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Synthesis of nitrogen heterocycle-fused 1,2,4-benzothiadiazine-1,1-dioxide, quinazolinone, and pyrrolidinone derivatives with a guanidine joint via sequential aza-Wittig reaction/intramolecular NH-addition cyclization/nucleophilic substitution ring closure methodology, using functionalized carbodiimides as key intermediates

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ABSTRACT

We achieved efficient synthesis of imidazo- and pyrimido[1,2-*b*]benzo-1,2,4-thiadiazine-1,1-dioxides by the tandem aza-Wittig reaction/intramolecular NH-nucleophilic addition/NH-nucleophilic substitution cyclization methodology, involving sulfonamide ester-containing carbodiimides as the key intermediates. Similarly, imidazo[2,1-*b*]quinazolinones, imidazo[1,2-*a*]pyrimidinediones, and imidazo[1,2-*a*]imidazolidinediones were also synthesized through the aza-Wittig reaction–tandem cyclization strategy. When homochiral (L)-alanine methyl ester was incorporated as a building block into the corresponding iminophosphorane starting materials, we obtained optically active imidazo[1,2-*b*]benzo-1,2,4-thiadiazine and imidazo[2,1-*b*]quinazolinone derivatives without any racemization through the one-pot tandem methodology.

1. Introduction

Cyclic guanidine moieties often occur in a variety of biologically active natural compounds such as marine alkaloids.[1] Amongst the most important cyclic guanidine representatives having a wide range of biological activities are compounds with 2-amino-4-quinazolinone cores.[2] Some of these polycyclic guanidine compounds show biological activities such as anti-tumor,[3] broncholytic,[4] antihypertensive,[5] and immunosuppressive activities.[6] Interestingly, despite the fact that all of these compounds have an identical 2-amino-4-quinazolinone structural core, they exhibit diverse biological activities. This diversity is mainly due to the attendant contribution of the ring-fused-heterocyclic moieties in addition to a variety of different substituents in the molecules.

In contrast, 3-amino-1,2,4-benzothiadiazine-1,1-dioxides, which are isosteric analogs[7] of 2-amino-4-quinazolinones, are also known to possess biological activities, including potassium[8] and calcium[9] channel modulations and adrenergic antagonistic effects.[2b,10] Furthermore, this class of compounds have recently been found to exhibit antagonism activities to the chemokine CXCR2 receptor.[11] In spite of the well studied quinazolinone system, known compounds of cyclic 3-amino-1,2,4-benzothiadiazine-1,1-dioxide isosters are still rare; hence, the development of facile and efficient methods for preparing such attractive heterocycles is very important and intriguing.[2b,10,12]

A survey of the literature shows that there are only very limited synthetic methods to access 2-amino-4-quinazolinones/3-amino-1,2,4-benzothiadiazine-1,1-dioxides with cyclic guanidine joints.[2b,3–6,10,12] One of the most convenient synthetic methods for cyclic guanidines would be nucleophilic addition of a nitrogen species to the functionalized carbodiimide carbon center. Desired monocyclic and bicyclic guanidines can be synthesized by arbitrarily selected cyclization reactions, as illustrated in Chart 1. These variously functionalized carbodiimides, which could be prepared preferably by the aza-Wittig reaction,[13] dehydration from urea, or elimination of hydrogen sulfide from thiourea,[14] undergo an initial reaction involving the cumulene functionality viz. (1) intermolecular nucleophilic addition of an amine (or imine) and subsequent various types of ring-forming reactions between the acyclic guanidine nitrogen (N) and the available inner functional group (F_G) (Eq.1),[15] or (2) intramolecular addition between a nitrogen functional group (N) and the cumulene carbon (Eq. 2),[16] to give monocyclic guanidines

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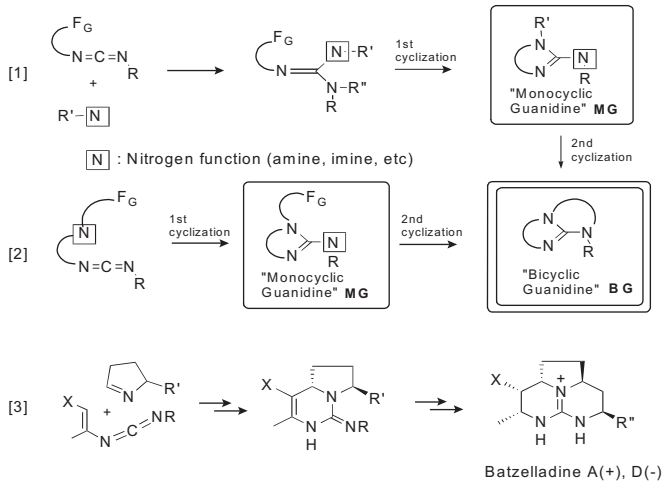


Chart 1. Various tandem cyclization pathways leading to cyclic guanidines.

(**MGs**).[13] The second cyclization of the **MGs**, in which the F_G or R′ group is a suitable functional group reacting with the internal nitrogen (amino) functionality (N), leads to the formation of bicyclic guanidines (**BGs**).[13] Indeed, researchers have successfully applied various types of second cyclization reactions such as nucleophilic substitution,[16g,h,j] nucleophilic addition,[15i,j,t,16i,17] Michael addition,[18] iodoamination,[15u–w,16h] and aromatic C–N coupling reaction.[19] Intramolecular ring-closing metathesis of **MGs** via Eq. 1 was also reported when *R* and *R′* were alkenyl (allyl) groups.[20] Pericyclic reactions such as electrocyclization[21] and [4+2] cycloaddition[22] were also employed in an initial reaction. For example, Gin et al. demonstrated a total synthesis of the marine alkaloid, (+)-batzelladine A and (−)-batzelladine D, using [4+2] cycloaddition as a key step for construction of the bicyclic guanidine core (Eq. 3).[23] Thus, synthetic methods for a variety of **BGs** have been developed by the tandem[24] double cyclization methodology using a wide range of bond-forming transformations.[25]

In our previous report,[26] we demonstrated the tandem cyclization methodology using 2-(*N*-alkenylsulfamoyl)phenylcarbodiimides as the key intermediates for the synthesis of a variety of diazaheterocyclic ring-fused 1,2,4-benzothiadiazine-1,1-dioxides, where we employed iodocyclization and hydroamination with Hg(II)–$NaBH_4$ (aminomercuration–demercuration) as the second ring-forming reaction between alkenyl and amine groups after the initial cyclization by internal nucleophilic sulfonamide–NH-addition onto the heterocumulene carbon.

In this paper, we report the novel and facile synthesis of cyclic guanidines, five- to six-membered diazaheterocyclic ring-fused 1,2,4-benzothiadiazine-1,1-dioxides **I**, quinazolinones **II**, and imidazolidinones and pyrimidinones **III** (Fig. 1) via the tandem[24] aza-Wittig reaction/double cyclizations methodology.[27]

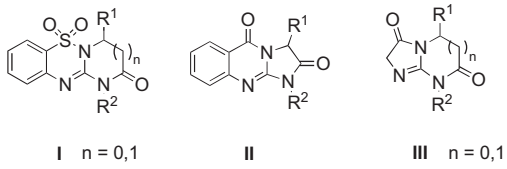
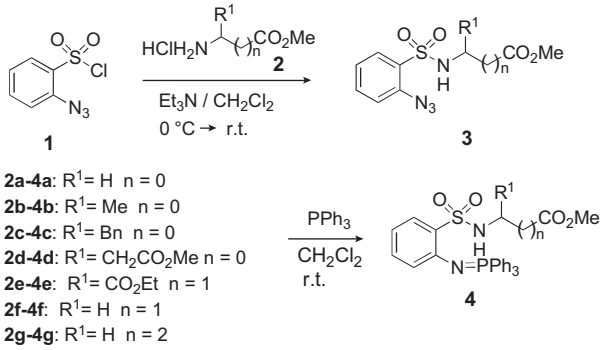


Figure 1. Targeted cyclic guanidines.

