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Transition-Metal-Free Synthesis of Imidazo[2,1-*b*]thiazoles and Thiazolo[3,2-*a*]benzimidazoles via an *S*-Propargylation/5-*exo*-*dig* Cyclization/Isomerization Sequence Using Propargyl Tosylates as Substrates

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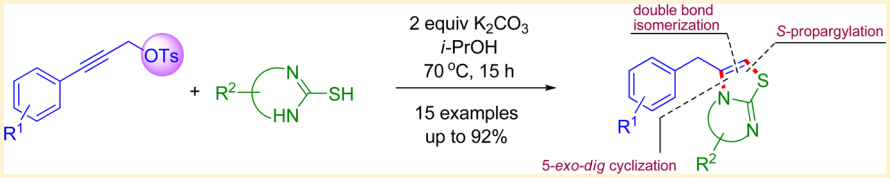
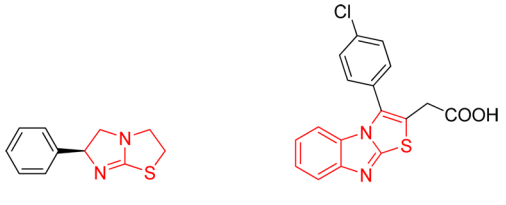
Supporting Information



ABSTRACT: A transition-metal-free route for the synthesis of several *N*-fused heterocycles, including thiazolo[3,2-*a*]-benzimidazoles and imidazo[2,1-*b*]thiazoles, is reported. The reaction between propargyl tosylates and 2-mercaptobenzimida-zoles under basic conditions results in 3-substituted thiazolo[3,2-*a*]benzimidazoles, in yields up to 92% in a single synthesis step. With 2-mercaptoimidazoles as the substrate, the corresponding imidazo[2,1-*b*]thiazoles were exclusively obtained. The trans-formation is considered to proceed as an intermolecular *S*-propargylation that is followed by 5-*exo*-*dig* ring closure and double-bond isomerization.

INTRODUCTION

N-Fused heterocycles, such as imidazo[2,1-*b*]thiazoles and thiazolo[3,2-*a*]benzimidazoles, are heterocyclic compounds with a wide range of interesting pharmacological properties, including antitumor,[1] mitogenic,[2] antiinflammatory,[3] cardiodepressant,[4] antimicrobial,[5] anticoccidial,[6] anthelmintic,[7] and antifungal activities.[8] Imidazo[2,1-*b*]thiazoles and thiazolo[3,2-*a*]benzimidazoles are also known as muscarinic acetylcholine receptor antagonists,[9] p53 inhibitors,[10] β-lactamase inhibitors,[11] thyroid adenylate cyclase inhibitors,[12] potentiators of cystic fibrosis transmembrane conductance regulator (CFTR) chloride channels,[13] and activators of SIRT1, an NAD^+-dependent deacetylase.[14] (*S*)-6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*][1,3]thiazole, also known as Levamisole (Figure 1, **I**), is an anthelmintic that has been employed to treat parasitic worm infections in humans and is still in use in veterinary medicine.[15] [3-(4-Chlorophenyl)-[1,3]thiazolo[3,2-*a*]benzimidazol-2-yl]acetic acid (Tilomisole) (Figure 1, **II**) exhibits immunomodulating and antimetastatic activities and has been studied for the treatment of colon cancer.[16]



Levamisole (**I**) Tilomisole (**II**)

Figure 1. Structures of Levamisole (**I**) and Tilomisole (**II**).

Because of their broad pharmacological activities, a number of approaches have been developed for the synthesis of imidazo-[2,1-*b*]thiazoles[17] and thiazolo[3,2-*a*]benzimidazoles.[18] Among the classical methods for the preparation of imidazo[2,1-*b*]-thiazoles is the reaction between an α-haloketone and a 2-mercaptoimidazole or 2-aminothiazole (Scheme 1a).[1c,d,2,3,5−7,9−11,13,17] This reaction is based on an intermolecular nucleophilic substitution that is followed by an intramolecular condensation. This approach has also been employed for the preparation of thiazolo[3,2-*a*]benzimidazoles.[8,18,19] However, many of these transformations need comparably harsh reaction conditions, such as high reaction temperatures, strong bases, or strong acids.[17,18]

Over the last few decades, transition-metal-catalyzed methods have become increasingly significant in the synthesis of *N*-fused heterocycles, such as imidazo[2,1-*b*]thiazoles and thiazolo[3,2-*a*]benzimidazoles. Some of these reactions rely on the combination of Pd/Cu-catalyzed Sonogashira coupling and intramolecular cyclization.[20] As an example, Heravi et al. have reported on the Pd/Cu-catalyzed reaction between 2-propargylmercaptbenzimidazole and aryl iodides, which delivered 3-substituted thiazolo[3,2-*a*]benzimidazoles as result

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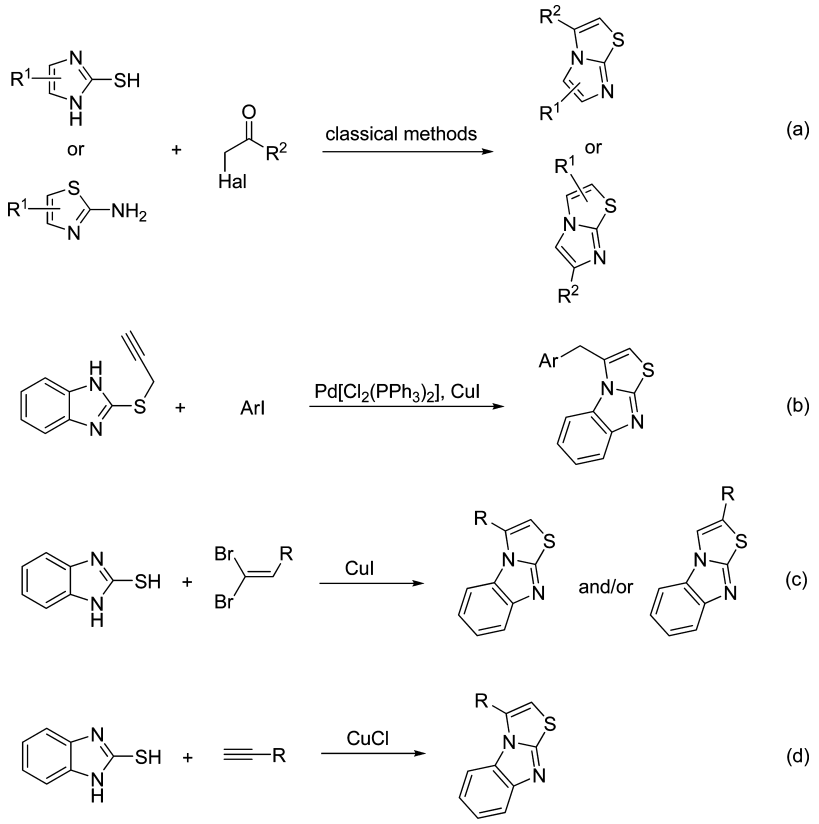
Scheme 1. Previous Routes for the Synthesis of Imidazo[2,1-*b*]thiazoles and Thiazolo[3,2-*a*]benzimidazoles

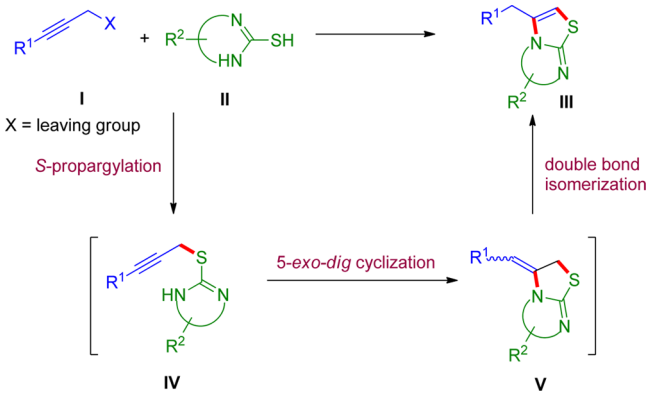


of Sonogashira coupling/5-*exo-dig* cyclization/isomerization (Scheme 1b).[20b]

Recently, Chen et al. published the copper-catalyzed aminothiolation of 1,1-dibromoalkenes with 2-mercaptobenzimidazole under basic conditions for the synthesis of 2- and 3-substituted thiazolo[3,2-*a*]benzimidazoles (Scheme 1c).[21] It is believed that the reaction starts with the in situ formation of a 1-bromoalkyne by the dehydrohalogenation of the 1,1-dibromoalkene, followed by a copper-catalyzed C(sp)-S coupling between the 2-mercaptobenzimidazole and the 1-bromoalkyne, to give the corresponding alkynyl thioether. Subsequent intramolecular hydroamination (5-*endo-dig* cyclization) delivers a 3-substituted thiazolo[3,2-*a*]benzimidazole. Alternatively, a copper-catalyzed C(sp)-N coupling may occur to form the corresponding *N*-alkynylated 2-mercaptobenzimidazole, which in turn undergoes an intramolecular hydrothiolation (5-*endo-dig* ring closure) to the 2-substituted thiazolo[3,2-*a*]benzimidazoles. The ratio between the regioisomeric thiazolo[3,2-*a*]benzimidazoles depends on the structure of the substrates, as well as the reaction conditions. Li et al. have demonstrated that the reaction between 2-mercaptobenzimidazole and terminal alkynes in the presence of 2 equiv of CuCl, 2 equiv of *N*,*N*′-dicyclohexylimidazolium chloride, and 5 equiv of triethyl amine in toluene at 110 °C exclusively yields the products of an *S*-alkynylation/5-*endo-dig* cyclization process, i.e., the 3-substituted thiazolo[3,2-*a*]benzimidazoles (Scheme 1d).[22] Despite these advances, there is still a need for new methods that allow the straightforward synthesis of imidazo[2,1-*b*]thiazoles, thiazolo[3,2-*a*]benzimidazoles and related skeletons from readily available starting materials using reasonably priced reagents, catalysts, and ligands.

