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New efficient synthesis of polysubstituted 3,4-dihydroquinazolines and 4*H*-3,1-benzothiazines through a Passerini/Staudinger/aza-Wittig/addition/nucleophilic substitution sequence

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Full Research Paper

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Abstract

A new efficient synthesis of polysubstituted 3,4-dihydroquinazolines and 4*H*-3,1-benzothiazines via sequential Passerini/Staudinger/aza-Wittig/addition/nucleophilic substitution reaction has been developed. The three-component Passerini reactions of 2-azidobenzaldehydes **1**, benzoic acid (**2**), and isocyanides **3** produced the azide intermediates **4**, which were treated sequentially with triphenylphosphine, isocyanates (or CS_2), and secondary amines to give polysubstituted 3,4-dihydroquinazolines **8** and 4*H*-3,1-benzothiazines **11** in good overall yields through consecutive Passerini/Staudinger/aza-Wittig/addition/nucleophilic substitution reactions.

Introduction

The chemistry of 3,4-dihydroquinazolines and 4*H*-3,1-benzothiazines is of constant interest owing to the occurrence of these ring systems in various biologically important compounds (Figure 1). A number of 3,4-dihydroquinazolines were found to show remarkable anticancer [1], antiviral [2], antidepressant [3], antifungal [4], selective somatostatin 2 (ss2) agonistical [5], β-site amyloid precursor protein cleaving enzyme 1 (BACE-1) inhibitive [6], and cholinesterase enzyme inhibitive activities [7]. The 3,4-dihydroquinazoline skeleton also exists in some natural products such as vasicine and vasicoline [8]. Some 4*H*-3,1-benzothiazine derivatives have also received attention due to their good biological activities, including anticancer [9],

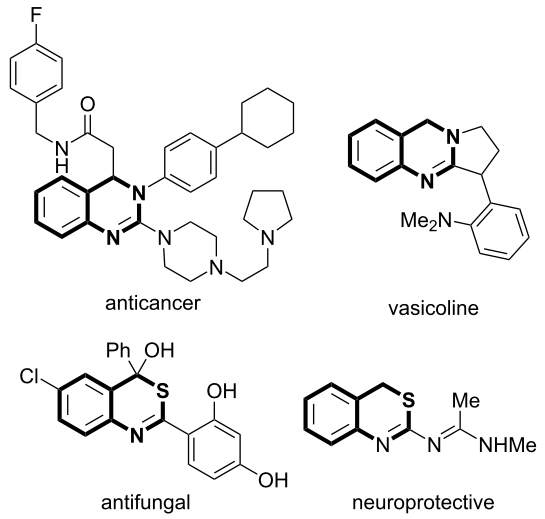
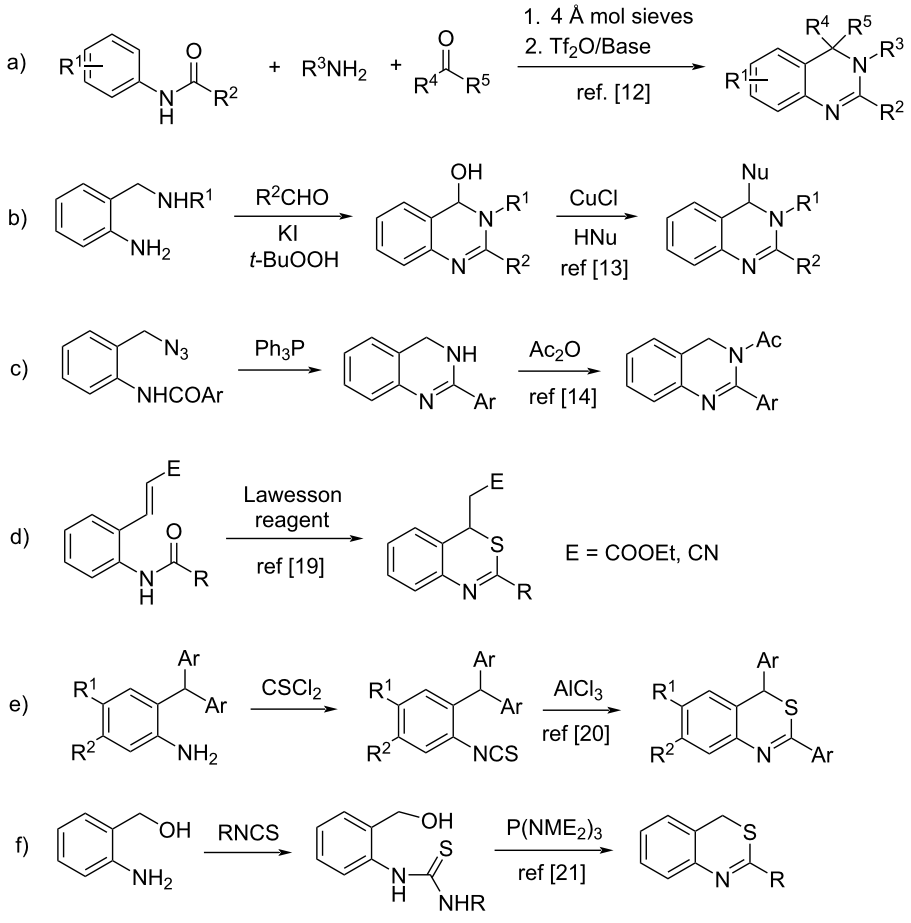