2. Results and discussion

For the synthesis of the first target heterocycles, benzothiadiazine-1,1-dioxide derivatives **I**, we prepared the pre-requisite iminophosphoranes **4** in high yields by the reaction of *o*-azidobenzenesulfonyl chloride **1**[26–28] with a variety of amino acid methyl ester-hydrogen chloride salts **2**[29] in the presence of triethylamine, followed by a Staudinger reaction[30] of the resultant sulfonamide-azides **3** with triphenylphosphine (Scheme 1, Table 1).



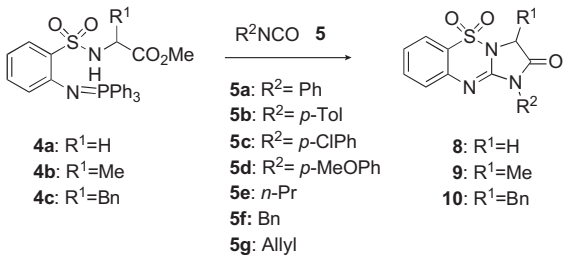
Scheme 1. Preparation of iminophosphoranes **4**.

Table 1
Preparation of sulfonamidic iminophosphoranes **4**

Entry	**2** (DL)	*n*	R^1	Iminophosphorane **4**	Yield [a](%)
1	**2a**	0	H	**4a**	88
2	**2b**	0	Me	**4b**	85
3	**2b***[b]	0	Me	**4b***	87
4	**2c**	0	Bn	**4c**	90
5	**2d**	0	CH_2CO_2Me	**4d**	92
6	**2e**	1	CO_2Et	**4e**	81
7	**2f**	1	H	**4f**	86
8	**2g**	2	H	**4g**	98

[a] Isolated overall yield of **4** from **1**.
[b] (L)-Alanine methyl ester was used. Symbol* denotes 'enantiomerically pure'.

When the reaction of iminophosphorane **4b** thus derived from sulfonyl chloride **1**+ alanine ester **2b** (R^1=Me) with phenyl isocyanate **5a** (R^2=Ph) was performed at room temperature in dichloromethane, the reaction proceeded slowly and required 32 h to produce imidazo[1,2-*b*]-benzo-1,2,4-thiadiazine-1,1-dioxide **9a**[2b,10,12a,b,e] in 92% yield (Scheme 2, Table 2, entry 7). When the same reaction was performed at 80 °C in benzene, the reaction time was shortened by 2 h yet maintaining a high yield (93%) of **9a** (entry 8). Similarly, aromatic isocyanates **5b–d** reacted with **4b** at 80 °C for 2.5–3.5 h to give **9b–d** in 92–96% yields (entries 9–11). With aliphatic isocyanates **5e–g** (R^1=*n*-Pr, benzyl, and allyl), the reaction required a higher temperature (110 °C) in toluene to be completed within 6 h affording 91–99% yields of **9e–g** (entries 12–14). Similarly, the iminophosphoranes **4a** and **4c** derived from glycine ester (R^1=H) and phenylalanine ester (R^1=Bn) also reacted with various aromatic and aliphatic isocyanates to give imidazobenzothiadiazines **8** and **10** in good to high yields (entries 1–6 and 15–20). We did not observe any marked substituent effects of the aromatic isocyanates (**5a–d**) on the overall reaction rates except for the case of **5d** with a MeO group,



Scheme 2. Tandem aza-Wittig/double cyclizations of **4** producing imidazobenzothiadiazine-1,1-oxides **8–10**.

Table 2
Synthesis of imidazo[1,2-*b*]benzo-1,2,4-thiadiazine-1,1-dioxides **8**–**10** via sequential aza-Wittig/tandem cyclization methodology

Entry	4	R^1	R^2	Temp[a] (°C)	Time (h)	8–10	Yield[b] (%)
1	**4a**	H	Ph	80	4	**8a**	88
2	**4a**	H	*p*-Tol	80	4.5	**8b**	87
3	**4a**	H	*p*-ClPh	80	5	**8c**	83
4	**4a**	H	*p*-MeOPh	80	6	**8d**	86
5	**4a**	H	*n*-Pr	110	3	**8e**	85
6	**4a**	H	Bn	110	1	**8f**	92
7	**4b**	Me	Ph	rt	32	**9a**	92
8	**4b**	Me	Ph	80	2	**9a**	93
9	**4b**	Me	*p*-Tol	80	2.5	**9b**	92
10	**4b**	Me	*p*-ClPh	80	2.5	**9c**	94
11	**4b**	Me	*p*-MeOPh	80	3.5	**9d**	96
12	**4b**	Me	*n*-Pr	110	5.5	**9e**	95
13	**4b**	Me	Bn	110	5	**9f**	99
14	**4b**	Me	Allyl	110	4	**9g**	91
15	**4c**	Bn	Ph	80	1	**10a**	97
16	**4c**	Bn	*p*-Tol	80	1	**10b**	96
17	**4c**	Bn	*p*-ClPh	80	1	**10c**	92
18	**4c**	Bn	*p*-MeOPh	80	4	**10d**	92
19	**4c**	Bn	*n*-Pr	110	5.5	**10e**	95
20	**4c**	Bn	Bn	110	6	**10f**	99

[a] rt in CH_2Cl_2; 80 °C in $(CH_2Cl)_2$ or benzene; 110 °C in toluene.
[b] Isolated yield.

which required longer reaction times (entries 4, 11, and 18). The functionalized carbodiimide **6** was the most probable intermediate formed by the initial aza-Wittig reaction of the iminophosphorane **4** with the isocyanate **5** (Scheme 3).[13,16f] Subsequent intramolecular nucleophilic addition of NH to the cumulene carbon of **6** to form the monocyclic guanidines **7**,[26–28] followed by intramolecular nucleophilic substitution ring closure, provided the pre-meditated bicyclic guanidine compounds **8**–**10** as the final products.[16g,h,j,26,27]

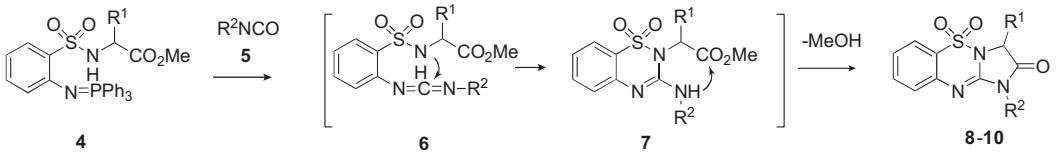
Table 3
Synthesis of imidazo[1,2-*b*]benzo-1,2,4-thiadiazine-1,1-dioxides **13** via the tandem cyclization with high regioselectivity

Entry	Isocyanate	R^2	Product	Yield [a](%)
1	**5a**	Ph	**13a**	98
2	**5b**	*p*-Tol	**13b**	88
3	**5c**	*p*-ClPh	**13c**	85
4	**5d**	*p*-MeOPh	**13d**	85
5	**5e**	*n*-Pr	**13e**	80
6	**5f**	Bn	**13f**	88

[a] Isolated yield of **13** from **4d**+**5** in a one-pot reaction.