On the basis of the aforementioned results, we anticipated that a transition-metal-catalyzed reaction between propargyl derivative **I** and 2-mercaptoimidazole **II** would allow for the synthesis of imidazo[2,1-*b*]thiazole and related heterocycles **III** by means of domino *S*-propargylation/5-*exo-dig* ring closure/double-bond isomerization (Scheme 2). Because thiols are known as excellent nucleophiles in nucleophilic substitutions, exclusive *S*-propargylation was expected to take place in the first step. Propargyl thioether **IV** formed could then undergo a Cu(I)-catalyzed 5-*exo-dig* cyclization[23] (**IV** → **V**), followed by a double-bond isomerization (**V** → **III**) to deliver a 3-substituted imidazo[2,1-*b*]thiazole or related heterocycle **III**. Herein, we disclose a new and straightforward approach for the selective

Scheme 2. Proposed Route for the Synthesis of Imidazo[2,1-*b*]thiazoles, Thiazolo[3,2-*a*]benzimidazoles, and Related Skeletons



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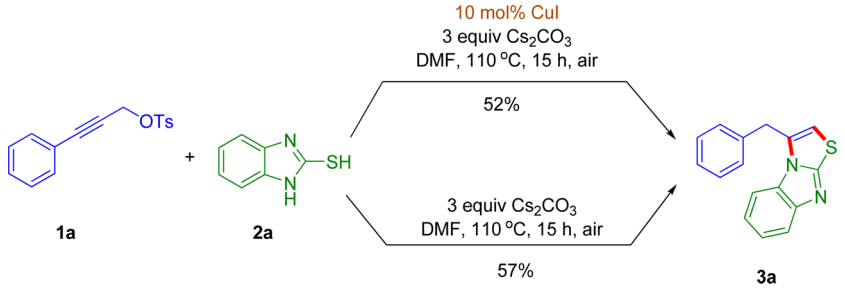
Scheme 3. Synthesis of 3a under Copper-Catalyzed Conditions, as Well as under Transition-Metal-Free Conditions



synthesis of imidazo[2,1-*b*]thiazoles, thiazolo[3,2-*a*]benzimidazoles, and thiazolo[3,2-*a*]perimidines.

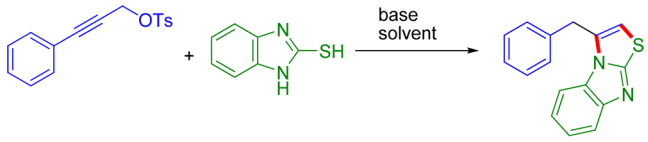
RESULTS AND DISCUSSION

The reaction between 1-(4-methylbenzenesulfonate)-3-phenyl-2-propyne (**1a**) and 2-mercaptobenzimidazole (**2a**) was chosen as the model reaction. The tosylate was chosen as the substrate because propargyl tosylates can be prepared from easily accessible propargylic alcohols in a simple and reliable way.[24] After some experimentation, it was found that the Cu(I)-catalyzed reaction between **1a** and **2a** occurred without any difficulty. The reaction between equimolar amounts of **1a** and **2a** in the presence of 10 mol % CuI and 3 equiv of Cs_2CO_3 in DMF at 110 °C for 15 h under air delivered 3-benzylthiazolo[3,2-*a*]-benzimidazole (**3a**) as the sole product in 52% yield (Scheme 3).

Surprisingly, the formation of 3-benzylthiazolo[3,2-*a*]benzimidazole (**3a**) also occurs in the absence of any copper salt. When equimolar amounts of **1a** and **2a** were reacted under the same conditions (3 equiv of Cs_2CO_3 in DMF at 110 °C for 15 h under air), except for the absence of CuI, the 3-benzylthiazolo-[3,2-*a*]benzimidazole (**3a**) was formed in 57% yield (Scheme 3). This unexpected observation prompted us to focus on the further development of the transition-metal-free variant of the new synthesis approach to thiazolo[3,2-*a*]benzimidazoles. The reaction between **1a** and **2a** was again chosen as the model reaction. The transformation was performed employing different bases, such as K_3PO_4, $NaHCO_3$, and K_2CO_3 (Table 1, entries 1−3) to identify optimal conditions for the reaction. With 3 equiv K_2CO_3, **3a** could be isolated in 78% yield (Table 1, entry 3). Interestingly, the amount of K_2CO_3 could be decreased to 2 equiv without affecting the yield (Table 1, entry 4). Further experiments were devoted to the influence of solvent type and reaction time. The formation of **3a** took place in DMF, CH_3CN, DMSO, and *i*-PrOH (Table 1, entries 5−7). With *i*-PrOH as the solvent, the yield of **3a** amounted to 76% (Table 1, entry 7). Interestingly, the yield of **3a** could be increased to 85% when the reaction was performed under argon (Table 1, entry 8). It was found that a decrease in the temperature to 70 °C had little effect on the yield of **3a** (Table 1, entry 9). A decrease of the reaction time is not advisable. When the reaction was run for 7 h the yield decreased from 80 to 59% (Table 1, entry 10). As expected, no cyclization product was formed in the absence a base (Table 1, entry 11). For comparison, the transformation was also performed under the conditions given in Table 1, entry 9, except for the presence of 10 mol % CuI (Table 1, entry 12); the yield of **3a** was slightly lower than it was under copper-free conditions.

In general, all reactions were run using technical-grade or analytical-grade base reagents. ICP-OES experiments revealed that the technical-grade K_2CO_3 employed throughout this study contains 0.00005% Cu, >0.00008% Fe, and >0.0003% Ni;

Table 1. Optimization of Conditions for the Reaction Between 1a and 2a[a]



1a 2a 3a

entry	base (equiv)	solvent	*T* (°C)	time (h)	yield of **3a** (%)
1	K_3PO_4 (3)	DMF	110	15	68[b,c]
2	$NaHCO_3$ (3)	DMF	110	15	43[b,d]
3	K_2CO_3 (3)	DMF	110	15	78[b,e]
4	K_2CO_3 (2)	DMF	110	15	75[b,e]
5	K_2CO_3 (2)	CH_3CN	100	15	59[b,e]
6	K_2CO_3 (2)	DMSO	100	15	64[b,e]
7	K_2CO_3 (2)	*i*-PrOH	100	15	76[b,e]
8	K_2CO_3 (2)	*i*-PrOH	100	15	85[e,f]
9	K_2CO_3 (2)	*i*-PrOH	70	15	80[e,f]
10	K_2CO_3 (2)	*i*-PrOH	70	7	59[e,f]
11		*i*-PrOH	70	15	[f,g]
12	K_2CO_3 (2)	*i*-PrOH	70	15	75[f,h]
13	K_2CO_3 (2)	*i*-PrOH	70	15	90[f,i]
14	K_2CO_3 (2)	*i*-PrOH	70	15	89[f,j]

[a]All reactions were performed using 1 mmol of **1a** and 1 mmol of **2a** in a sealed vial. [b]The reaction was performed under air. [c]Reagent-grade K_3PO_4 (≥98%) was used. [d]Technical-grade $NaHCO_3$ was used. [e]Technical-grade K_2CO_3 was used. [f]The reaction was performed under argon. [g]The thioether **4a** was formed in 30% yield. [h]The reaction was performed in the presence of 10 mol % CuI. [i]K_2CO_3 (≥99.0%) was used. [j]K_2CO_3 (99.995%) was used.

the Cs_2CO_3 contains 0.000052% Cu, >0.00008% Fe, and >0.0003% Ni. The reaction between **1a** and **2a** was also performed with K_2CO_3 samples of different origin, in order to exclude the possibility that the reactions are catalyzed by trace impurities of Cu and/or other transition metals. Using K_2CO_3 (≥99.0%), containing ≤0.0005% Cu, ≤0.001% Pd, and 0.0005% Fe,[25] resulted in **3a** isolated in 90% yield (Table 1, entry 13). Using K_2CO_3 with a purity of 99.995%[25] resulted in **3a** isolated in 89% yield (Table 1, entry 14). These results support the view that the *S*-propargylation/5-exo-dig cyclization/isomerization sequence presented here is a transition-metal-free transformation.

The scope of the new synthesis method was evaluated using the optimized reaction conditions (Table 1, entry 9). When 1-(4-methylbenzenesulfonate)-3-phenyl-2-propyne (**1a**) was reacted with the substituted 2-mercaptobenzimidazoles **2b,c**, the corresponding 3-benzylthiazolo[3,2-*a*]benzimidazoles **3b,c** were obtained in yields of 79 and 70%, respectively (Table 2, entries 2 and 3). Further experiments revealed that the new method is not restricted to 2-mercaptobenzimidazoles; it can

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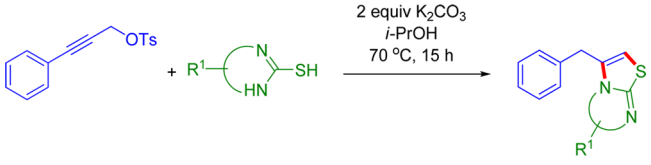
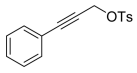
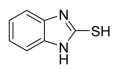
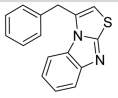
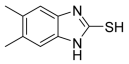
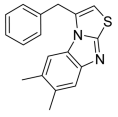
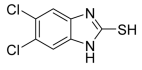
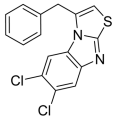
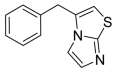
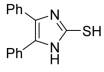
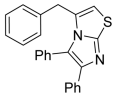
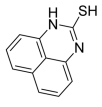
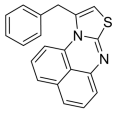
Table 2. Reaction of Propargyl Tosylate 1a with 2-Mercaptoimidazoles 2a–f[a]



1a 2a-f 3a-f

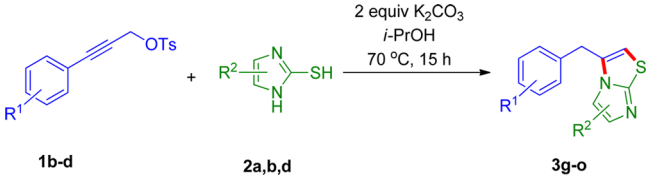
entry	1	2	3	yield of 3 (%)
1	 1a	 2a	 3a	80
2	1a	 2b	 3b	79
3	1a	 2c	 3c	70 / 68[b]
4	1a	 2d	 3d	86 / 85[b]
5	1a	 2e	 3e	86 / 90[b]
6	1a	 2f	 3f	74

[a]All reactions were performed using 1 mmol of **1a** and 1 mmol of **2** in a sealed vial under argon. [b]The reaction was performed in the presence of 10 mol % CuI.

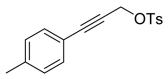
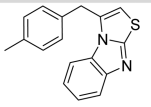
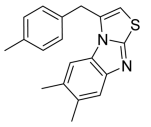
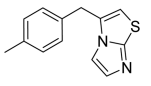
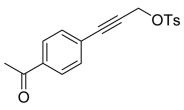
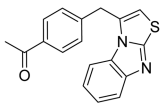
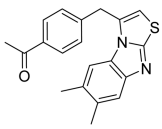
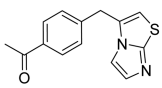
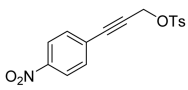
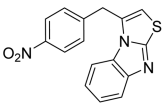
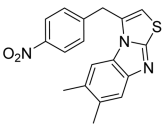
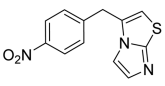
also be applied to 2-mercaptoimidazoles as substrates. When **1a** was reacted with 2-mercaptoimidazole (**2d**) and 4,5-diphenyl-2-mercaptoimidazole (**2e**), the corresponding 3-benzylimidazo-[2,1-*b*]thiazoles **3d,e** were formed in 86% yield (Table 2, entries 4 and 5). Next, **1a** was reacted with perimidine-2-thione (**2f**) to deliver the 3-benzylthiazolo[3,2-*a*]perimidine (**3f**) in 74% yield (Table 2, entry 6). Some of the transformations were also run in the presence of 10 mol % CuI (Table 2, entries 3–5). It was found that the yields of **3c–e** were in the same range as those under copper-free conditions.

