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Abstract: In the last decade, a number of metal-catalyzed technologies for the functionalization of C-H bonds in carbonaceous aromatic substrates have been developed. However, similar reactions with aza-heteroaromatic precursors are more challenging and have been much less developed. Herein we report for the first time catalytic formal cycloadditions of *N,S*-heterocycles featuring carboxylic acid substituents, with unsaturated partners (alkynes). The reaction, which works with different symmetrical and unsymmetrical alkynes, produces appealing tricyclic α-pyrones in a straightforward manner. The optimized conditions established for a model reaction employing thieno[2,3-*b*]pyridine-2-carboxylic acid as substrate, involved the use of Ag_2CO_3/$AgSbF_6$ as additives, and proved to be general for different alkynes. Moreover, analogous cycloadditions using thieno[3,2-*b*]pyridine-2-carboxylic acid and thieno[2,3-*b*]pyrazine-6-carboxylic acid were successfully developed. Overall, this catalytic technology allows to build, in a single step, an interesting variety of pharmaceutically relevant tricyclic α-pyrones exhibiting nitrogen and sulfur heteroatoms.

Introduction

2*H*-pyran-2-ones (α-pyrones) and 1*H*-2-benzopyran-1-ones (isocoumarins) are present in numerous natural[1] and synthetic[2] products that exhibit a wide range of biological activities such as antibacterial,[1a-c] anti-fungal,[1a,1d-h] antitumor,[1i-m, 2a] anti-inflammatory,[2b] anti-diabetic,[1n] and anti-HIV properties.[1o-q] Especially interesting are those derivatives exhibiting heterocyclic skeletons with sulfur and nitrogen atoms. However, a straightforward entry to this type of systems is lacking.

Thiophene fused bicyclic or tricyclic α-pyrones were earlier prepared by Pal *et al.*[3a-c] and Queiroz *et al.*[4a,b], by reaction between α-halothiophene derivatives bearing carboxylic acids or methyl esters, and terminal alkynes, using a Pd/Cu-catalyzed Sonogashira coupling followed by (halo)electrophilic cyclization. Using this protocol, several thiophene,[3c] benzo[*b*]thiophene derivatives,[4a] and thieno[3,2-*b*]pyridines[4b] with promising pharmacological properties were assembled. Examples of some of these synthetic products that present antitumoral properties are shown in Figure 1.[3c,4a-b] Unfortunately, the synthetic processes requires several steps and the use of specifically prefunctionalized precursors, and present limitations in terms of structural versatility.

In the last decade, a variety of transition-metal catalyzed annulations relying on the activation and cleavage of ubiquitous C-H bonds have been described.[5] These synthetic strategies are very attractive, among other reasons because they avoid the need of functionalized precursors e.g., halogenated compounds, and favor atom and step economy. Usually, the C-H activation requires the presence of a directing group that assists the metalation step and controls the regioselectivity.

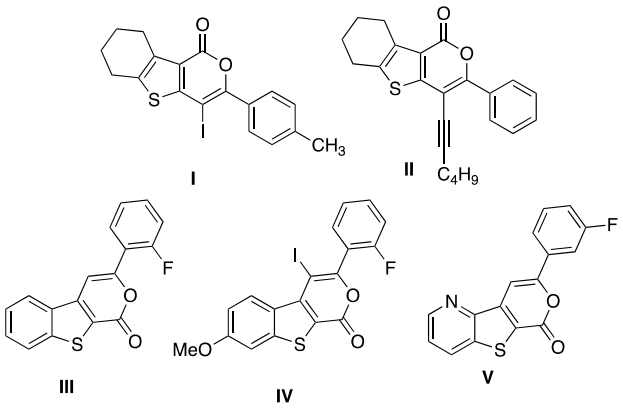


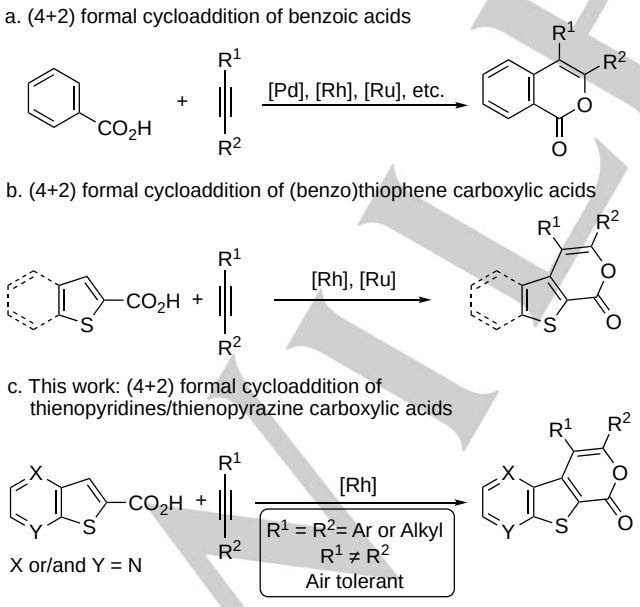
Figure 1. Previous synthesized promising thieno[3,2-*c*]pyran-4-ones (I and II),[3c] benzothieno[2,3-*c*]pyran-1-ones (III and IV)[4a] and pyrano[4',3':4,5]thieno[3,2-*b*]pyridine (V)[4b] with potential antitumor activity.