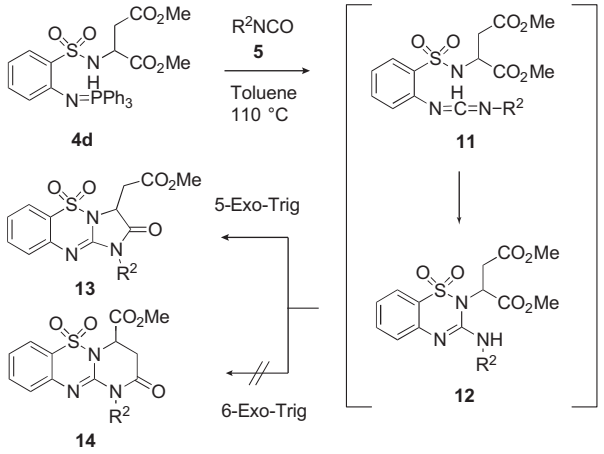
1–5 h gave single cyclization products in good yields (Table 3), which were assigned as imidazobenzothiadiazine-1,1-dioxides **13** formed via the cyclization of **12** in a 5-*exo*-*trig* mode instead of pyrimidine-fused **14** via 6-*exo*-*trig* mode cyclization.[31] In order to confirm the structures of **13** and the cyclization mode, the reaction of **5b** with iminophosphorane **4e** derived from aspartic methyl ethyl ester was examined (Scheme 5). As a result, the single cyclization product **13b** was exclusively obtained in 98% yield and its ^1H and ^{13}C NMR and IR spectra clearly showed the existence of a methyl ester group. We did not detect the pyrimidine-fused compound **14b** (Et) by 6-*exo*-*trig* mode cyclization. Thus, 5-*exo*-*trig* mode cyclization of **12** was preferred over 6-*exo*-*trig* mode, although the both modes are 'allowed' according to the Baldwin rule.[31]

Next, we examined the reaction of isocyanates **5** with iminophosphorane **4f**, which had a β-alanine methyl ester group in which 6-*exo*-*trig* mode cyclization (**16**→**17**) should be involved to yield pyrimidine-fused compounds **17** (Scheme 6). When we reacted **4f** with isocyanates **5a**–**f** in toluene under gentle refluxing (110 °C) for 2–15 h (Method A), we obtained the initial cyclization products **16a**–**f** in good yields (Table 4). The reactions even in the presence of additives such as Et_3N, DBU, silica gel, and *p*-toluenesulfonic acid as well as at higher



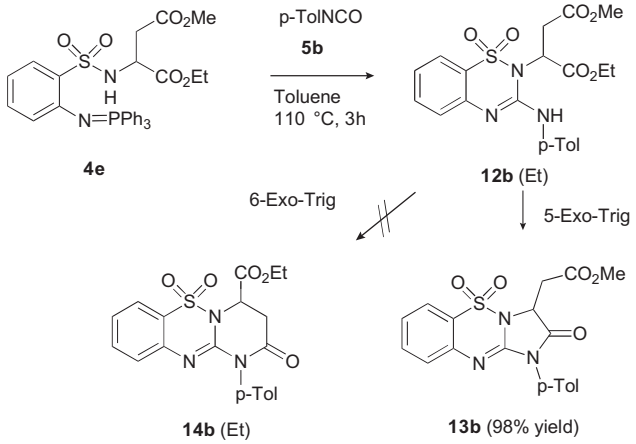
Scheme 3. Tandem aza-Wittig reaction/nucleophilic NH-addition cyclization/nucleophilic NH-substitution cyclization methodology via functionalized carbodiimides **6** producing imidazobenzothiadiazine-1,1-oxides **8**–**10**.

Next, we examined the tandem reaction using aspartic dimethyl ester-derived iminophosphorane **4d** (Scheme 4). The reaction of **4d** with aromatic and aliphatic isocyanate **5** in toluene at 110 °C for

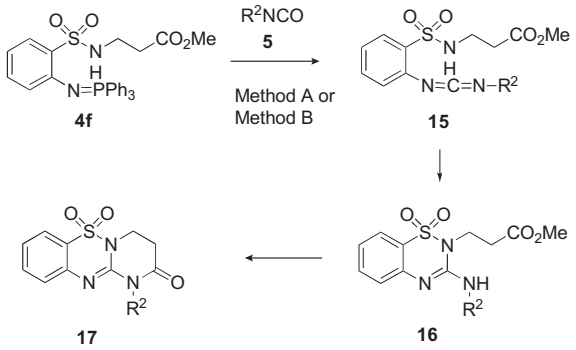


Scheme 4. Tandem aza-Wittig/double cyclizations reaction with high regioselectivity to give imidazobenzothiadiazine-1,1-oxides **13**.

temperatures (e.g., 143 °C in xylene) afforded compounds **16a**–**f** in variable amounts, but the double cyclization products **17a**–**f** were not detected. These observations are consistent with the facts that the 6-*exo*-*trig* mode of the cyclization **12**→**14** does not easily proceed compared to the 5-*exo*-*trig* mode cyclization of **7**→**8**–**10** and **12**→**13**.



Scheme 5. Regioselectivity of 5-*exo*-*trig* vs 6-*exo*-*trig* mode cyclizations giving **13b** or **14b**.



Scheme 6. Tandem aza-Wittig/cyclization of **4f**. Method A: 110 °C in toluene, 2–15 h; Method B: 80 °C in $(CH_2Cl)_2$, followed by addition of TiCl4 (5.0 equiv) in one pot.

Table 4
Synthesis of benzo-1,2,4-thiadiazine-1,1-dioxides **16** via the tandem aza-Wittig/cyclization reaction (Method A)

Entry	Isocyanate	R^2	Time (h)	Product	Yield [a](%)
1	**5a**	Ph	3.5	**16a**	81
2	**5b**	*p*-Tol	2	**16b**	82
3	**5c**	*p*-ClPh	2.5	**16c**	80
4	**5d**	*p*-MeOPh	2.5	**16d**	87
5	**5e**	*n*-Pr	15	**16e**	83
6	**5f**	Bn	4.5	**16f**	93

[a] Isolated yield of **16** from **4f**+**5** in a one-pot reaction.

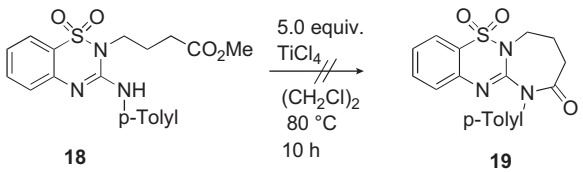
However, during our search for an effective additive to the 6-*exo*-*trig* mode cyclization **16**→**17**,[32–34] we fortunately found that in the presence of $TiCl_4$ (5.0 equiv),[35] compound **16a** was converted to the cyclization product **17a** (99% yield) after refluxing in CH_2Cl_2 for 5 h. Therefore, we performed the one-pot tandem reaction starting from the aza-Wittig reaction of iminophosphorane **4f** with isocyanates **5a**–**f** and the initial cyclization at 80 °C in $(CH_2Cl)_2$ followed by the amidation cyclization caused by subsequent addition of $TiCl_4$ (5.0 equiv) in one pot under the same conditions (see Table 5). As expected, pyrimido[1,2-*b*]benzo-1,2,4-thiadiazine-1,1-dioxides **17** were obtained in good yields.