Figure 1: Some bioactive 3,4-dihydroquinazolines and 4*H*-3,1-benzothiazines.

neuroprotective [10], antiproliferative and antifungal activities [11]. Due to the significant bioactive properties of the 3,4-dihydroquinazoline and 4*H*-3,1-benzothiazine moieties, many preparation procedures have appeared in the literature for the synthesis of their derivatives [12-22]. For example (Scheme 1), a one-pot Tf_2O-mediated assembly of amides, amines, and ketones provided 3,4-dihydroquinazolines in good yields via successive triflic anhydride-mediated amide dehydration, ketimine addition, and Pictet–Spengler-like cyclization processes [12]. Some 4-substituted 3,4-dihydroquinazolines were prepared by copper-catalyzed oxidative cross coupling of hydroxy intermediates with various nucleophiles [13]. Other 3,4-dihydroquinazolines were also obtained efficiently by intramolecular aza-Wittig reactions [14]. Some 4*H*-3,1-benzothiazines were prepared by intramolecular thia-Michael addition with broad reaction scopes [19]. The rearrangement of 2-isothiocyano triarylmethanes in the presence of $AlCl_3$ were also used for the synthesis 2,4-diaryl-4*H*-3,1-benzothiazines through aromatic ring transfer [20]. A facile protocol towards the synthesis of 4*H*-3,1-benzothiazines was established by using



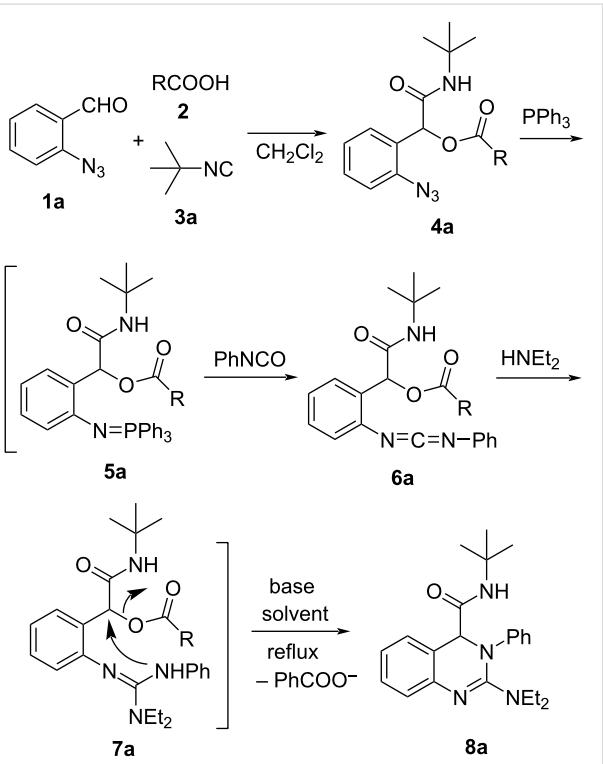
Scheme 1: Representative preperation of 3,4-dihydroquinazolines and 4*H*-3,1-benzothiazines.

a $P(NMe_2)_3$-mediated C–N/C–S bond formation reaction of 2-aminobenzyl alcohol with isothiocyanates under aerobic conditions [21]. Despite of the above achievements, the development of new efficient methods for the synthesis of polysubstituted 3,4-dihydroquinazolines and 4*H*-3,1-benzothiazines under mild reaction conditions is still of high demand in the discovery of biologically active compounds.