Especially attractive are those reactions in which the directing group is also engaged in the bonding process, as this can lead to formal cycloaddition reactions.[6a,b,7a-e] This is the case with benzoic acids, that can participate as four-atom components in catalytic cycloadditions with alkynes to give isocoumarins, in a formal (4+2) process (Scheme 1a).[8a-b] Pioneering work in this area was published by Satoh, Miura *et*

al.[9a] based on the use of Rh(III) precatalysts, and $Cu(OAc)_2$ as oxidant. In several cases they observed that the reaction is accompanied by the minor formation of naphthalene products, resulting from decarboxylation and insertion of two alkyne units. Curiously, using iridium catalysts and silver salts, the naphthalene products are majoritarian. [9b]

The formal (4+2) cycloaddition strategies were also demonstrated with (benzo)thiophene precursors, either using Rh or Ru catalysts (Scheme 1b). With regard to Rh catalysts, Satoh, Miura *et al.* reported an annulation of these type of compounds to give the corresponding isocoumarin analogs. However, in most of the examples, good results required careful degassed conditions, and were limited to the use of diphenylacetylene as coupling partner.[9c] Moreover, related annulations using Ru(II) precatalysts were described by Chinnagolla and Jeganmohan in 2012[10] and by Ackermann *et al.* in 2015, although only very few examples using thiophene precursors were demonstrated.[11] In 2017, Urriolabeitia *et al.* described an interesting protocol for the synthesis of heterocyclic fused α-pyrones from carboxylic acids featuring electron-rich thiophenes. The reaction required a high amount of the Ru dimer precatalyst (10 mol%), and was only effective with aliphatic alkynes. Thus, in presence of diphenylacetylene as coupling partner the reaction only gave a 10% yield of the expected cycloadduct.[7c] More recently, Wu, Shang *et al.* reported a Ru(II)-catalyzed C-H annulation of aromatic carboxylic acids with internal alkynes using air as the sole oxidant, in water, although the study included only one example with a thiophene derivative.[12]

Despite all these advances, annulations engaging the thiophene ring of fused azaheterocyclic derivatives have never been described. This could be associated to the potential incompatibility of the reaction conditions with the presence of nitrogen atoms that can coordinate to the metal center and prevent the metal catalyst from participating in the reaction.



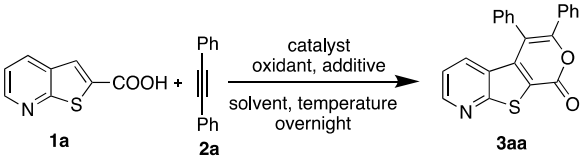
Scheme 1. Metal-catalyzed C-H activation/alkyne annulation of (hetero)aromatic carboxylic acids with internal alkynes to give the corresponding fused α-pyrones.

Herein, we report the discovery and development of formal cycloadditions between thieno[2,3-*b*]pyridine-2-carboxylic acid, thieno[3,2-*b*]pyridine-2-carboxilic acid and thieno[2,3-*b*]pyrazine-6-carboxylic acid with different types of internal alkynes (Scheme 1c). The strategy, which lies on Rh(III) catalysts, allows to assemble, in a single step, pharmacologically attractive fused thienopyridine and thienopyrazine α-pyrones. To the best of our knowledge, this represents the fastest and more atom economical synthetic route to this type of products, and the first application of C-H activation/annulation tactics to heterocyclic reaction partners exhibiting *N,S*-fused heterocycles.