Table 5
Synthesis of pyrimido[1,2-*b*]benzo-1,2,4-thiadiazine-1,1-dioxides **17** via the tandem aza-Wittig/double cyclization one-pot reaction (Method B)

Entry	Isocyanate	R^2	Time (h)		Product	Yield [a](%)
			4→**16**[b]	**16**→**17**		
1	**5a**	Ph	3	5	**17a**	72
2	**5b**	*p*-Tol	4.5	4.5	**17b**	82
3	**5c**	*p*-ClPh	5	3	**17c**	72
4	**5d**	*p*-MeOPh	5	1	**17d**	72
5	**5e**	*n*-Pr	10	3	**17e**	81
6	**5f**	Bn	9.5	3	**17f**	72

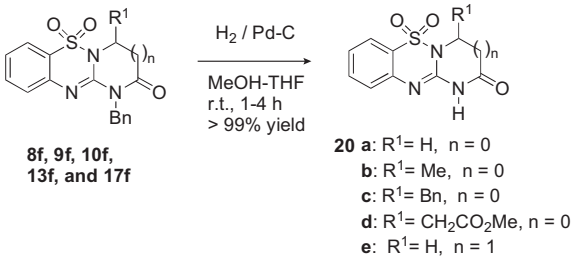
[a] Isolated yield of **17** from **4f**+**5** in a one-pot reaction.
[b] Addition of $TiCl_4$ after consumption of **4f** checked by TLC.

However, similar treatment of **18**, which had one more longer methylene chain than **16** with $TiCl_4$ (5.0 equiv), did not give diazepane ring-fused benzo-1,2,4-thiadiazine-1,1-dioxide **19** (Scheme 7).



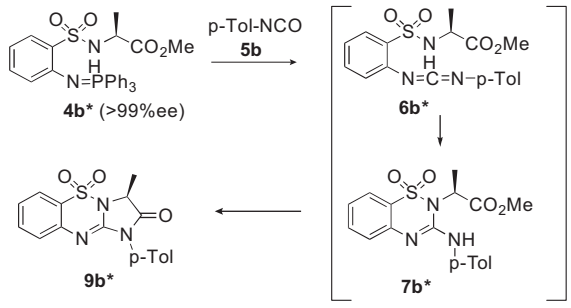
Scheme 7.

The diazaheterocyclic ring-fused benzo-1,2,4-thiadiazine-1,1-dioxides of type **I** thus obtained had a substituent (R^2) that originated from its starting isocyanate. In order to synthesize such benzo-1,2,4-thiadiazine-1,1-dioxide derivatives of the unsubstituted NH group (R^2=H) in this position,[36] amino deprotection cleavage of an allyl group or a benzyl group in the corresponding compounds was performed. Although the cleavage of the allyl group in compound **9g** using Pd-$[Ph_3P]_4$/dimethylbarbituric acid[37] was unsuccessful, catalytic hydrogenolysis[37] of *N*-benzyl-substituted compounds (**8f**–**10f**, **13f**, and **17f**) gave the corresponding deprotected compounds **20a**–**e** quantitatively (Scheme 8).



Scheme 8. Preparation of *N*-unsubstituted compounds **20**.

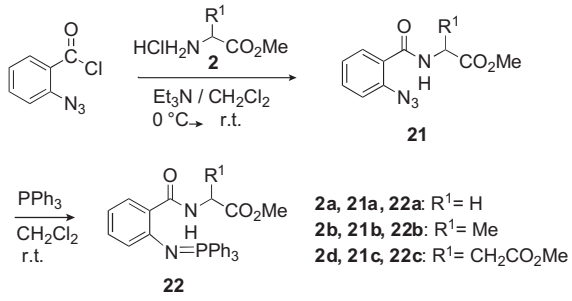
The advantages of introducing amino acids as building blocks into target molecules in organic synthesis include the availability of amino acids possessing diverse substituents, their versatile reactivities, and their utility as a chiral pool in asymmetric synthesis.[38] We therefore examined whether this one-pot tandem methodology can be applicable to the non-racemic, asymmetric heterocycle synthesis. When the optically pure iminophosphorane **4b*** (>99% ee) derived from L-alanine methyl ester HCl salt (**2b***), was allowed to react with *p*-tolyl isocyanate (**5b**) in toluene at room temperature for 27 h or even at 110 °C for 3 h, we obtained enantiomerically pure product **9b*** (>99% ee) without any racemization in 88% and 72% yields, respectively (Scheme 9).



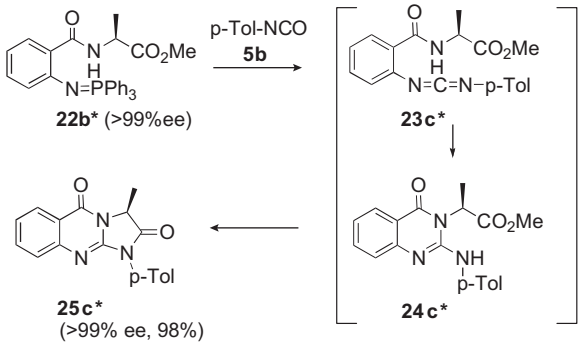
Scheme 9. Preparation of optically active **9b*** via the one-pot tandem methodology.

We next applied this tandem methodology to the synthesis of the guanidine-jointing ring-fused heterocycles of types **II** and **III** (Fig. 1). The iminophosphoranes **22** were prepared in good yields via the amidation of amino acid methyl esters **2** with *o*-azidobenzoyl chloride,[39] followed by the Staudinger reaction of the azide **21** with triphenylphosphine according to the literature (Scheme 10).[40]

The reaction of iminophosphoranes **22a**–**c** with *p*-tolyl isocyanate (**5b**) in toluene at 110 °C for 1–6 h produced imidazoquinazolines **25a**, **c**, **e** in good yields (Scheme 11, Table 6, entries 1, 3, and 5).[41] In contrast, when we performed the reaction with benzyl isocyanate **5f** under similar reaction conditions, the reaction step **22**→**24** smoothly proceeded but the reaction step **24**→**25** was reluctant to yield **25b**, **d**, **f** (entries 2, 4, and 6). After we ascertained the consumption of **22** and formation of **24** by TLC and then added powdered K_2CO_3 to the reaction upon heating for another 0.5–1.5 h under the same reaction conditions, we obtained compounds **25b**,



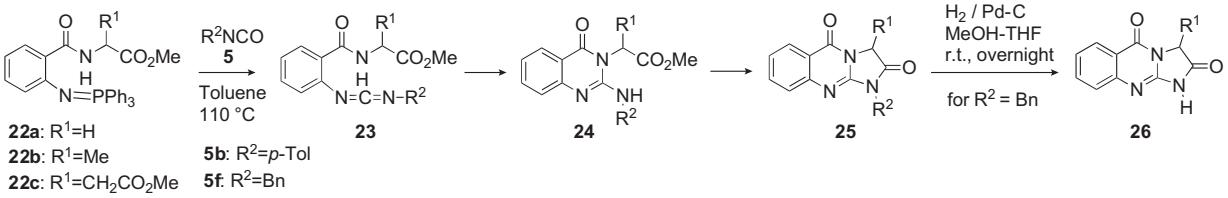
Scheme 10. Preparation of iminophosphoranes **22**.