Furthermore, it was found that the annulation is not limited to the unsubstituted 1-(4-methylbenzenesulfonate)-3-phenyl-2-propyne (**1a**). Substituted derivatives, such as 1-(4-methylbenzenesulfonate)-3-(4-methylphenyl)-2-propyne (**1b**), 1-(4-methylbenzenesulfonate)-3-(4-acetylphenyl)-2-propyne (**1c**), and 1-(4-methylbenzenesulfonate)-3-(4-nitrophenyl)-2-propyne (**1d**), were also tolerated as substrates. The reaction between **1b–d** and 2-mercaptoimidazoles **2a,b,d** under optimal conditions gave corresponding imidazo[2,1-*b*]thiazoles **3i,l,o** and thiazolo[3,2-*a*]benzimidazoles **3g,h,j,k,m,n** in yields ranging from 40 to 92% (Table 3, entries 1–9).

Table 3. Reaction of Substituted Propargyl Tosylates 1b–d with 2-Mercaptoimidazoles 2a,b,d[a]



1b-d 2a,b,d 3g-o

entry	1	2	3	yield of 3 (%)
1	 1b	2a	 3g	66
2	1b	2b	 3h	92
3	1b	2d	 3i	79
4	 1c	2a	 3j	83
5	1c	2b	 3k	81
6	1c	2d	 3l	77
7	 1d	2a	 3m	65
8	1d	2b	 3n	40
9	1d	2d	 3o	46

[a]All reactions were performed using 1 mmol of **1** and 1 mmol of **2** in a sealed vial under argon.

A plausible reaction mechanism for the transformation, exemplified by the reaction between **1a** and **2a**, is given in Scheme 4. It is assumed that the annulation starts with the intermolecular *S*-propargylation of 2-mercaptobenzimidazole (**2a**) to give propargyl thioether **4a** as an intermediate. This is

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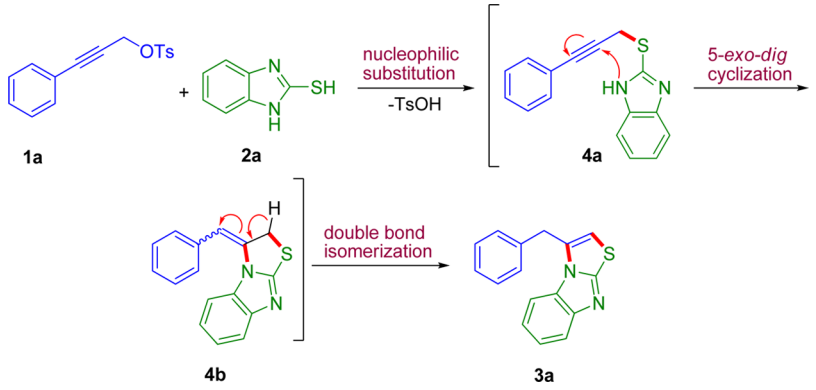
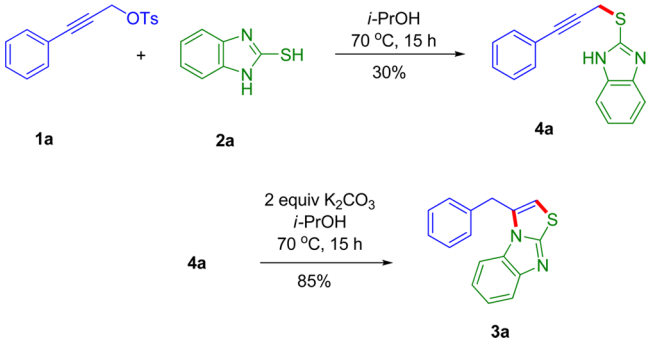
Scheme 4. Plausible Reaction Mechanism



followed by 5-*exo-dig* cyclization and double-bond isomerization to deliver *N*-fused heterocyclic compound **3a**.

To support the reaction mechanism, a control experiment, namely, the 5-*exo-dig* cyclization of **4a**, i.e., the proposed intermediate of the annulation, was performed. Propargyl thioether **4a** was prepared in 30% yield by *S*-propargylation of **2a** with **1a** in the absence of any base (Scheme 5; see also Table 1, entry 11).

Scheme 5. Synthesis of Putative Intermediate 4a and Its 5-*exo-dig* Cyclization to 3a



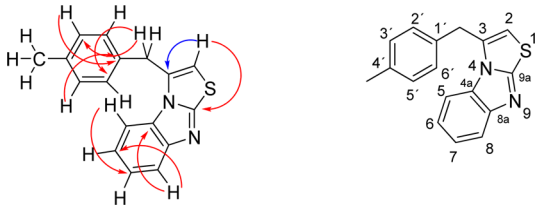


Figure 2. Important HMBC correlations of **3g**. Red arrows, ^{3}J; blue arrows, ^{2}J.

Subsequently, **4a** was reacted with 2 equiv of K_2CO_3 in *i*-PrOH at 70 °C for 15 h to deliver 3-benzylthiazolo[3,2-*a*]benzimidazole (**3a**) in 85% yield. The exclusive formation of **3a** provides strong evidence that propargyl thioether **4a** is an intermediate in the annulation process.

The structures of all *N*-fused heterocyclic compounds **3a**–**o** were unambiguously elucidated by NMR spectroscopy and mass spectrometry. Full assignment of the ^{1}H and ^{13}C chemical shifts and structure elucidation of all compounds were achieved by evaluating their gCOSY, gHSQC, and gHMBC spectra. As an example, the HMBC spectrum of **3g** quaternary carbon C-9a shows ^{3}J-HMBC-correlations to proton 2-H. Quaternary carbon C-1′ displays strong $^{3}J_{CH}$ correlations to protons 3′-H and 5′-H and a $^{2}J_{CH}$ correlation to the benzylic protons. Carbon C-3 exhibits a $^{2}J_{CH}$ correlation to the benzylic protons (Figure 2). A 1D NOESY spectrum between the benzylic protons and 5-H in compound **3g** enabled the unequivocal assignment of aromatic protons 5-H and 8-H (Supporting Information). The structure of **3a** was additionally confirmed by X-ray crystal structure analysis.[26]

CONCLUSIONS

A transition-metal-free method for the efficient and selective preparation of substituted thiazolo[3,2-*a*]benzimidazoles and imidazo[2,1-*b*]thiazoles in a single synthesis step from easily accessible starting materials is reported. The reaction between propargyl tosylates and 2-mercaptobenzimidazoles under basic conditions (K_2CO_3 in *i*-PrOH) delivers 3-substituted thiazolo-[3,2-*a*]benzimidazoles in yields up to 92%. With 2-mercapto-imidazoles as substrates, the corresponding 3-substituted imidazo-[2,1-*b*]thiazoles were obtained. The *N*-fused heterocycles are formed as the result of a domino intermolecular *S*-propargylation/5-*exo-dig* ring closure/double-bond isomerization.

EXPERIMENTAL SECTION

General Remarks. All commercially available reagents were used without further purification. Glassware was dried for 4 h at 140 °C. Solvents used in reactions were distilled over appropriate drying agents prior to use. Solvents used for extraction and purification were distilled prior to use. Reaction temperatures are reported as bath temperature. Thin-layer chromatography (TLC) was performed on TLC silica gel 60 F_{254}. Compounds were visualized with UV light (λ = 254 nm) and/or by immersion in an ethanolic vanillin solution or by immersion in $KMnO_4$ solution followed by heating. Products were purified by flash chromatography on silica gel (0.04–0.063 mm). Melting points were obtained on a melting-point apparatus with open capillary tubes and are uncorrected. IR spectra were measured on an FT-IR spectrometer. UV spectra were recorded with a spectrophotometer. ^{1}H (^{13}C) NMR spectra were recorded at 300 (75) and 500 (125) MHz using $CDCl_3$, CD_3COCD_3, or DMSO-d_6 as the solvent. The ^{1}H and ^{13}C chemical shifts were referenced to residual solvent signals at δ H/C 7.26/77.00 ($CDCl_3$), 2.05/29.9 (CD_3COCD_3), and 2.5/39.5 (DMSO-d_6) relative to TMS as the internal standard. HSQC, HMBC, and COSY spectra were recorded on an NMR spectrometer at 300 and 500 MHz. Coupling constants *J* [Hz] were taken directly from the spectra and are not averaged. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), m (multiplet), and br (broad). 1D and 2D homonuclear NMR spectra were measured with standard pulse sequences. Copies of the NMR spectra were prepared using SpinWorks.[27] Low-resolution electron impact mass spectra (EI) and exact mass electron impact mass spectra [HRMS (EI)] for compounds **3f**–**h**, **3j**, **3l**, **3n**, and **3o** were obtained at 70 eV using a double-focusing sector field mass spectrometer. Low-resolution electron spray ionization mass spectra (ESI)

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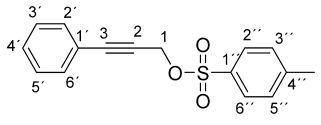
and exact electron spray ionization mass spectra [HRMS (ESI)] for compounds **1b**, **3c**−**e**, **3i**, and **3k** were obtained using a TOF mass spectrometer. Intensities are reported as percentages relative to the base peak (I = 100%).

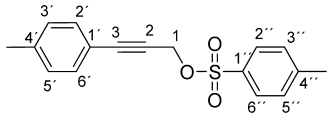
General Procedure I for the Synthesis of Propargyl Tosylates 1a−d.[24c] Propargyl alcohol (1 mmol) and *p*-toluene sulfonyl chloride (*p*-TsCl) (29 mg, 1.2 mmol) were dissolved in diethyl ether (15 mL). The solution was cooled to 0 °C, and freshly powdered K_2CO_3 (56 mg, 10 mmol) was added portionwise over a 20 min period. After complete addition, the reaction mixture was stirred for 3.5 h at 0 °C. Ice water (20 mL) was added, and the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed under reduced pressure.

*1-(4-Methylbenzenesulfonate)-3-phenyl-2-propyne (**1a**).*[24c] According to general procedure I, KOH (4.2 g, 75 mmol), 3-phenyl-2-



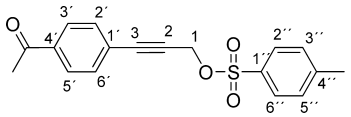
propyn-1-ol (1 g, 7.5 mmol), and *p*-TsCl (1.73 g, 9.1 mmol) were reacted in diethyl ether (15 mL) for 3.5 h at 0 °C. Flash chromatography of the crude product over silica gel (petroleum ether/ethyl acetate = 5:1) gave **1a** as a colorless solid in 88% yield (1.86 g, 6.5 mmol). Mp: 78—79 °C (ref 24c, 76—77 °C). R_f 0.36 (petroleum ether/EtOAc = 5:1). ^{1}H NMR (300 MHz, CD_3COCD_3): δ 2.41 (s, 3H, CH_3), 7.28 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 7.7 Hz, ^3J (2′-H or 6′-H, 4′-H) = 1.5 Hz, 2H, 2′-H and 6′-H), 7.33 (t like, ^3J (4′-H, 3′-H or 5′-H) = 1.5 Hz, 1H, 4′-H), 7.39 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 7.7 Hz, 2H, 3′-H and 5′-H), 7.47 (d like, ^3J (2″-H, 3″-H or 5″-H, 6″-H) = 8.0 Hz, 2H, 3″-H and 5″-H), 7.88 (d like, ^3J (2″-H, 3″-H or 5″-H, 6″-H) = 8.5 Hz, 2H, 2″-H and 6″-H). ^{13}C NMR (75 MHz, CD_3COCD_3): δ 21.6 (CH_3), 59.6 (CH_2), 82.1 (C-2), 89.1 (C-3), 122.4 (C-1′), 129.0 (C-2′ and C-6′), 129.4 (C-3′ and C-5′), 130.1 (C-4′), 130.9 (C-3″ and C-5″), 132.6 (C-2″ and C-6″), 134.7 (C-1″), 146.3 (C-4″). MS (EI, 70 eV) m/z (%) 286 (11) $[M]^+$, 192 (8), 138 (30), 131 (42), 115 (100), 91 (19).

