KBr): 3275, 3174, 3053, 2924, 1686 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.83 (s, 9 H, *t*-Bu), 1.19 (t, *J* = 7.1 Hz, 6 H, $COOCH_2CH_3$), 2.28 (s, 6 H, CH_3), 2.96 (s, 3 H, CH_3), 3.09 (br s, 1 H, NH), 3.99–4.11 (m, 4 H, $COOCH_2CH_3$), 4.97 (s, 1 H, DHP H-4), 6.47 (d, *J* = 6.7 Hz, 1 H, ArH), 7.03–7.07 (m, 1 H, ArH), 7.37–7.42 (m, 3 H, ArH), 7.63 (d, *J* = 7.9 Hz, 2 H, ArH), 8.15 (br s, 1 H, DHP NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.3, 17.8, 19.8, 28.5, 38.8, 55.4, 58.4, 102.5, 112.9, 113.9, 123.5, 124.7, 126.9, 127.4, 131.9, 136.2, 140.7, 141.9, 144.0, 147.2, 166.8. Anal. Calcd for $C_{31}H_{38}N_4O_4$: C, 70.16; H, 7.22; N, 10.56. Found: C, 69.92; H, 7.27; N, 10.32.

(40) Bose, D. S.; Fatima, L.; Mereyala, H. B. *J. Org. Chem.* **2003**, *68*, 587.

(41) **General Procedure for the Synthesis of GBB/Biginelli Products 10a,b**: As with the GBB/Hantzsch procedure, after formation of the carbaldehyde intermediate, ethyl acetoacetate (0.5 mmol), urea (1.5 mmol) and $CeCl_3·7H_2O$ (25 mol%) were added and the reaction mixture was refluxed for 4 h. The mixture was concentrated under reduced pressure and the crude product was purified by silica gel preparative layer chromatography (EtOAc–$CHCl_3$–*n*-hexane, 1:1:2) to give the desired product. **10a**: yellow solid; mp 216–218 °C. FT-IR (KBr): 3205, 3086, 2926, 1689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.98–1.05 (m, 5 H, CH_2 of cyclohexyl), 1.14 (t, *J* = 7.1 Hz, 3 H, $COOCH_2CH_3$), 1.47–1.67 (m, 5 H, CH_2 of cyclohexyl), 2.38 (s, 3 H, CH_3), 2.74–2.76 (m, 1 H, CHN of cyclohexyl), 2.93 (s, 3 H, CH_3), 3.09 (br s, 1 H, NH), 4.02–4.10 (m, 2 H, $COOCH_2CH_3$(, 5.44 (s, 1 H, pyrimidone H-4), 5.63 (br s, 1 H, NH), 6.43 (d, *J* = 6.7 Hz, 1 H, ArH), 6.99–7.03 (dd, *J* = 7.0, 8.8 Hz, 1 H, ArH), 7.37 (d, *J* = 8.1 Hz, 2 H, ArH), 7.41 (d, *J* = 8.8 Hz, 1 H, ArH), 7.66 (br s, 1 H, NH), 7.90 (d, *J* = 8.1 Hz, 2 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 17.8, 19.2, 23.8, 24.7, 32.1, 54.8, 57.8, 58.9, 100.0, 112.6, 114.7, 123.3, 125.8, 126.9, 128.1, 133.7, 135.3, 141.4, 142.1, 142.9, 144.4, 151.6, 164.7. Anal. Calcd for $C_{28}H_{33}N_5O_3$: C, 68.97; H, 6.82; N, 14.36. Found: C, 68.67; H, 6.75; N, 14.15.