Scheme 12. Preparation of optically active **25c*** via the one-pot tandem methodology.

d, **f** in good yields (entries 2, 4, and 6). In the reaction of **22c** derived from aspartic dimethyl ester involving cyclization of **24e**, **f**, the 5-*exo*-*trig* cyclization mode also dominated the 6-*exo*-*trig* mode, similar to the reaction of **4d** (Scheme 4 and Table 3). The greater reluctance for the cyclization **24**→**25** of **24b**, **d**, **f** (R^2=Bn) than that of **24a**, **c**, **e** (R^2=*p*-tolyl) could be ascribed mainly to the steric hindrance between the NHR^2 group and the CO_2Me group rather than to the factor of nucleophilicity of the NHR^2 group because the nucleophilicity of the NHBn group would be stronger than that of the NHTol-*p* group.[42] Thus, obtained **25b**, **d**, **f** bearing a benzyl group each were debenzylated by hydrogenolysis to give the N^1-unsubstituted **26a–c** in excellent yields (Table 6).

Fortunately, however, the formation of **33b** (R^1=Me) was realized, albeit in low yield, by heating **32b** in the presence of silica gel at 140 °C in Ph_2O. Furthermore, we found that removing the formed EtOH under a reduced pressure (19 mmHg) raised the yield of **33b** to 46% (entry 2). Similarly, imidazoimidazolidinediones **33c** and **33d** (R^1=Me) were obtained in 58 and 56% yields (entries 3 and 4), respectively. In the case of **32e**, which possessed two ester groups in a molecule, compounds **34** and **35** of both cyclization modes, 5-*exo*-*trig* and 6-*exo*-*trig*, formed with the latter predominating (entry 5). As the bulkiness of the substituent R^1 increases (H<Me<CO_2Et), the reactivity of compounds **32** for the cyclization and the yield increase.



Scheme 11. Tandem aza-Wittig/double cyclizations of **22** producing imidazoquinazolinones **25** and their hydrogenolysis to afford **26**.

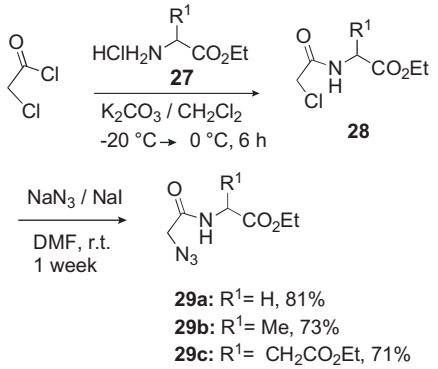
Table 6
Synthesis of imidazo[2,1-*b*]quinazolin-4-ones **25**/**26** via the tandem aza-Wittig/double cyclization one-pot reaction and hydrogenolysis

Entry	Iminophosphorane	R^1	R^2	Time (h)	Product	Yield (%)	Product	Yield (%)
1	**22a**	H	*p*-Tol	5	**25a**	80	—	—
2	**22a**	H	Bn	1.5+1.5[a]	**25b**	80	**26a**	92
3	**22b**	Me	*p*-Tol	1	**25c**	97	—	—
4	**22b**	Me	Bn	6.5+1.5[a]	**25d**	80	**26b**	91
5	**22c**	CH_2CO_2Me	*p*-Tol	6	**25e**	81	—	—
6	**22c**	CH_2CO_2Me	Bn	1.5+0.5[a]	**25f**	70	**26c**	96

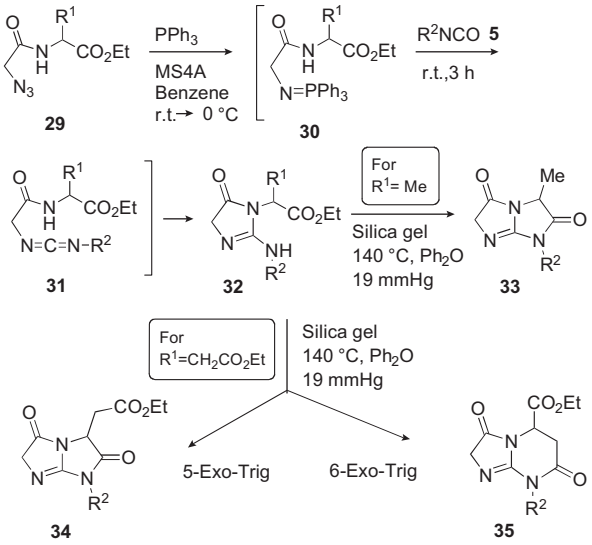
[a] In the presence of K_2CO_3 (powder, 1 equiv).

The optically pure iminophosphorane **22b*** (>99% ee) derived from L-alanine methyl ester HCl salt (**2b***) reacted with **5b** at 110 °C for 1 h to furnish the imidazoquinazoline **25c*** in 98% yield with >99% ee even at the higher temperature of 110 °C without any racemization (Scheme 12).

The aliphatic azides **29** were prepared via the amidation of amino acid ethyl ester HCl salts **27** with α-chloro-acetyl chloride followed by the azidation of the formed amides **28** (Scheme 13). Thus, obtained azides **29** underwent the Staudinger reaction with triphenylphosphine to yield the aliphatic iminophosphoranes **30** (Scheme 14). As the iminophosphoranes **30** were too labile to allow isolation (as they were apt to hydrolyze), we performed the aza-Wittig reaction with isocyanates **5** in one pot by slow dropwise addition of **5** to produce the initial cyclization products, imidazolinones **32** in 80–91% yields (Table 7). Upon heating in one pot at 80 °C or at a higher temperature (210 °C), or even in the presence of silica gel, *p*-TsOH, $TiCl_4$, Et_3N, or DBU, compound **32a** (R^1=H) did not undergo the second cyclization to give the expected imidazoimidazolidinedione **33a** (entry 1).[43] This is consistent with the known 'substituent effect (facilitated transition or reactive rotamer).'[44]



Scheme 13. Preparation of azides **29**.



Scheme 14. Synthesis of bicyclic guanidines **33**–**35**.

Table 7
Synthesis of imidazo[1,2-*a*]imidazolidinediones **33**/**34** and imidazo[1,2-*a*]pyrimidinediones **35** via the tandem aza-Wittig/double cyclization reaction

Entry	R^1	R^2	Product	Yield (%)	Product	Time (h)	Yield (%)
1	H	Ph	**32a**	80	**33a**	—	—[a]
2	Me	Ph	**32b**	90	**33b**	4	46
3	Me	*p*-Tol	**32c**	83	**33c**	6	58
4	Me	*p*-ClPh	**32d**	91	**33d**	6	56
5	CH_2CO_2Et	Ph	**32e**	91	**34**, **35**	4	28, 44 (72)[b]

[a] No cyclization product was obtained.
[b] In parentheses, total yield of **34**+**35**.

3. Conclusion

In conclusion, we have developed a new, facile, and practical one-pot synthetic method for diazaheterocyclic ring-fused 1,2,4-benzothiadiazine-1,1-dioxides **I** via the tandem aza-Wittig reaction/intramolecular NH-nucleophilic addition/NH-nucleophilic substitution cyclization, mediated by the sulfonamide ester–carbodiimide bifunctions. The advantages of this methodology are that it is simple, and it produces high yields of the target compounds, owing to easiness and efficiency of the procedure based on the one-pot reaction and tandem sequences and to the diversity, versatility, and utility/chirality of the targeted molecules based on the characteristics of the amino acid and isocyanate reactants. We have extended this methodology to the synthesis of diaza-ring-fused derivatives of quinazolinones **II** and imidazolidinones and pyrimidinones **III**.