*1-(4-Methylbenzenesulfonate)-3-(4-methylphenyl)-2-propyne (**1b**).* According to general procedure I, KOH (3.8 g, 68 mmol),



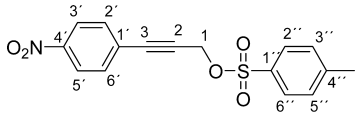
3-(4-methylphenyl)-2-propyn-1-ol (1 g, 6.8 mmol), and *p*-TsCl (1.56 g, 8.2 mmol) were reacted in diethyl ether (15 mL) for 3.5 h at 0 °C. Flash chromatography of the crude product over silica gel (petroleum ether/ethyl acetate = 10:1) gave **1b** as a yellow solid in 64% yield (1.2 g, 4.0 mmol). Mp: 55—56 °C. R_f: 0.32 (petroleum ether/EtOAc = 10:1). IR (ATR) $\tilde{\nu}$: 3032 (CH), 2919 (CH), 2222 (C≡C), 1365 (S═O asym), 1266, 1187 (S═O sym), 1092, 987 (S−O−C), 802, 669, 574 cm^{-1}. UV (MeCN) λ_{max} (log ε): 247 (4.31), 229 (4.31) nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, 4′-CH_3), 2.40 (s, 3H, 4″-CH_3), 4.94 (s, 2H, CH_2), 7.07 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 8.0 Hz, 2H, 3′-H and 5′-H), 7.15 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 8.3 Hz, 2H, 2′-H and 6′-H), 7.32 (d like, ^3J (2″-H, 3″-H or 5″-H, 6″-H) = 8.0 Hz, 2H, 3″-H and 5″-H), 7.85 (d like, ^3J (2″-H, 3″-H or 5″-H, 6″-H) = 8.3 Hz, 2H, 2″-H and 6″-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 2.33 (4′-CH_3), 2.40 (4″-CH_3), 4.94 (CH_2), 79.9 (C-2), 89.2 (C-3), 118.3 (C-1′), 128.2 (C-2″ and 6″), 128.9 (C-3′ and C-5′), 129.8 (C-3″ and C-5″), 131.7 (C-2′ and C-6′), 133.4 (C-1″), 139.3 (C-4′), 144.9 (C-4″). MS (ESI) m/z (%): 323 (100) $[M + Na]^+$, 301 (30) $[M + 1]^+$. HRMS (ESI) for $C_{17}H_{16}O_3SNa$: calcd: 323.0712; found: 323.0706.

*1-(4-Methylbenzenesulfonate)-3-(4-acetylphenyl)-2-propyne (**1c**).*[24c] According to general procedure I, KOH (3.2 g, 57 mmol), 3-(4-acetylphenyl)-2-propyn-1-ol (1 g, 5.7 mmol) and *p*-TsCl (1.3 g, 6.9 mmol) were reacted in diethyl ether (15 mL) for 3.5 h at 0 °C. Flash chromatography of the crude product over silica gel (petroleum



ether/ethyl acetate = 2:1) gave **1c** as a yellow solid in 51% yield (0.96 g, 2.9 mmol). Mp: 93—94 °C (ref 24c, 69—73 °C). R_f: 0.18 (petroleum ether/EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 2.58 (s, 3H, CH_3CO), 4.96 (s, 2H, CH_2), 7.32 (overlapped, 2H, 3″-H and 5″-H), 7.34 (overlapped, 2H, 2′-H and 6′-H), 7.84 (overlapped, 2H, 2″-H and 6″-H), 7.87 (overlapped, 2H, 3′-H and 5′-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6 (CH_3), 26.6 (CH_3CO), 58.2 (CH_2), 83.7 (C-2), 87.9 (C-3), 126.1 (C-1′), 128.1 (C-3′ and C-5′), 128.2 (C-2″ and C-6″), 129.8 (C-3″ and C-5″), 131.8 (C-2′ and C-6′), 133.2 (C-1″), 136.9 (C-4′), 114.1 (C-4″), 197.1 (CO). MS (EI, 70 eV) m/z (%): 328 (48) $[M]^+$, 313 (68) $[M - CH_3]^+$, 285 (7) $[M - COCH_3]^+$, 219 (15), 174 (27), 157 (100), 142 (67), 114 (71), 91 (65).

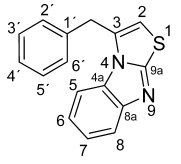
*1-(4-Methylbenzenesulfonate)-3-(4-nitrophenyl)-2-propyne (**1d**).*[24e] According to general procedure I, KOH (3.2 g, 56 mmol),



3-(4-nitrophenyl)-2-propyn-1-ol (1 g, 5.7 mmol), and *p*-TsCl (1.3 g, 6.9 mmol) were reacted in diethyl ether (15 mL) for 3.5 h at 0 °C. Flash chromatography of the crude product over silica gel (petroleum ether/ethyl acetate = 2:1) gave **1d** as a colorless solid in 77% yield (1.44 g, 4.4 mmol). Mp: 109—110 °C (ref 24e, 103—104 °C). R_f: 0.24 (petroleum ether/EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 (s, 3H, CH_3), 4.96 (s, 2H, CH_2), 7.34 (d like, ^3J (2″-H, 3″-H or 5″-H, 6″-H) = 8.0 Hz, 2H, 3″-H and 5″-H), 7.42 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 9.0 Hz, 2H, 2′-H and 6′-H), 7.86 (d like, ^3J (2″-H, 3″-H or 5″-H, 6″-H) = 8.0 Hz, 2H, 2″-H and 6″-H), 8.16 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 9.0 Hz, 2H, 3′-H and 5′-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6 (CH_3), 57.8 (CH_2), 85.7 (C-2), 86.6 (C-3), 123.5 (C-3′ and C-5′), 128.1 (C-1′), 128.2 (C-2″ and C-6″), 129.9 (C-3″ and C-5″), 132.5 (C-2′ and C-6′), 133.1 (C-4″), 145.3 (C-1″), 147.6 (C-4′). MS (ESI) m/z (%): 354 (100) $[M + Na]^+$.

General Procedure II for the Synthesis of *N*-Fused Heterocycles 3a−o. An oven-dried 10 mL vial was equipped with a magnetic stir bar and charged with K_2CO_3 (277 mg, 2 mmol), 1-(4-methylbenzenesulfonate)-3-phenyl-2-propyne derivative **1** (1 mmol), and 2-mercaptoimidazole **2** (1 mmol) under air. The vial was sealed, evacuated, and backfilled with argon three times, then dry *i*-PrOH (2 mL) was added. The reaction mixture was stirred at 70 °C for 15 h. The reaction mixture was cooled to room temperature and then partitioned between CH_2Cl_2 (30 mL) and brine (20 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue thus obtained was purified by flash column chromatography over silica gel to afford the desired product.

*3-Benzylthiazolo[3,2-a]benzimidazole (**3a**).*[28] According to general procedure II, a mixture of K_2CO_3 (277 mg, 2 mmol),



1-(4-methylbenzenesulfonate)-3-phenyl-2-propyne (**1a**) (286 mg, 1 mmol), and 2-mercaptobenzimidazole (**2a**) (150 mg, 1 mmol) was reacted in dry *i*-PrOH (2 mL) in a sealed vial at 70 °C for 15 h. Flash chromatography over silica gel (petroleum ether/EtOAc = 2:1) gave **3a** as a colorless solid in 80% yield (211 mg, 0.8 mmol). Mp: 75—76 °C (ref 28, 80—81 °C). R_f: 0.36 (petroleum ether/EtOAc = 5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.41 (brs, 2H, CH_2), 6.16 (t, ^4J

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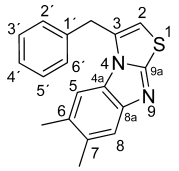
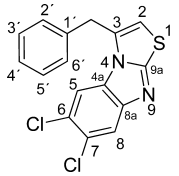
(CH_2, 2-H) = 1.3 Hz, 1H, 2-H), 7.17 (ddd, ^3J (5-H, 6-H) = 8.2 Hz, ^3J (6-H, 7-H) = 7.3 Hz, ^4J (6-H, 8-H) = 1.1 Hz, 1H, 6-H), 7.31 (overlapped, 2H, 2′-H and 6′-H), 7.33 (t like, ^3J (4′-H, 3′-H or 5′-H) = 8.1 Hz, 1H, 4′-H), 7.34 (t like, ^3J (7-H, 6-H or 8-H) = 8.0 Hz, 1H, 7-H), 7.39 (overlapped, 2H, 3′-H and 5′-H), 7.62 (dd, ^3J (5-H, 6-H) = 8.2 Hz, ^4J (5-H, 7-H) = 1.1 Hz, 1H, 5-H), 7.79 (dd, ^3J (7-H, 8-H) = 8.2 Hz, ^4J (6-H, 8-H) = 1.2 Hz, 1H, 8-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.6 (CH_2), 106.5 (C-2), 110.9 (C-5), 119.1 (C-8), 120.7 (C-6), 123.5 (C-7), 127.5 (C-4′), 128.8 (C-2′ and C-6′), 129.1 (C-3′ and C-5′), 130.1 (C-4a), 133.2 (C-3), 134.9 (C-1′), 148.5 (C-8a), 157.4 (C-9a). MS (EI, 70 eV) m/z (%): 263 (100) $[M]^+$, 231 (6), 204 (10), 115 (15).