The Passerini reaction is an isocyanide-based multicomponent reaction, which has been used in preparing various α-acyloxy adducts starting from aldehydes, a carboxylic acid, and a isonitrile as the three components [23]. The sequences of Passerini reactions, followed by post-condensation reactions, constitute useful synthetic methods in the preparation of structurally diverse heterocyclic compounds [24-29]. The aza-Wittig reaction has also been utilized widely in preparation of various heterocycles under mild neutral conditions [30-32]. Recently we have reported the synthesis of 3*H*-2-benzoxepin-1-ones, 4*H*-3,1-benzoxazines and oxazoles by combination of a Passerini with an intramolecular aza-Wittig reaction [33-35]. Continuing our interest in the synthesis of *N*-heterocycles via the aza-Wittig reaction and multicomponent reactions [36-38], we wish to report herein a facile synthesis of polysubstituted 3,4-dihydroquinazolines and 4*H*-3,1-benzothiazines via sequential Passerini/Staudinger/aza-Wittig/addition/nucleophilic substitution reactions. Compared with the synthetic method to 4*H*-3,1-benzothiazines in Scheme 1f, we provide another new sequential synthetic route to 4*H*-3,1-benzothiazines, especially for *N*,*N*-disubstituted 2-amino-4*H*-3,1-benzothiazines.

Results and Discussion

We initially selected 2-azidobenzaldehyde (**1a**), benzoic acid (**2a**) and *tert*-butyl isocyanide (**3a**) as the reactants (Scheme 2). When a mixture of **1a**, **2a**, and **3a** in CH_2Cl_2 was stirred at room temperature for 48 h, the three-component Passerini reaction was carried out smoothly and the azide **4a** (R = Ph) was finally obtained in 87% yield. Compound **4a** was then allowed to react with triphenylphosphine in CH_2Cl_2 at room temperature for 2 h to produce the iminophosphorane **5a** by Staudinger reaction. Aza-Wittig reaction of **5a** with phenyl isocyanate generated carbodiimide **6a**, which was then treated with diethylamine to form the guanidine intermediate **7a**. In the presence of K_2CO_3 in CH_3CN at refluxing temperature, the 3,4-dihydroquinazoline **8a** was finally obtained in 84% yield (Table 1, entry 1, the overall yield is 73%) by intramolecular nucleophilic substitution. The reaction conditions for the transformation of guanidine intermediate **7a** into 3,4-dihydroquinazoline **8a** was then optimized (Table 1). As K_2CO_3 in different solvents (DMF, CH_2Cl_2 and toluene) were used, 0–72% yields of the product **8a** were obtained (Table 1, entries 2–4). Utilizing a stronger base (NaOH and EtONa) resulted in a dark solution and no product was received (entries 5 and 6) owning to side reactions under the stronger base conditions. No product **8a** was obtained when NEt_3 in CH_3CN was used (Table 1, entry 7) probably due to the weaker basic conditions. The effect of different R groups on the reaction yield was also investigated. With R = methyl, no product **8a** was obtained in the presence of K_2CO_3/CH_3CN probably due to the lower reactivity of the -OAc leaving group. In case when R was a 4-$NO_2C_6H_4$ group, 86% yield of the product **8a** was obtained, however, in this case the Passerini product **4a** (R = 4-$NO_2C_6H_4$) was obtained only in 62% yield and the overall yield of product **8a** was 53%. There-



Scheme 2: Preparation of 3,4-dihydroquinazoline **8a**.

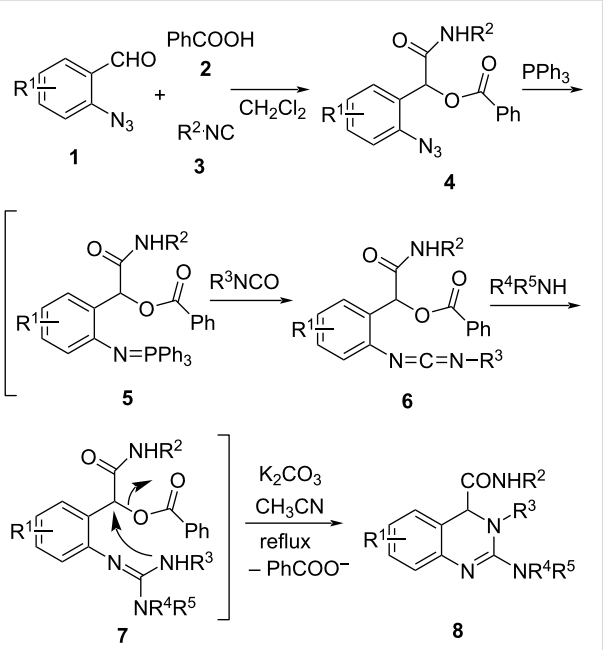
Table 1: Optimization of the reaction conditions for the preparation of compound **8a**.