4. Experimental

4.1. General

All melting points were determined on a Yanaco melting point apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 270-30 or a Horiba FT-710 spectrophotometer. ^{1}H and ^{13}C NMR spectral data were obtained with a Bruker AV 600, a JEOL JNM-EX 500, a JEOL JNM-LA 400, a Bruker DPX 300, a JEOL JNM-EX 300, or a JEOL JNM-EX 270 instrument. Chemical shifts (δ) are quoted in parts per million using tetramethylsilane (δ=0) for ^{1}H NMR spectroscopy, and $CDCl_3$ (δ=77.0) or DMSO-d_6 (δ=39.7) for ^{13}C NMR spectroscopy. Mass spectra were measured on a Bruker Daltonics microTOF, a Hitachi double-focusing M-80B, or a JEOL JMS-SX 102 spectrometer. Elemental analyses were performed with a YANACO CHN-CODER MT-6 model analyzer. Column chromatography was conducted on silica gel (Kanto Chemical Co. or Merck Co. Ltd). Enantiomeric excess values were determined by chiral HPLC measurement using a Dicel Chiralpak AD column on a Millipore-WatersTM 996. Optical rotations were recorded on a Nippon Bunko Model DIP-370 digital polarimeter and are reported in units of 10^{-1} deg cm^2 g^{-1}. All reactions were performed under an argon atmosphere except for hydrogenolysis.

4.2. Typical procedure for preparation of sulfonamidic azides 3

A solution of *o*-azidobenzenesulfonyl chloride **1**[26–28] (500 mg, 2.30 mmol) in CH_2Cl_2 (3 mL) was dropwise added to a mixture of alanine methyl ester hydrochloride salt (320 mg, 2.30 mmol) and Et_3N (0.95 mL, 6.90 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was warmed to room temperature with stirring for 4 h and then quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL×2). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (1:2) as the eluent to yield **3b** (600 mg, 91%) as brown oil.

*4.2.1. Methyl 2-{[(2-azidophenyl)sulfonyl]amino}propanoate (**3b**).* Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (d, *J*=7.2 Hz, 3H), 3.51 (s, 3H), 4.04 (dq, *J*=7.2, 8.0 Hz, 1H), 6.03 (d, *J*=8.0 Hz, 1H), 7.24 (ddd, *J*=0.8, 7.7, 7.7 Hz, 1H), 7.31 (dd, *J*=0.5, 8.0 Hz, 1H), 7.61 (ddd, *J*=1.5, 7.8, 7.9 Hz, 1H), 7.93 (dd, *J*=1.3, 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.08 (CH_3), 51.44 (CH_3), 52.06 (CH), 119.26 (CH), 124.18 (CH), 129.46 (C), 129.56 (CH), 133.79 (CH), 137.68 (C), 171.82 (C). IR (KBr): 3293, 2136, 1743, 1465, 1342, 1126, 1064, 763 cm^{-1}. Anal. Calcd for $C_{10}H_{12}N_4O_4S$: C, 42.25; H, 4.25; N, 19.71. Found: C, 42.63; H, 4.44; N, 19.77.

4.3. Typical procedure for preparation of sulfonamidic iminophosphoranes 4 (Table 1, entry 2)

Triphenylphosphine (450 mg, 1.70 mmol) was added to a solution of **3b** (440 mg, 1.55 mmol) in CH_2Cl_2 (7 mL). The reaction mixture was stirred at room temperature for 7 h and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography with CH_2Cl_2 as the eluent followed by recrystallization from CH_2Cl_2/hexane to yield **4b** (740 mg, 93%) as colorless crystals.

*4.3.1. Methyl 2-[({2-[(triphenylphosphoranylidene)amino]phenyl}sulfonyl)amino]propanoate (**4b**).* Colorless crystals; mp 155.7–156.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (d, *J*=7.0 Hz, 3H), 3.32 (s, 3H), 3.97 (dq, *J*=6.7, 7.0 Hz, 1H), 6.46 (d, *J*=8.0 Hz, 1H), 6.62 (dd, *J*=7.3, 7.6 Hz, 1H), 6.94–7.02 (m, 1H), 7.41–7.49 (m, 6H), 7.50–7.57 (m, 4H), 7.76–7.89 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.00 (CH_3), 51.61 (CH_3), 51.89 (CH), 115.84 (CH), 121.85 (d, $^3J_{P,C}$=12.4 Hz, CH), 128.43 (d, $^4J_{P,C}$=1.5 Hz, CH), 128.72 (d, $^3J_{P,C}$=12.7 Hz,6CH), 128.97 (d, $^1J_{P,C}$=100.3 Hz, 3C), 130.71 (d, $^2J_{P,C}$=24.0 Hz, C), 132.06 (d, $^4J_{P,C}$=2.0 Hz, 3CH), 132.28 (d, $^2J_{P,C}$=10.3 Hz, 6CH), 132.46 (CH), 149.09 (C), 172.07 (C). IR (KBr): 1743, 1581, 1465, 1342, 1157, 1110, 1049, 755, 717, 524 cm^{-1}. HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{28}H_{27}N_2NaO_4PS$, 541.1321; found 541.1309.

4.4. Typical procedure for tandem aza-Wittig reaction/double cyclization reaction from sulfonamidic iminophosphoranes 4a–e to produce imidazo[1,2-*b*][1,2,4]benzothiadiazine-5,5-dioxides 8–10 and 13 (Table 2, entry 11)

p-Methoxyphenyl isocyanate (**5d**, 0.051 mL, 0.386 mmol) was added to a solution of **4b** (200 mg, 0.386 mmol) in benzene (13 mL) with stirring and then the reaction mixture was heated at 80 °C for 3.5 h. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (1:2) as the eluent followed by recrystallization from CH_2Cl_2/hexane to yield **9d** (132 mg, 96%) as colorless needles. The enantiomeric excess of **9b*** was determined by HPLC using a chiral column (column: Dicel Chiralpak AD, mobile phase: hexane/2-propanol 90/10, flow rate:0.9 mL/min).

*4.4.1. 1-(4-Methoxyphenyl)-3-methyl-1H-imidazo[1,2-b][1,2,4]benzothiadiazin-2(3H)-one 5,5-dioxide (**9d**).* Colorless needles; mp 184–185 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.86 (d, J=7.0 Hz, 3H), 3.86 (s, 3H), 5.03 (q, J=7.0 Hz, 1H), 7.04 (d, J=8.9 Hz, 2H), 7.34–7.39 (m, 4H), 7.61 (ddd, J=1.4, 7.8, 8.1 Hz, 1H), 7.92 (dd, J=1.4, 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.59 (CH_3), 53.62 (CH), 55.50 (CH_3), 114.59 (2CH), 122.05 (CH), 123.31 (C), 125.63 (CH), 125.87 (C), 127.48 (CH), 128.36 (2CH), 134.35 (CH), 142.38 (C), 148.74 (C), 159.93 (C), 169.92 (C). IR (KBr): 1766, 1635, 1581, 1511, 1457, 1334, 1303, 1257, 1180, 1133, 1025, 779, 586 cm^{-1}. Anal. Calcd for $C_{17}H_{15}N_3O_4S$: C, 57.13; H, 4.23; N, 11.76. Found: C, 57.00; H, 4.27; N, 11.73.