*3-Benzyl-6,7-dimethylthiazolo[3,2-a]benzimidazole (**3b**).*[28] According to general procedure II, a mixture of K_2CO_3 (277 mg,



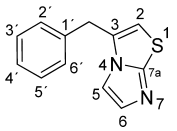
2 mmol), 1-(4-methylbenzenesulfonate)-3-phenyl-2-propyne (**1a**) (286 mg, 1 mmol), and 5,6-dimethyl-2-mercaptobenzimidazole (**2b**) (178 mg, 1 mmol) was reacted in dry *i*-PrOH (2 mL) in a sealed vial at 70 °C for 15 h. Flash chromatography over silica gel (petroleum ether/EtOAc = 2:1) gave **3b** as a colorless solid in 79% yield (232 mg, 0.79 mmol). Mp: 204—205 °C (ref 28, 201—202 °C). R_f: 0.33 (petroleum ether/EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.33 (s, 3H, 6-CH_3), 2.37 (s, 3H, 7-CH_3), 4.37 (s, 2H, CH_2), 6.05 (t, ^4J (CH_2, 2-H) = 1.3 Hz, 1H, 2-H), 7.31 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 7.9 Hz, 2H, 2′-H and 6′-H), 7.33 (overlapped, 1H, 4′-H), 7.37 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 7.9 Hz, 2H, 3′-H and 5′-H), 7.38 (s, 1H, 5-H), 7.53 (s, 1H, 8-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3 (6-CH_3), 20.4 (7-CH_3), 34.7 (CH_2), 105.8 (C-2), 111.2 (C-5), 119.2 (C-8), 127.4 (C-4′), 128.6 (C-4a), 128.8 (C-2′ and C-6′), 128.9 (C-3′ and C-5′), 129.6 (C-6), 132.1 (C-7), 133.1 (C-3), 135.1 (C-1′), 147.1 (C-8a), 156.4 (C-9a). MS (ESI) m/z (%): 315 (10) $[M + Na]^+$, 293 (15) $[M + 1]^+$.

*3-Benzyl-6,7-dichlorothiazolo[3,2-a]benzimidazole (**3c**).* According to general procedure II, a mixture of K_2CO_3 (277 mg, 2 mmol),



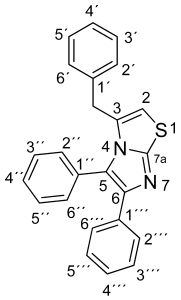
1-(4-methylbenzenesulfonate)-3-phenyl-2-propyne (**1a**) (286 mg, 1 mmol), and 5,6-dichloro-2-mercaptobenzimidazole (**2c**) (219 mg, 1 mmol) was reacted in dry *i*-PrOH (2 mL) in a sealed vial at 70 °C for 15 h. Flash chromatography over silica gel (petroleum ether/EtOAc = 2:1) gave **3c** as a yellow solid in 70% yield (232 mg, 0.70 mmol). Mp: 199—201 °C. R_f: 0.33 (petroleum ether/EtOAc = 2:1). IR (ATR) $\tilde{\nu}$: 3028 (CH), 1494 (C═N), 1447, 1409, 1273, 1135, 963, 849, 752, 654 (C−S), 526 cm^{-1}. UV (MeCN) λ_{max} (log ε): 293 (3.88), 257 (4.42), 248 (4.41), 206 (4.43) nm. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.55 (s, 2H, CH_2), 6.76 (t, ^4J (CH_2, 2-H) = 1.3 Hz, 1H, 2-H), 7.30 (overlapped, 1H, 4′-H), 7.35 (overlapped, 4H, 2′-H, 3′-H, 5′-H and 6′-H), 7.94 (overlapped, 2H, 5-H and 8-H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 34.9 (CH_2), 108.7 (C-2), 113.4 (C-5), 119.3 (C-8), 122.5 (C-6), 125.7 (C-7), 127.1 (C-4′), 128.6 (C-2′ and C-6′), 128.7 (C-4a), 128.9 (C-3′ and C-5′), 133.1 (C-3), 135.7 (C-1′), 147.1 (C-8a), 159.2 (C-9a). MS (ESI) m/z (%): 356 (55) $[M + Na]^+$, 333 (15) $[M]^+$. HRMS (ESI) for $C_{16}H_{10}Cl_2N_2SNa$: calcd: 356.9806; found: 356.9792.

*3-Benzylimidazo[2,1-b]thiazole (**3d**).* According to general procedure II, a mixture of K_2CO_3 (277 mg, 2 mmol), 1-(4-methylbenzenesulfonate)-3-phenyl-2-propyne (**1a**) (286 mg, 1 mmol), and



2-mercaptoimidazole (**2d**) (100 mg, 1 mmol) was reacted in dry *i*-PrOH (2 mL) in a sealed vial at 70 °C for 15 h. Flash chromatography over silica gel (petroleum ether/EtOAc = 1:1) gave **3d** as a yellow solid in 86% yield (184 mg, 0.86 mmol). Mp: 48—50 °C. R_f: 0.33 (petroleum ether/EtOAc = 1:1). IR (ATR) $\tilde{\nu}$: 3105 (CH), 3027 (CH), 1494 (C═N), 1327, 1289, 1128, 1028, 917, 702 (C−S) cm^{-1}. UV (MeCN) λ_{max} (log ε): 254 (3.65) nm. ^{1}H NMR (300 MHz, CD_3COCD_3): δ 4.19 (s, 2H, CH_2), 6.77 (t, ^4J (CH_2, 2-H) = 1.3 Hz, 1H, 2-H), 7.19 (t like, ^3J (5-H, 6-H) = 1.3 Hz, 1H, 6-H), 7.28 (overlapped, 1H, 4′-H), 7.34 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 6.4 Hz, 2H, 3′-H and 5′-H), 7.36 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 6.4 Hz, 2H, 2′-H and 6′-H), 7.45 (d like, ^3J (5-H, 6-H) = 1.3 Hz, 1H, 5-H). ^{13}C NMR (75 MHz, CD_3COCD_3): δ 34.4 (CH_2), 108.9 (C-2), 112.4 (C-5), 128.0 (C-4′), 129.7 (C-3′ and C-5′), 129.8 (C-2′ and C-6′), 132.4 (C-3), 135.2 (C-6), 136.8 (C-1′), 149.8 (C-7a). MS (ESI) m/z (%): 237 (22) $[M + Na]^+$, 215 (100) $[M + 1]^+$, 201 (6). HRMS (ESI) for $C_{12}H_{11}N_2S$: calcd: 215.0637; found: 215.0629.

*3-Benzyl-5,6-diphenylimidazo[2,1-b]thiazole (**3e**).* According to general procedure II, a mixture of K_2CO_3 (277 mg, 2 mmol),



1-(4-methylbenzenesulfonate)-3-phenyl-2-propyne (**1a**) (286 mg, 1 mmol), and 4,5-diphenyl-2-mercaptoimidazole (**2e**) (252 mg, 1 mmol) was reacted in dry *i*-PrOH (2 mL) in a sealed vial at 70 °C for 15 h. Flash chromatography over silica gel (petroleum ether/EtOAc = 1:1) gave **3e** as a yellow solid in 86% yield (314 mg, 0.86 mmol). Mp: 212—214 °C. R_f: 0.32 (petroleum ether/EtOAc = 2:1). IR (ATR) $\tilde{\nu}$: 3110 (CH), 3027 (CH), 2920 (CH), 1546 (C═N), 1477, 1366, 1281, 1130, 960, 800, 698 (C−S) cm^{-1}. UV (MeCN) λ_{max} (log ε): 254 (4.25) nm. ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.62 (s, 2H, CH_2), 6.63 (t, ^4J (CH_2, 2-H) = 1.0 Hz, 1H, 2-H), 6.76—6.81 (overlapped, 2H, 2′-H and 6′-H), 7.13 (tt like, ^3J (4‴-H, 3‴-H or 5‴-H) = 6.4 Hz, ^4J (4‴-H, 2‴-H or 6‴-H) = 1.4 Hz, 1H, 4‴-H), 7.17 (t like, ^3J (4′-H, 3′-H or 5′-H) = 8.1 Hz, 1H, 4′-H), 7.18 (overlapped, 2H, 3′-H and 5′-H), 7.19 (overlapped, 2H, 3‴-H, 5‴-H), 7.36 (d like, ^3J (2″-H, 3″-H or 5″-H, 6″-H) = 8.5 Hz, 2H, 2″-H and 6″-H), 7.37 (d like, ^3J (2‴-H, 3‴-H or 5‴-H, 6‴-H) = 8.8 Hz, 2H, 2‴-H, 6‴-H), 7.39 (t like, ^3J (2″-H, 3″-H or 5″-H, 6″-H) = 8.5 Hz, 2H, 3″-H and 5″-H), 7.47 (tt like, ^3J (4″-H, 3″-H or 5″-H) = 7.0 Hz, ^4J (4″-H, 2″-H or 6″-H) = 1.5 Hz, 1H, 4″-H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 34.5 (CH_2), 109.7 (C-2), 123.4 (C-5), 126.4 (C-6‴), 126.5 (C-4′), 126.6 (C-4‴), 128.0 (C-3‴ and C-5‴), 128.1 (C-2′ and C-6′), 128.2 (C-3′ and C-5′), 128.3 (C-3″ and C-5″), 129.0 (C-4″), 129.7 (C-1″), 131.8 (C-2″ and C-6″), 132.6 (C-3), 134.4 (C-1‴), 135.8 (C-1′), 142.3 (C-6), 148.7 (C-7a). MS (ESI) m/z (%): 389 (25) $[M + Na]^+$, 367 (100) $[M + 1]^+$. HRMS (ESI) for $C_{24}H_{19}N_2S$: calcd: 367.1263; found: 367.1264.

*3-Benzylthiazolo[3,2-a]perimidine (**3f**).* According to general procedure II, a mixture of K_2CO_3 (277 mg, 2 mmol), 1-(4-methylbenzenesulfonate)-3-phenyl-2-propyne (**1a**) (286 mg, 1 mmol), and 2-mercaptoperimidine (**2f**) (200 mg, 1 mmol) was reacted in dry *i*-PrOH (2 mL) in a sealed vial at 70 °C for 15 h. Flash chromatography over silica gel (petroleum ether/EtOAc = 4:1) gave **3f** as a

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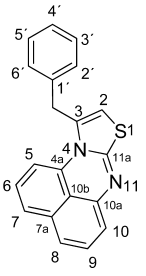
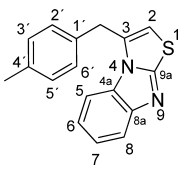


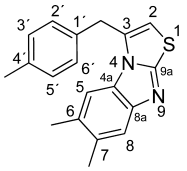
yellow solid in 74% yield (232 mg, 0.74 mmol). Mp: 257—259 °C. R_f: 0.30 (petroleum ether/EtOAc = 4:1). IR (ATR) $\tilde{\nu}$: 3113 (CH), 3026 (CH), 2897 (CH), 1603 (C═N), 1452, 1376, 1180, 1099, 963, 850, 738, 659 (C−S), 530 cm^{-1}. UV (MeCN) λ_{max} (log ε): 325 (4.17), 257 (4.33), 231 (4.22) nm. ^1H NMR (300 MHz, CD_3COCD_3): δ 4.42 (brs, 2H, CH_2), 6.08 (t, ^4J (CH_2, 2-H) = 1.0 Hz, 1H, 2-H), 6.60 (dd, ^3J (9-H, 10-H) = 7.4 Hz, ^4J (8-H, 10-H) = 1.0 Hz, 1H, 10-H), 7.02 (t like, ^3J (6-H, 5-H or 7-H) = 7.9 Hz, 1H, 6-H), 7.06 (dd, ^3J (8-H, 9-H) = 8.1 Hz, ^4J (8-H, 10-H) = 1.0 Hz, 1H, 8-H), 7.07 (dd, ^3J (5-H, 6-H) = 7.9 Hz, ^4J (5-H, 7-H) = 1.5 Hz, 1H, 5-H), 7.18 (dd, ^3J (6-H, 7-H) = 7.7 Hz, ^4J (5-H, 7-H) = 1.5 Hz, 1H, 7-H), 7.19 (t like, ^3J (8-H, 9-H) = 8.1 Hz, ^3J (9-H, 10-H) = 7.4 Hz, 1H, 9-H), 7.23—7.30 (overlapped, 1H, 4′-H), 7.32—7.40 (overlapped, 4H, 2′-H, 3′-H, 5′-H and 6′-H). ^{13}C NMR (75 MHz, CD_3COCD_3): δ 38.3 (CH_2), 104.2 (C-2), 106.7 (C-5), 114.3 (C-10), 119.7 (C-8), 121.9 (C-10b), 122.4 (C-7), 127.8 (C-6), 127.9 (C-4′), 129.5 (C-9), 129.6 (C-3′ and C-5′), 129.7 (C-2′ and C-6′), 137.1 (C-7a), 137.6 (C-4a), 138.1 (C-1′), 138.7 (C-3), 144.4 (C-10a), 162.9 (C-11a). MS (EI, 70 eV) m/z (%): 314 (18) $[M]^+$, 281 (4), 199 (5). HRMS (EI, M^+) for $C_{20}H_{14}N_2S$: calcd: 314.0878; found: 314.0880.