entry	R	Conditions	Yield (%)
1	Ph	K_2CO_3/CH_3CN	84
2	Ph	K_2CO_3/DMF	72
3	Ph	K_2CO_3/CH_2Cl_2	0
4	Ph	K_2CO_3/toluene	41
5	Ph	$NaOH/CH_3CN$	0
6	Ph	NaOEt/EtOH	0
7	Ph	NEt_3/CH_3CN	0
8	Me	K_2CO_3/CH_3CN	0
9	4-$NO_2C_6H_4$	K_2CO_3/CH_3CN	86

fore, the reaction conditions of entry 1 in Table 1 were optimal for the above transformation.

The optimal reaction conditions were then utilized for the sequential reactions of different 2-azidobenzaldehydes **1**, benzoic acid (**2a**), isocyanides **3**, isocyanates and secondary amines. Most of the reactions took place smoothly to give the corresponding 3,4-dihydroquinazolines **8** in good yields (Scheme 3 and Table 2). Various isocyanates and secondary amines can be used in the above one-pot cyclization to prepare 3,4-dihydroquinazolines **8**. As indicated in Table 2, when aromatic isocyanates (Table 2, compounds **8a–l**, R^3 = Ph, 4-ClC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4 and 4-$CF_3OC_6H_4$) were used, good yields (69–86%) of the products were obtained, whereas moderate yields (54–57%) were obtained when the more steric secondary amines were utilized (Table 2, compound **8m** and **8n**, NR^4R^5 = $N(Cy)_2$, $N(iPr)_2$). In cases when aliphatic isocyanates (compounds **8o–q**, R^3 = *n*-Bu, cyclohexyl and $PhCH_2$) were used, 65–74% yields of the products were obtained. Even as the steric *tert*-butyl isocyanate was applied, the 3,4-dihydroquinazoline **8r** was obtained in 42% yield, but when diphenylamine was used, no product was obtained (compounds **8s**, NR^4R^5 = NPh_2).

The aza-Wittig reaction of iminophosphoranes **5** with an excess of CS_2 took place smoothly at 40 °C to produce isothiocyanates **9**, which were allowed to react with secondary amines to generate thiourea intermediates **10**. In the presence of K_2CO_3 in CH_3CN at refluxing temperature, thioureas **10** were also successfully transformed into 4*H*-3,1-benzothiazines **11** via intra-



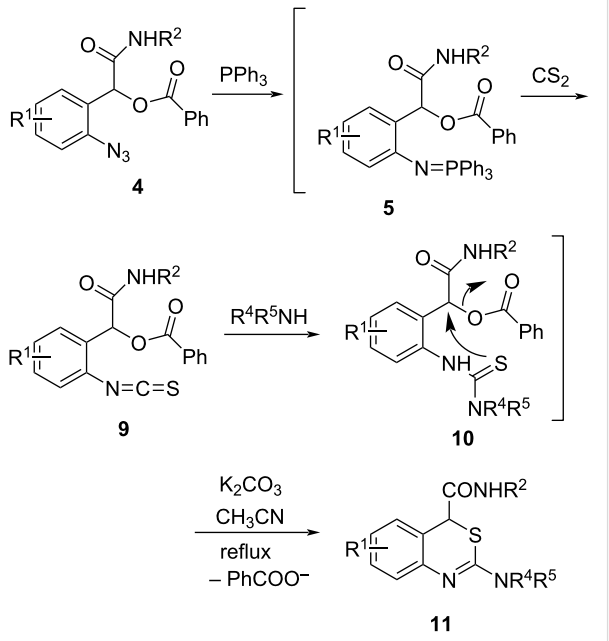
Scheme 3: Preparation of 3,4-dihydroquinazolines **8**.

Table 2: Yields of 3,4-dihydroquinazolines **8**.