4.5. Typical procedure for tandem aza-Wittig reaction/cyclization reaction from sulfonamidic iminophosphorane 4f to produce benzo-1,2,4-thiadiazine-1,1-dioxides 16 (Method A) (Table 4, entry 3)

p-Chlorophenyl isocyanate (**5c**, 0.081 mL, 0.64 mmol) was added to a solution of **4f** (300 mg, 0.58 mmol) in toluene (10 mL) with stirring and then the mixture was heated at 110 °C for 2.5 h. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (1:2) as the eluent followed by recrystallization from CH_2Cl_2/hexane to yield **16c** (182 mg, 80%) as colorless crystals.

*4.5.1. Methyl 3-{3-[(4-chlorophenyl)amino]-1,1-dioxido-2H-1,2,4-benzothiadiazin-2-yl}propanoate (**16c**).* Colorless crystals; mp 136–137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.07–3.12 (m, 2H), 3.86 (s, 3H), 3.95–4.00 (m, 2H), 7.24–7.29 (m, 1H), 7.33 (d, J=8.8 Hz, 2H), 7.43 (br d, J=8.0 Hz, 1H), 7.56–7.61 (m, 1H), 7.74–7.79 (m, 3H), 9.59 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.40 (CH_2), 44.06 (CH_2), 52.93 (CH_3), 121.12 (2CH), 121.40 (CH), 123.97 (CH), 126.32 (C), 126.44 (CH), 128.33 (C), 128.89 (2CH), 133.64 (CH), 137.65 (C), 143.74 (C), 146.70 (C), 175.13 (C). IR (KBr): 3270, 1720, 1612, 1581, 1334, 1180 cm^{-1}. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{17}H_{16}ClN_3NaO_4S$, 416.0442; found 416.0437.

4.6. Typical procedure for tandem aza-Wittig reaction/cyclization reaction from sulfonamidic iminophosphorane 4f to produce pyrimido[1,2-*b*][1,2,4]benzothiadiazine-6,6-dioxides 17 in one pot (Method B) (Table 5, entry 2)

p-Tolyl isocyanate (**5b**, 0.026 mL, 0.21 mmol) was added to a solution of **4f** (100 mg, 0.19 mmol) in $(CH_2Cl)_2$ (2 mL). The reaction mixture was heated at 80 °C for 4.5 h with stirring and cooled to room temperature. Titanium tetrachloride (0.95 mL, 1.0 M solution in CH_2Cl_2, 0.95 mmol) was added to the reaction mixture, which was then heated at 80 °C for 4.5 h. After being cooled to room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (30 mL×2). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (1:2) as the eluent followed by recrystallization from CH_2Cl_2/hexane to yield **17b** (54 mg, 82%) as colorless needles.

*4.6.1. 1-(4-Methylphenyl)-3,4-dihydropyrimido[1,2-b][1,2,4]benzothiadiazin-2(1H)-one 6,6-dioxide (**17b**).* Colorless needles; mp 267–268 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.06–3.16 (m, 2H), 4.17–4.30 (m, 2H), 7.11 (d, J=8.3 Hz, 2H), 7.15–7.22 (m, 1H), 7.26–7.38 (m, 3H), 7.48–7.57 (m, 1H), 7.83 (dd, J=1.5, 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.38 (CH_3), 33.22 (CH_2), 35.63 (CH_2), 121.37 (CH), 124.79 (C), 125.62 (CH), 127.82 (CH), 128.55 (2CH), 129.00 (2CH), 132.84 (C), 133.84 (CH), 138.57 (C), 142.02 (C), 145.34 (C), 167.33 (C). IR (KBr): 1720, 1565, 1511, 1465, 1334, 1180 cm^{-1}. Anal. Calcd for $C_{17}H_{15}N_3O_3S$: C, 59.81; H, 4.43; N, 12.31. Found: C, 60.11; H, 4.51; N, 12.26.

4.7. Typical procedure for hydrogenolysis of *N*-benzylimidazo/pyrimido[1,2-*b*][1,2,4]benzothiadiazine-5,5/6,6-dioxides 8f, 9f, 10f, 13f and 17f to produce N_1-unsubstituted compounds 20

A solution of imidazobenzothiadiazine dioxide **8f** (50 mg, 0.15 mmol) in THF/MeOH (3 mL, v/v=1/2) in the presence of palladium on carbon (10%, 50 mg) was stirred vigorously under a hydrogen atmosphere at room temperature for 1 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc as the eluent to yield **20a** (37 mg, quant.) as colorless solid.

*4.7.1. 1H-Imidazo[1,2-b][1,2,4]benzothiadiazin-2(3H)-one 5,5-dioxide (**20a**).* Colorless solid; mp (sublim.) 247–249 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.59 (s, 2H), 7.33–7.50 (m, 2H), 7.74 (dd, J=7.9, 7.3 Hz, 1H), 7.96 (d, J=7.9 Hz, 1H), one signal (NH) missing; ^{13}C NMR (125 MHz, DMSO-d_6) δ 45.48 (CH_2), 122.10 (CH), 124.49 (C), 125.21 (CH), 125.90 (CH), 134.80 (CH), 142.21 (C), 169.75 (C), one signal (C) missing. IR (KBr): 2761, 2699, 1766, 1681, 1581, 1473, 1334, 1211, 1203, 1187, 763, 586 cm^{-1}. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_9H_7N_3NaO_3S$, 260.0100; found 260.0101.

4.8. Typical procedure for preparation of iminophosphoranes 22

Thionyl chloride (1.2 ml, 18 mmol) and catalytic amount of DMF were added to a solution of *o*-azidobenzoic acid (980 mg, 6.0 mmol) in benzene (20 mL). The reaction mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), and glycine methyl ester hydrochloride salt (1.5 g, 12 mmol) and Et_3N (2.5 mL, 18 mmol) were added successively to the solution. The reaction mixture was stirred overnight at room temperature and then quenched with water. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (30 mL×2). The combined organic extracts were washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL), and triphenylphosphane (1.6 g, 6.0 mmol) was added to the solution. The mixture was stirred at room temperature for overnight and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (1:1) as the eluent followed by recrystallization from EtOAc/hexane to yield **22a** (2.07 g, 75%) as colorless powder.

*4.8.1. Methyl ({2-[(triphenylphosphoranylidene)amino]benzoyl}amino)-acetate (**22a**).* Colorless powder; mp 136.6–138.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (s, 3H), 4.20 (br d, J=5.5 Hz, 2H), 6.45 (dd, J=0.8, 8.0 Hz, 1H), 6.68–6.79 (m, 1H), 6.87–6.96 (m, 1H), 7.40–7.65 (m, 9H), 7.67–7.81 (m, 6H), 8.21–8.30 (m, 1H), 11.60–11.90 (br t, J=5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.30 (CH_2), 51.82 (CH_3), 117.47 (CH), 122.45 (d, $^3J_{P,C}$=12.0 Hz, CH), 124.44 (d, $^2J_{P,C}$=20.0 Hz, C), 128.90 (d, $^3J_{P,C}$=12.0 Hz, 6CH), 129.45 (d, $^1J_{P,C}$=100.0 Hz, 3C), 131.08 (CH), 131.54 (d, $^4J_{P,C}$=2.0 Hz, CH), 132.27 (d, $^4J_{P,C}$=2.7 Hz, 3CH), 132.56 (d, $^2J_{P,C}$=10.0 Hz, 6CH), 150.07 (C), 168.23 (C), 170.23 (C). IR (KBr): 3463, 3347, 3023, 2954, 2931, 1751, 1643, 1542, 1465, 1442, 1342, 1195, 1164, 1110, 1010, 755, 516 cm^{-1}. HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{28}H_{26}N_2O_3P$, 469.1676; found 469.1664.