*3-(4-Methylbenzyl)thiazolo[3,2-a]benzimidazole (**3g**).* According to general procedure II, a mixture of K_2CO_3 (277 mg, 2 mmol),



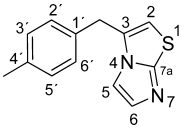
1-(4-methylbenzenesulfonate)-3-(4-methylphenyl)-2-propyne (**1b**) (300 mg, 1 mmol), and 2-mercaptonbenzimidazole (**2a**) (150 mg, 1 mmol) was reacted in dry *i*-PrOH (2 mL) in a sealed vial at 70 °C for 15 h. Flash chromatography over silica gel (petroleum ether/EtOAc = 3:1) gave **3g** as a yellow solid in 66% yield (184 mg, 0.66 mmol). Mp: 151—152 °C. R_f: 0.32 (petroleum ether/EtOAc = 3:1). IR (ATR) $\tilde{\nu}$: 2920 (CH), 1570 (C═N), 1513, 1463, 1210, 1170, 1115, 1013, 916, 721, 568 (C−S) cm^{-1}. UV (MeCN) λ_{max} (log ε): 278 (4.13), 249 (4.33), 241 (4.35) nm. ^1H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 4.36 (s, 2H, CH_2), 6.14 (t, ^4J (CH_2, 2-H) = 1.5 Hz, 1H, 2-H), 7.18 (overlapped, 4H, 2′-H, 3′-H, 5′-H and 6′-H), 7.19 (ddd, ^3J (5-H, 6-H) = 8.2 Hz, ^3J (6-H, 7-H) = 7.3 Hz, ^4J (6-H, 8-H) = 1.3 Hz, 1H, 6-H), 7.33 (ddd, ^3J (6-H, 7-H) = 7.3 Hz, ^3J (7-H, 8-H) = 8.3 Hz, ^4J (5-H, 7-H) = 1.3 Hz, 1H, 7-H), 7.63 (dd, ^3J (5-H, 6-H) = 8.2 Hz, ^4J (5-H, 7-H) = 1.3 Hz, 1H, 5-H), 7.78 (dd, ^3J (7-H, 8-H) = 8.3 Hz, ^3J (6-H, 8-H) = 1.3 Hz, 1H, 8-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1 (CH_3), 34.2 (CH_2), 106.4 (C-2), 111.0 (C-5), 119.1 (C-8), 120.7 (C-6), 123.2 (C-7), 128.6 (C-2′ and C-6′), 129.7 (C-3′ and C-5′), 130.0 (C-4a), 131.7 (C-1′), 133.5 (C-3), 137.2 (C-4′), 148.3 (C-8a), 157.4 (C-9a). MS (EI, 70 eV) m/z (%): 278 (100) $[M]^+$, 263 (7) $[M—CH_3]^+$, 245 (7), 204 (4), 129 (8). HRMS (EI, M^+) for $C_{17}H_{14}N_2S$: calcd: 278.0878; found: 278.0876.

*3-(4-Methylbenzyl)-6,7-dimethylthiazolo[3,2-a]benzimidazole (**3h**).* According to general procedure II, a mixture of K_2CO_3 (277 mg, 2 mmol), 1-(4-methylbenzenesulfonate)-3-(4-methylphenyl)-2-propyne (**1b**) (300 mg, 1 mmol), and 5,6-dimethyl-2-mercaptobenzimidazole (**2b**) (178 mg, 1 mmol) was reacted in dry *i*-PrOH (2 mL) in a sealed vial at 70 °C for 15 h. Flash chromatography over silica gel (petroleum ether/EtOAc = 2:1) gave **3h** as a yellow solid in 92% yield



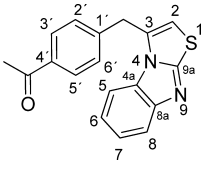
(283 mg, 0.92 mmol). Mp: 137—138 °C. R_f: 0.26 (petroleum ether/EtOAc = 2:1). IR (ATR) $\tilde{\nu}$: 3017 (CH), 2917 (CH), 1589 (C═N), 1483, 1425, 1340, 1255, 1020, 838, 753, 669 (C−S) cm^{-1}. UV (MeCN) λ_{max} (log ε): 280 (4.17), 246 (4.38) nm. ^1H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H, 6-CH_3), 2.35 (s, 3H, 4′-CH_3), 3.38 (s, 3H, 7-CH_3), 4.33 (brs, 2H, CH_2), 6.04 (s, 1H, 2-H), 7.19 (overlapped, 4H, 2′-H, 3′-H, 5′-H and 6′-H), 7.40 (s, 1H, 5-H), 7.53 (s, 1H, 8-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3 (6-CH_3), 20.4 (4′-CH_3), 21.1 (7-CH_3), 34.3 (CH_2), 105.6 (C-2), 111.3 (C-5), 119.2 (C-8), 128.6 (C-4a), 128.7 (C-2′ and C-6′), 129.5 (C-6), 129.6 (C-3′ and C-5′), 131.9 (C-4′), 132.1 (C-7), 133.4 (C-3), 137.1 (C-1′), 147.1 (C-8a), 156.4 (C-9a). MS (EI, 70 eV) m/z (%): 306 (100) $[M]^+$, 291 (15) $[M—CH_3]^+$, 273 (3), 129 (8). HRMS (EI, M^+) for $C_{19}H_{18}N_2S$: calcd: 306.1191; found 306.1186.

*3-(4-Methylbenzyl)imidazo[2,1-b]thiazole (**3i**).* According to general procedure II, a mixture of K_2CO_3 (277 mg, 2 mmol),



1-(4-methylbenzenesulfonate)-3-(4-methylphenyl)-2-propyne (**1b**) (300 mg, 1 mmol), and 2-mercaptoimidazole (**2d**) (100 mg, 1 mmol) was reacted in dry *i*-PrOH (2 mL) in a sealed vial at 70 °C for 15 h. Flash chromatography over silica gel (petroleum ether/EtOAc = 2:1) gave **3i** as a yellow solid in 79% yield (180 mg, 0.79 mmol). Mp: 67—68 °C. R_f: 0.34 (petroleum ether/EtOAc = 1:1). IR (ATR) $\tilde{\nu}$: 3120 (CH), 2931 (CH), 1587 (C═N), 1511, 1460, 1323, 1125, 1035, 912, 808, 740, 687 (C−S) cm^{-1}. UV (MeCN) λ_{max} (log ε): 255 (3.79) nm. ^1H NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3H, CH_3), 4.00 (brs, 2H, CH_2), 6.36 (t, ^4J (CH_2, 2-H) = 1.0 Hz, 1H, 2-H), 7.14 (overlapped, 4H, 2′-H, 3′-H, 5′-H and 6′-H), 7.22 (d, ^3J (5-H, 6-H) = 1.2 Hz, 1H, 5-H), 7.28 (t like, ^3J (5-H, 6-H) = 1.2 Hz, 1H, 6-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0 (CH_3), 33.9 (CH_2), 108.3 (C-2), 110.9 (C-5), 128.6 (C-2′ and C-6′), 129.6 (C-3′ and C-5′), 131.0 (C-3), 131.6 (C-1′), 134.6 (C-6), 137.1 (C-4′), 149.7 (C-7a). MS (ESI) m/z (%): 229 (100) $[M + 1]^+$. HRMS (ESI) for $C_{13}H_{13}N_2S$: calcd: 229.0794; found: 229.0778.

*3-[(4-Acetylphenyl)methyl]thiazolo[3,2-a]benzimidazole (**3j**).* According to general procedure II, a mixture of K_2CO_3 (277 mg,



2 mmol), 1-(4-methylbenzenesulfonate)-3-(4-acetophenyl)-2-propyne (**1c**) (328 mg, 1 mmol), and 2-mercaptobenzimidazole (**2a**) (150 mg, 1 mmol) was reacted in dry *i*-PrOH (2 mL) in a sealed vial at 70 °C for 15 h. Flash chromatography over silica gel (petroleum ether/EtOAc = 1:1) gave **3j** as a yellow solid in 83% yield (253 mg, 0.83 mmol). Mp: 173—174 °C. R_f: 0.13 (petroleum ether/EtOAc = 1:1). IR (ATR) $\tilde{\nu}$: 3119 (CH), 1676 (C═O), 1605 (C═N), 1450, 1412, 1305, 1225, 1017, 839, 765, 694 (C−S), 616, 580 cm^{-1}. UV (MeCN) λ_{max} (log ε): 279 (4.13), 243 (4.55), 203 (4.68) nm. ^1H NMR (500 MHz, $CDCl_3$): δ 2.59 (s, 3H, CH_3), 4.47 (brs, 2H, CH_2), 6.21 (t, ^4J (CH_2, 2-H) = 1.3 Hz, 1H, 2-H), 7.14 (ddd, ^3J (5-H, 6-H) = 8.2 Hz, ^3J (6-H, 7-H) = 7.3 Hz, ^4J (6-H, 8-H) = 0.9 Hz, 1H, 6-H), 7.33 (ddd, ^3J (6-H, 7-H) = 7.3 Hz, ^3J (7-H, 8-H) = 8.2 Hz, ^4J (5-H, 7-H) = 1.1 Hz, 1H, 7-H), 7.39 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 8.2 Hz, 2H, 2′-H and 6′-H), 7.53 (brd, ^3J (5-H, 6-H) = 8.2 Hz, 1H, 5-H), 7.78

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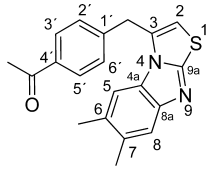
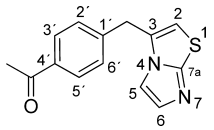
(brd, ^3J (7-H, 8-H) = 8.2 Hz, 1H, 8-H), 7.96 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 8.2 Hz, 2H, 3′-H and 5′-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.6 (CH_3), 34.5 (CH_2), 106.9 (C-2), 110.7 (C-5), 119.3 (C-8), 120.8 (C-6), 123.4 (C-7), 128.9 (C-2′ and C-6′), 129.1 (C-3′ and C-5′), 129.9 (C-4a), 131.9 (C-3), 136.4 (C-1′), 140.3 (C-4′), 148.5 (C-8a), 157.4 (C-9a). MS (EI, 70 eV) m/z (%): 306 (100) $[M]^+$, 291 (30) $[M—CH_3]^+$, 263 (74) $[M—COCH_3]^+$, 204 (10), 187 (7), 145 (22), 131 (21). HRMS (EI, M^+) for $C_{18}H_{14}N_2OS$: calcd: 306.0827; found: 306.0857.