	R^1	R^2	R^3	NR^4R^5	Yield[a] (%)
8a	H	*t*-Bu	Ph	NEt_2	84
8b	H	*t*-Bu	4-ClC_6H_4	NEt_2	80
8c	H	*t*-Bu	3-MeC_6H_4	NEt_2	76
8d	H	*t*-Bu	4-MeC_6H_4	NEt_2	79
8e	H	*t*-Bu	Ph	morpholin-4-yl	72
8f	H	*t*-Bu	4-MeC_6H_4	NPr_2	85
8g	H	*t*-Bu	4-MeC_6H_4	NBu_2	69
8h	H	Cy[b]	4-MeC_6H_4	NEt_2	71
8i	H	Cy[b]	Ph	NEt_2	86
8j	H	Cy[b]	4-ClC_6H_4	NEt_2	78
8k	H	Cy[b]	4-$CF_3OC_6H_4$	NEt_2	80
8l	H	*t*-Bu	4-MeC_6H_4	morpholin-4-yl	70
8m	H	*t*-Bu	4-MeC_6H_4	NCy_2[b]	57
8n	4-Cl	Cy[b]	4-$CH_3OC_6H_4$	$N(iPr)_2$	54
8o	4-Cl	*n*-Bu	*n*-Bu	N(Ph)Me	65
8p	5-Me	*t*-Bu	Cy[b]	$N(CH_2Ph)Me$	74
8q	4-Cl	Cy[b]	$PhCH_2$	$N(CH_2Ph)_2$	67
8r	5-Me	Cy[b]	*t*-Bu	NEt_2	42
8s	H	*n*-Bu	Ph	NPh_2	0

[a]Isolated yields based on the azides **4**. [b]Cyclohexyl.

molecular nucleophilic substitution (Scheme 4). The results were listed in Table 3. Various secondary amines can be used in this one-pot cyclization to prepare 4*H*-3,1-benzothiazines **11**. As indicated in Table 3, when dialkylamines including cyclic dialkylamines (Table 3, compounds **11a**–**k**, NR^4R^5 = NEt_2, NPr_2, $N(CH_2Ph)Me$, $N(CH_2Ph)_2$, piperidin-1-yl, morpholin-4-yl and pyrrolidin-1-yl) were used, good yields (72–84%) of the products were obtained, whereas mederate yield (48–54%) was obtained when the more steric dialkylamines were utilized (Table 3, compounds **11l** and **11m**, NR^4R^5 = $N(Cy)_2$, $N(iPr)_2$). In cases when phenylmethylamine (compounds **11n** and **11o**, NR^4R^5 = N(Ph)Me) was used, 51–56% yields of the products were obtained, but when diphenylamine was used, no product was obtained (compound **11p**, NR^4R^5 = NPh_2).



Scheme 4: Preparation of 4*H*-3,1-benzothiazines **11**.

Conclusion

In conclusion, we have developed a new Passerini/Staudinger/aza-Wittig/addition/nucleophilic substitution sequence for the synthesis of polysubstituted 3,4-dihydroquinazolines and 4*H*-3,1-benzothiazines. By this method, 3,4-dihydroquinazolines and 4*H*-3,1-benzothiazines were prepared in good overall yields with the advantages of mild one-pot operation conditions and easily accessible starting materials containing various common substituents.

Supporting Information

Supporting Information File 1

Experimental section and copies of NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-18-32-S1.pdf]

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Table 3: Yields of 4*H*-3,1-benzothiazines **11**.

	R^1	R^2	NR^4R^5	Yield[a] (%)
11a	H	*t*-Bu	NEt_2	82
11b	H	*t*-Bu	piperidin-1-yl	83
11c	H	*t*-Bu	morpholin-4-yl	84
11d	H	*n*-Bu	morpholin-4-yl	78
11e	H	Cy[b]	pyrrolidin-1-yl	77
11f	H	Cy[b]	$N(CH_2Ph)Me$	79
11g	5-Me	Cy[b]	NEt_2	72
11h	5-Me	*n*-Bu	piperidin-1-yl	81
11i	5-Me	Cy[b]	$N(CH_2Ph)_2$	78
11j	5-Me	*t*-Bu	NPr_2	75
11k	4-Cl	Cy[b]	NEt_2	83
11l	4-Cl	*t*-Bu	NCy_2[b]	54
11m	5-Me	Cy[b]	$N(iPr)_2$	48
11n	H	Cy[b]	N(Ph)Me	56
11o	5-Me	Cy[b]	N(Ph)Me	51
11p	H	*n*-Bu	NPh_2	0

[a]Isolated yields based on the azides **4**. [b]Cyclohexyl.

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