4.9. Typical procedure for tandem aza-Wittig reaction/double cyclization reaction from iminophosphoranes 22 to produce imidazo[2,1-*b*]quinazolin-4-ones 25 (Table 6, entry 3)

p-Tolyl isocyanate (**5b**, 0.061 mL, 0.48 mmol) was added to a solution of **22b** (200 mg, 0.40 mmol) in toluene (15 mL) with stirring and then the reaction mixture was heated at 110 °C for 1 h. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (1:2) as the eluent followed by recrystallization from EtOAc/hexane to yield **25c** (119 mg, 97%) as colorless powder.

*4.9.1. 3-Methyl-1-(4-methylphenyl)imidazo[2,1-b]quinazoline-2,5(1H,3H)-dione (**25c**).* Colorless powder; mp 223.4–225.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90 (d, J=7.0 Hz, 3H), 2.44 (s, 3H), 4.91 (q, J=7.0 Hz, 1H), 7.30–7.47 (m, 5H), 7.50–7.56 (m, 1H), 7.67 (ddd, J=1.5, 7.2, 8.1 Hz, 1H), 8.24 (dd, J=1.6, 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.33 (CH_3), 21.33 (CH_3), 54.89 (CH), 120.10 (C), 125.51 (CH), 126.63 (CH), 126.66 (2CH), 126.80 (CH), 128.21 (C), 130.03 (2CH), 134.74 (CH), 139.25 (C), 148.08 (C), 148.74 (C), 159.41 (C), 170.97 (C). IR (KBr): 1758, 1689, 1627 cm^{-1}. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{18}H_{15}N_3NaO_2$, 328.1056; found 328.1056.

4.10. Typical procedure for hydrogenolysis of *N*-benzylimidazo[2,1-*b*]quinazolin-4-ones 25b, d, f to produce *N*-unsubstituted compounds 26 (Table 6, entry 2)

A solution of **25b** (53.2 mg, 0.18 mmol) in THF/MeOH (10 mL, v/v=1/1) in the presence of palladium on carbon (10%, 50 mg) was stirred vigorously under a hydrogen atmosphere at room temperature for 6.5 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc as the eluent to yield **26a** (36.2 mg, 92%) as colorless solid.

*4.10.1. Imidazo[2,1-b]quinazoline-2,5(1H,3H)-dione (**26a**)*[45]. ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.54 (s, 2H), 7.41–7.47 (m, 1H), 7.56 (d, J=8.1 Hz, 1H), 7.78–7.85 (m, 1H), 8.13 (d, J=8.0 Hz, 1H), one signal (NH) missing; ^{13}C NMR (125 MHz, DMSO-d_6) δ 47.90 (CH_2), 118.91 (C), 124.49 (CH), 125.59 (CH), 126.06 (CH), 134.58 (CH), 148.51(C), 151.89 (C), 158.35 (C), 170.83 (C).

4.11. Typical procedure for preparation of azides 29

Chloroacetyl chloride (2.24 g, 19.9 mmol) was added dropwise to a mixture of glycine ethyl ester hydrochloride salt (2.79 g, 19.9 mmol) and K_2CO_3 (5.51 g, 39.9 mmol) in CH_2Cl_2 (100 mL) at −60 °C with stirring. The reaction mixture was warmed to 0 °C with stirring for 6 h and then quenched with water. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (100 mL×2). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and then concentrated under reduced pressure. NaN_3 (1.29 g, 19.9 mmol) and catalytic amount of NaI (149 mg, 0.99 mmol) were added to a solution of the residue in DMF (100 mL). The mixture was stirred at room temperature for a week and then quenched with water. The solution was extracted with Et_2O (300 mL×2). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography with EtOAc/hexane (1:1) as the eluent to yield **29a** (3.0 g, 81%) as yellow solid.

*4.11.1. Ethyl [(azidoacetyl)amino]acetate (**29a**).* Yellow solid; mp 29.3–29.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J=7.1 Hz, 3H), 4.04 (s, 2H), 4.07 (d, J=5.6 Hz, 2H), 4.24 (q, J=7.1, 2H), 6.91 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.13 (CH_3), 41.17 (CH_2), 52.47 (CH_2), 61.75 (CH_2), 166.99 (C), 169.38 (C). IR (KBr): 3336, 2992, 2116, 1748, 1674, 1540, 1206 cm^{-1}.

4.12. Typical procedure for tandem Staudinger reaction/aza-Wittig reaction/cyclization reaction from azides 29 to produce imidazolinoes 32 (Table 7, entry 1)

Triphenylphosphine (52.4 mg, 0.20 mmol) was added to a mixture of **29a** (37.3 mg, 0.20 mmol) and molecular sieve 4 Å (100 mg) in benzene (5 mL). The reaction mixture was stirred for 0.5 h, and heated at 80 °C for 3 h. After being cooled to room temperature, a solution of phenyl isocyanate (**5a**, 0.0196 ml, 0.18 mmol) in benzene (5 mL) was added dropwise to the reaction mixture at a rate of 2.5 mL/h by syringe pump with stirring. The reaction mixture was stirred for 1 h at same temperature, and then filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography with EtOAc/hexane (1:1) as the eluent to yield **32a** (41.8 mg, 80%) as colorless solid.

*4.12.1. Ethyl (2-anilino-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetate (**32a**).* Colorless solid; mp 111.3–113.0 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.29 (t, J=7.3 Hz, 3H), 3.96 (s, 2H), 4.23 (q, J=7.3 Hz, 2H), 4.40 (s, 2H), 4.80 (s, 1H), 6.93–7.32 (m, 5H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.05 (CH_3), 39.96 (CH_2), 46.92 (CH_2), 61.63 (CH_2), 122.22 (2CH), 123.27 (CH), 129.34 (2CH), 146.54 (C), 149.43 (C), 167.18 (C), 170.90 (C). IR (KBr): 3304, 1760, 1732, 1674, 1206 cm^{-1}.

4.13. Typical procedure for cyclization reaction of imidazolinoes 32 to produce imidazo[1,2-*a*]imidazolidindiones 33/34 and imidazo[1,2-*a*]pyrimidinones 35 (Table 7, entry 2)

A mixture of **32b** (48.3 mg, 0.175 mmol) and silica gel (4.8 mg) in Ph_2O (3 mL) was stirred at 140 °C for 9 h under reduce pressure (19 mmHg). After being cooled to room temperature, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silicagel column chromatography with EtOAc/hexane (1:1) as the eluent to yield **33b** (18.5 mg, 46%) as yellow oil.

*4.13.1. 3-Methyl-1-phenyl-1H-imidazo[1,2-a]imidazole-2,5(3H,6H)-dione (**33b**).* Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74 (t, J=7.1 Hz, 3H), 4.35 (s, 2H), 4.54 (q, J=7.1 Hz, 1H), 7.27–7.65 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.30 (CH_3), 52.90 (CH), 61.20 (CH_2), 124.40 (2CH), 128.48 (CH), 129.42 (2CH), 131.24 (C), 156.37 (C),

172.95 (C), 174.74 (C). IR (neat): 1744, 1678, 1598, 1504, 1444, 1342 cm^{-1}. LRMS-EI (*m*/*z*): 229 (M^+, 100%), 201 (M^+-28, 45%), 173 (M^+-58, 36%), 145 (M^+-84, 96%). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{12}H_{11}N_3O_2$, 229.0851; found 229.0845.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.11.064.

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