*3-[(4-Acetylphenyl)methyl]-6,7-dimethylthiazolo[3,2-a]-benzimidazole (**3k**).* According to general procedure II, a mixture of



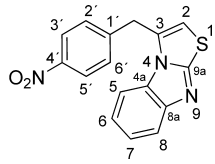
K_2CO_3 (277 mg, 2 mmol), 1-(4-methylbenzenesulfonate)-3-(4-acetophenyl)-2-propyne (**1c**) (328 mg, 1 mmol), and 2-mercapto-5,6-dimethylbenzimidazole (**2b**) (178 mg, 1 mmol) was reacted in dry *i*-PrOH (2 mL) in a sealed vial at 70 °C for 15 h. Flash chromatography over silica gel (petroleum ether/EtOAc = 1:1) gave **3k** as a yellow solid in 81% yield (271 mg, 0.81 mmol). Mp: 165—166 °C. R_f: 0.19 (petroleum ether/EtOAc = 1:1). IR (ATR) $\tilde{\nu}$: 2895 (CH), 1673 (C═O), 1608 (C═N), 1455, 1358, 1263, 1167, 993, 852, 713, 637 (C−S), 585 cm^{-1}. UV (MeCN) λ_{max} (log ε): 280 (4.11), 246 (4.54), 203 (4.65) nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, 6-CH_3), 2.36 (s, 3H, 7-CH_3), 2.59 (s, 3H, CH_3CO), 4.43 (s, 2H, CH_2), 6.11 (t, ^4J (CH_2, 2-H) = 1.3 Hz, 1H, 2-H), 7.29 (s, 1H, 5-H), 7.40 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 8.2 Hz, 2H, 2′-H and 6′-H), 7.52 (s, 1H, 8-H), 7.96 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 8.2 Hz, 2H, 3′-H and 5′-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3 (7-CH_3), 20.4 (6-CH_3), 26.6 (CH_3CO), 34.5 (CH_2), 106.2 (C-2), 110.9 (C-5), 119.3 (C-8), 127.4 (C-7), 129.0 (C-2′ and C-6′), 129.1 (C-3′ and C-5′), 129.7 (C-6), 131.9 (C-3), 132.3 (C-4a), 136.4 (C-4′), 140.6 (C-1′), 147.1 (C-8a), 156.2 (C-9a), 197.4 (CO). MS (ESI) m/z (%): 335 (100) $[M + 1]^+$. HRMS (ESI) for $C_{20}H_{19}N_2OS$: calcd: 335.1213; found: 335.1192.

*3-[(4-Acetylphenyl)methyl]imidazo[2,1-b]thiazole (**3l**).* According to general procedure II, a mixture of K_2CO_3 (277 mg, 2 mmol),



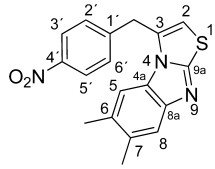
1-(4-methylbenzenesulfonate)-3-(4-acetophenyl)-2-propyne (**1c**) (328 mg, 1 mmol), and 2-mercaptoimidazole (**2d**) (100 mg, 1 mmol) was reacted in dry *i*-PrOH (2 mL) in a sealed vial at 70 °C for 15 h. Flash chromatography over silica gel (petroleum ether/EtOAc = 1:3) gave **3l** as a yellow solid in 77% yield (198 mg, 0.77 mmol). Mp: 131—132 °C. R_f: 0.32 (petroleum ether/EtOAc = 1:3). IR (ATR) $\tilde{\nu}$: 3134 (CH), 3098 (CH), 1676 (C═O), 1603 (C═N), 1464, 1420, 1195, 1081, 866, 706, 679 (C−S) cm^{-1}. UV (MeCN) λ_{max} (log ε): 247 (4.44) nm. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.59 (s, 3H, CH_3), 4.11 (s, 2H, CH_2), 6.42 (s, 1H, 2-H), 7.18 (brd, ^3J (5-H, 6-H) = 1.4 Hz, 1H, 5-H), 7.26 (t like, ^3J (5-H, 6-H) = 1.4 Hz, 1H, 6-H), 7.34 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 8.3 Hz, 2H, 2′-H and 6′-H), 7.93 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 8.3 Hz, 2H, 3′-H and 5′-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.6 (CH_3), 34.2 (CH_2), 109.0 (C-2), 110.8 (C-5), 128.9 (C-2′ and C-6′), 129.0 (C-3′ and C-5′), 129.6 (C-3), 134.8 (C-6), 136.4 (C-4′), 140.1 (C-1′), 149.6 (C-7a), 197.4 (CO). MS (EI, 70 eV) m/z (%): 256 (100) $[M]^+$, 241 (100) $[M—CH_3]^+$, 213 (49) $[M—COCH_3]^+$, 184 (15), 154 (7), 120 (13). HRMS (EI, M^+) for $C_{14}H_{12}N_2OS$: calcd: 256.0670; found: 256.0680.

*3-(4-Nitrobenzyl)thiazolo[3,2-a]benzimidazole (**3m**).*[20b] According to general procedure II, a mixture of K_2CO_3 (277 mg, 2 mmol), 1-(4-methylbenzenesulfonate)-3-(4-nitrophenyl)-2-propyne (**1d**) (331 mg,



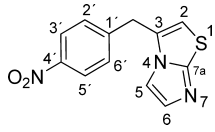
1 mmol), and 2-mercaptobenzimidazole (**2a**) (150 mg, 1 mmol) was reacted in dry *i*-PrOH (2 mL) in a sealed vial at 70 °C for 15 h. Flash chromatography over silica gel (petroleum ether/EtOAc = 1:1) gave **3m** as a yellow solid in 65% yield (200 mg, 0.65 mmol). Mp: 191—192 °C (ref 20b, 191—192 °C). R_f: 0.15 (petroleum ether/EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.52 (s, 2H, CH_2), 6.26 (s, 1H, 2-H), 7.15 (ddd, ^3J (5-H, 6-H) = 8.2 Hz, ^3J (6-H, 7-H) = 7.3 Hz, ^4J (6-H, 8-H) = 1.0 Hz, 1H, 6-H), 7.34 (ddd, ^3J (6-H, 7-H) = 7.3 Hz, ^3J (7-H, 8-H) = 8.2 Hz, ^4J (5-H, 7-H) = 1.0 Hz, 1H, 7-H), 7.47 (overlapped, 1H, 5-H), 7.49 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 8.6 Hz, 2H, 2′-H and 6′-H), 7.78 (brd, ^3J (7-H, 8-H) = 8.2 Hz, 1H, 8-H), 8.22 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 8.6 Hz, 2H, 3′-H and 5′-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.3 (CH_2), 107.4 (C-2), 110.5 (C-5), 119.4 (C-8), 120.9 (C-6), 123.5 (C-7), 124.3 (C-3′ and C-5′), 129.5 (C-2′ and C-6′), 129.8 (C-4a), 131.0 (C-3), 142.5 (C-1′), 147.4 (C-4′), 148.5 (C-8a), 157.4 (C-9a). MS (EI, 70 eV) m/z (%): 309 (100) $[M]^+$, 263 (30) $[M—NO_2]^+$, 204 (7), 187 (5).

*3-(4-Nitrobenzyl)-6,7-dimethylthiazolo[3,2-a]benzimidazole (**3n**).* According to general procedure II, a mixture of K_2CO_3 (277 mg,



2 mmol), 1-(4-methylbenzenesulfonate)-3-(4-nitrophenyl)-2-propyne (**1d**) (331 mg, 1 mmol), and 5,6-dimethyl-2-mercaptobenzimidazole (**2b**) (178 mg, 1 mmol) was reacted in dry *i*-PrOH (2 mL) in a sealed vial at 70 °C for 15 h. Flash chromatography over silica gel (petroleum ether/EtOAc = 1:1) gave **3n** as a yellow solid in 40% yield (131 mg, 0.40 mmol). Mp: 185—187 °C. R_f: 0.14 (petroleum ether/EtOAc = 2:1). IR (ATR) $\tilde{\nu}$: 2919 (CH), 1602 (C═N), 1516, 1453, 1343, 1166, 1104, 997, 876, 836, 707 (C−S) cm^{-1}. UV (MeCN) λ_{max} (log ε): 279 (4.16), 249 (4.25), 214 (4.40) nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, 6-CH_3), 2.40 (s, 3H, 7-CH_3), 4.40 (s, 2H, CH_2), 6.15 (t, ^4J (CH_2, 2-H) = 1.3 Hz, 1H, 2-H), 7.24 (s, 1H, 5-H), 7.48 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 8.6 Hz, 2H, 2′-H and 6′-H), 7.53 (s, 1H, 8-H), 8.23 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 8.6 Hz, 2H, 3′-H and 5′-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.3 (6-CH_3), 20.5 (7-CH_3), 34.3 (CH_2), 106.7 (C-2), 110.8 (C-5), 119.4 (C-8), 124.2 (C-3′ and C-5′), 128.3 (C-4a), 129.6 (C-2′ and C-6′), 129.9 (C-6), 131.0 (C-3), 132.5 (C-7), 142.7 (C-1′), 147.1 (C-8a), 147.4 (C-4′), 156.1 (C-9a). MS (EI, 70 eV) m/z (%): 337 (47) $[M]^+$, 291 (30) $[M—NO_2]^+$, 115 (5). HRMS (EI, M^+) for $C_{18}H_{15}N_3O_2S$: calcd: 337.0885; found: 337.0879.

*3-(4-Nitrobenzyl)imidazo[2,1-b]thiazole (**3o**).* According to general procedure II, a mixture of K_2CO_3 (277 mg, 2 mmol),



1-(4-methylbenzenesulfonate)-3-(4-nitrophenyl)-2-propyne (**1d**) (331 mg, 1 mmol), and 2-mercaptoimidazole (**2d**) (100 mg, 1 mmol) was reacted in dry *i*-PrOH (2 mL) in a sealed vial at 70 °C for 15 h. Flash chromatography over silica gel (petroleum ether/EtOAc = 1:3) gave **3o** as a pale-brown solid in 46% yield (118 mg, 0.46 mmol). Mp: 156—157 °C. R_f: 0.36 (petroleum ether/EtOAc = 3:1). IR (ATR) $\tilde{\nu}$: 3136 (CH), 3075 (CH), 1601 (C═N), 1342, 1208, 1119, 856, 711, 686 (C−S) cm^{-1}. UV (MeCN) λ_{max} (log ε): 263 (4.18)nm. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.18 (s, 2H, CH_2), 6.47 (brd, ^3J (CH_2, 2-H) = 1.0 Hz,

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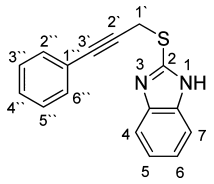
1H, 2-H), 7.17 (brd, ^3J (5-H, 6-H) = 1.5 Hz, 1H, 5-H), 7.26 (t like, ^3J (5-H, 6-H) = 1.5 Hz, 1H, 6-H), 7.43 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 8.6 Hz, 2H, 2′-H and 6′-H), 8.21 (d like, ^3J (2′-H, 3′-H or 5′-H, 6′-H) = 8.6 Hz, 2H, 3′-H and 5′-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.9 (CH_2), 109.6 (C-2), 110.6 (C-5), 124.2 (C-3′ and C-5′), 128.8 (C-3), 129.6 (C-2′ and C-6′), 135.0 (C-6), 142.3 (C-4′), 147.4 (C-1′), 149.6 (C-7a). MS (EI, 70 eV) m/z (%): 259 (100) $[M]^+$, 213 (100) $[M—NO_2]^+$, 187 (14), 154 (6), 115 (5), 89 (5). HRMS (EI, M^+) for $C_{12}H_9N_3O_2S$: calcd: 259.0415; found: 259.0414.

*2-[(3-Phenyl-2-propyn-1-yl)thio]-1H-benzimidazole (**4a**).*[20b] A mixture of 1-(4-methylbenzenesulfonate)-3-phenyl-2-propyne (**1a**)



(286 mg, 1 mmol) and 2-mercaptobenzimidazole (**2a**) (150 mg, 1 mmol) was reacted in dry *i*-PrOH (2 mL) in a sealed vial at 70 °C for 15 h. Flash chromatography over silica gel (petroleum ether/EtOAc = 2:1) gave **4a** as a colorless solid in 30% yield (78 mg, 0.30 mmol). Mp: 145—146 °C (ref 20b, 144—145 °C). R_f: 0.14 (petroleum ether/EtOAc = 2:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.26 (2H, CH_2), 6.00 (br, 1H, NH), 7.16—7.28 (m, 5H, aromatic H), 7.27—7.35 (m, 2H, aromatic H), 7.50—7.58 (m, 2H, aromatic H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.7, 84.0, 84.4, 114.4, 122.3, 122.9, 128.3, 128.6, 131.7, 138.8, 148.4. MS (EI, 70 eV) m/z (%): 264 (72) $[M]^+$, 231 (39), 185 (12), 166 (14), 149 (17), 115 (22), 89 (28).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for compounds **1a—d**, **3a—o**, and **4a**; crystal X-ray structure of **3a**; 1D NOESY spectrum of **3g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Ali, A. R.; El-Bendary, E. R.; Ghaly, M. A.; Shehata, I. A. *Eur. J. Med. Chem.* **2014**, *75*, 492. (b) Andreani, A.; Burnelli, S.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Varoli, L.; Calonghi, N.; Cappadone, C.; Voltattorni, M.; Zini, M.; Stefanelli, C.; Masotti, L.; Shoemaker, R. H. *J. Med. Chem.* **2008**, *51*, 7508. (c) Gürsoy, E.; Güzeldemirci, N. U. *Eur. J. Med. Chem.* **2007**, *42*, 320. (d) Andreani, A.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Garaliene, V.; Welsh, W.; Arora, S.; Farruggia, G.; Masotti, L. *J. Med. Chem.* **2005**, *48*, 5604. (e) Andreani, A.; Rambaldi, M.; Locatelli, A.; Bossa, R.; Fraccari, A.; Galatulas, I. *J. Med. Chem.* **1992**, *35*, 4634.

(2) Andreani, A.; Rambaldi, M.; Locatelli, A.; Isetta, A. M. *Eur. J. Med. Chem.* **1991**, *26*, 335.

(3) Lantos, I.; Bender, P. E.; Razgaitis, K. A.; Sutton, B. M.; DiMartino, M. J.; Griswold, D. E.; Walz, D. T. *J. Med. Chem.* **1984**, *27*, 72.

(4) Budriesi, R.; Ioan, P.; Locatelli, A.; Cosconati, S.; Leoni, A.; Ugenti, M. P.; Andreani, A.; Di Toro, R.; Bedini, A.; Spampinato, S.; Marinelli, L.; Novellino, E.; Chiarini, A. *J. Med. Chem.* **2008**, *51*, 1592.

(5) Güzeldemirci, N. U.; Küçükbasmacı, Ö. *Eur. J. Med. Chem.* **2010**, *45*, 63.

(6) Scribner, A.; Meitz, S.; Fisher, M.; Wyvratt, M.; Leavitt, P.; Liberator, P.; Gurnett, A.; Brown, C.; Mathew, J.; Thompson, D.; Schmatz, D.; Biftu, T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5263.

(7) Raeymaekers, A. H. M.; Allewijn, F. T. N.; Vandenberk, J.; Demoen, P. J. A.; Van Offenwert, T. T. T.; Janssen, P. A. J. *J. Med. Chem.* **1966**, *9*, 545.

(8) Joshi, K. C.; Pathak, V. N.; Arya, P. *Agric. Biol. Chem.* **1977**, *41*, 543.

(9) Jin, J.; Wang, Y.; Shi, D.; Wang, F.; Davis, R. S.; Jin, Q.; Fu, W.; Foley, J. J.; Webb, E. F.; Dehaas, C. J.; Berlanga, M.; Burman, M.; Sarau, H. M.; Morrow, D. M.; Rao, P.; Kallal, L. A.; Moore, M. L.; Rivero, R. A.; Palovich, M.; Salmon, M.; Belmonte, K. E.; Busch-Petersen, J. *J. Med. Chem.* **2008**, *51*, 4866.

(10) Pietrancosta, N.; Moumen, A.; Dono, R.; Lingor, P.; Planchamp, V.; Lamballe, F.; Bähr, M.; Kraus, J.-L.; Maina, F. *J. Med. Chem.* **2006**, *49*, 3645.

(11) Venkatesan, A. M.; Gu, Y.; Dos Santos, O.; Abe, T.; Agarwal, A.; Yang, Y.; Petersen, P. J.; Weiss, W. J.; Mansour, T. S.; Nukaga, M.; Hujer, A. M.; Bonomo, R. A.; Knox, J. R. *J. Med. Chem.* **2004**, *47*, 6556.

(12) Metaye, T.; Millet, C.; Kraimps, J. L.; Saunier, B.; Barbier, J.; Begon, F. *Biochem. Pharmacol.* **1992**, *43*, 1507.

(13) Budriesi, R.; Ioan, P.; Leoni, A.; Pedemonte, N.; Locatelli, A.; Micucci, M.; Chiarini, A.; Galietta, L. J. V. *J. Med. Chem.* **2011**, *54*, 3885.

(14) Milne, J. C.; Lambert, P. D.; Schenk, S.; Carney, D. P.; Smith, J. J.; Gagne, D. J.; Jin, L.; Boss, O.; Perni, R. B.; Vu, C. B.; Bemis, J. E.; Xie, R.; Disch, J. S.; Ng, P. Y.; Nunes, J. J.; Lynch, A. V.; Yang, H.; Galonek, H.; Israelian, K.; Choy, W.; Iffland, A.; Lavu, S.; Medvedik, O.; Sinclair, D. A.; Olefsky, J. M.; Jirousek, M. R.; Elliott, P. J.; Westphal, C. H. *Nature* **2007**, *450*, 712.

(15) Thienpont, D.; Vanparijs, O. F. J.; Raeymaekers, A. H. M.; Vandenberk, J.; Demoen, P. J. A.; Allewijn, F. T. N.; Marsboom, R. P. H.; Niemegeers, C. J. E.; Schellekens, K. H. L.; Janssen, P. A. J. *Nature* **1966**, *209*, 1084.

(16) (a) Dillman, R. O.; Ryan, K. P.; Dillman, J. B.; Shawler, D. L.; Maguire, R. *Mol. Biother.* **1992**, *4*, 10. (b) Fenichel, R. L.; Dheer, S. K.; Grant, N. H.; Scott, D. P.; Bloom, R.; Gregory, F. J. *J. Immunopharmacol.* **1983**, *5*, 333. (c) Fenichel, R. L.; Alburn, H. E.; Schreck, P. A.; Bloom, R.; Gregory, F. J. *J. Immunopharmacol.* **1980**, *2*, 491.

(17) For a review, see Mohamed, H. A.; Abdel-Wahab, B. F. *J. Sulfur Chem.* **2012**, *33*, 589.

(18) For a review, see Al-Rashood, K. A.; Abdel-Aziz, H. A. *Molecules* **2010**, *15*, 3775.

(19) Krasovskii, A. N.; Kochergin, P. M. *Chem. Heterocycl. Compd.* **1969**, *5*, 243.

(20) (a) Kamali, T. A.; Bakherad, M.; Nasrollahzadeh, M.; Farhangi, S.; Habibi, D. *Tetrahedron Lett.* **2009**, *50*, 5459. (b) Heravi, M. M.; Keivanloo, A.; Rahimizadeh, M.; Bakavoli, M.; Ghassemzadeh, M. *Tetrahedron Lett.* **2004**, *45*, 5747.

(21) Xu, H.; Zhang, Y.; Huang, J.; Chen, W. *Org. Lett.* **2010**, *12*, 3704.

(22) Xiao, D.; Han, L.; Sun, Q.; Chen, Q.; Gong, N.; Lv, Y.; Suzenet, F.; Guillaumet, G.; Cheng, T.; Li, R. *RSC Adv.* **2012**, *2*, 5054.

(23) For a review on Baldwin's rules, see Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, *111*, 6513.

(24) (a) Fang, F.; Vogel, M.; Hines, J. V.; Bergmeier, S. C. *Org. Biomol. Chem.* **2012**, *10*, 3080. (b) Hastings, C. J.; Fiedler, D.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10977. (c) Sheldrake, H. M.; Wallace, T. W. *Tetrahedron Lett.* **2007**, *48*, 4407. (d) Scott, E. E.; Donnelly, E. T.; Welker, M. E. *J. Organomet. Chem.* **2003**, *673*, 67. (e) Hurley, A. L.; Welker, M. E.; Day, C. S. *J. Organomet. Chem.* **2000**, *598*, 150.
(25) Purity specified by the supplier.
(26) File CCDC-1020754 (**3a**) contains the supplementary crystallographic data for this article. This can be obtained free of charge from the Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/Community/Requestastructure/Pages/DataRequest.aspx.
(27) Marat, K. *SpinWorks 3.18*; Univeristy of Manitoba: Winnipeg, Canada, 2011.
(28) Balasubramanian, K. K.; Nagarajan, R. *Synthesis* **1976**, 189.