Results and Discussion

Initially, the first attempts to obtain the fused *N,S*-heterocycle α-pyrones were performed using thieno[2,3-*b*]pyridine-2-carboxylic acid (**1a**) and diphenylacetylene (**2a**), using reaction conditions described by Ackerman *et al.* with Ru(II) catalysis, however no reaction was observed (Table 1, entry 1).[11] Using conditions described by Urriolabeitia *et al.*,[7c] we observed a complex mixture of products (entry 2). As these attempts were not successful, we decided to use Rh(III) catalysis applying the conditions of Satoh, Miura *et al.*[9c] and, the ones recently reported by Gulías, Mascareñas *et al.*[13] relying on a different oxidant [Ag_2CO_3 instead of $Cu(OAc_2)$]. The latter reaction conditions had been applied for the intramolecular annulation of acrylic and benzoic acids to alkynes to give bicyclic pyran-2-ones and tricyclic isocoumarin derivatives. After an intensive evaluation we found conditions that allowed to build the product **3aa** (5,6-diphenyl-8*H*-pyrano[4',3':4,5]thieno[2,3-*b*]pyridin-8-one), using $[Cp^*RhCl_2]_2$ as precatalyst. Therefore, the desired annulation could be promoted by using $Cu(OAc)_2.H_2O$ as oxidant, 2.5 mol% of the Rh catalyst, and heating the mixture at 140 ºC in DMF (64%, entry 3). When AgOAc was used as an oxidant the yield decreased to 53% (entry 4), however with Ag_2CO_3 instead of $Cu(OAc)_2.H_2O$ we observed comparable yields (entry 5).

Table 1. Optimization of the reaction conditions for the synthesis of compound **3aa**.



Entry	Catalyst	Oxidant (equiv.)	Additive (equiv)	Solvent (Δ)	Yield (%)
1	$[Ru(p\text{-cymene})Cl_2]_2$[a]	O_2[b]	NaOAc (1)	MeOH (45 ºC)	-
2	$[Ru(p\text{-cymene})Cl_2]_2$[c]	$Cu(OAc)_2.H_2O$ (1)	NaOAc (2)	Toluene (120 ºC)	-[d]
3	$[RhCp^*Cl_2]_2$[e]	$Cu(OAc)_2.H_2O$ (2)	-	DMF (140 ºC)	64
4	$[RhCp^*Cl_2]_2$[e]	AgOAc (2)	-	DMF (140 ºC)	53
5	$[RhCp^*Cl_2]_2$[e]	Ag_2CO_3 (2)	-	DMF (140 ºC)	63

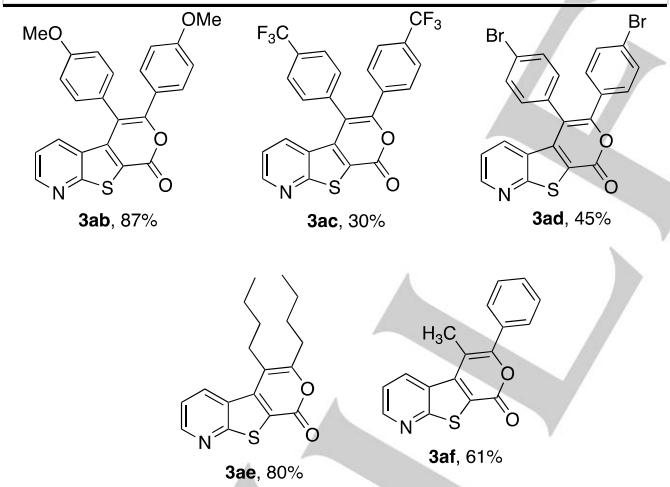
6	$[RhCp^*Cl_2]_2$[e]	Ag_2CO_3 (2)	$AgSbF_6$[c]	DMF (140 ºC)	86

Conditions: **1a** (0.2 mmol), **2a** (0.2 mmol). [a]5 mol%. [b]1 atm. [c]10 mol%. [d]Complex mixture. [e]2.5 mol%.

Earlier reports pointed to the advantageous use of $AgSbF_6$ as an additive in these reactions. Therefore, in Ru(II)-catalyzed processes to form isocoumarins,[10] this additive had been shown to completely suppress the formation of naphthalene derivatives. In the case of Rh(III) catalysis, it may generate a highly electrophilic Rh species resulting upon removal of the chloride ligands by the silver salt.[14a-c] Gratifyingly, the addition of 10 mol% of $AgSbF_6$ in combination with Ag_2CO_3 (2 equiv.) led to an excellent yield of **3aa** (86%, entry 6). Thus, the best conditions found for the annulation of compound **1a** with **2a** (1 equiv) were $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%) and Ag_2CO_3 (2 equiv.) in DMF at 140 ºC, overnight. With these optimized conditions we explored the scope with different internal alkynes (symmetrical aryl/aryl or alkyl/alkyl or unsymmetrical alkyl/aryl, Table 2).

In contrast with previous results,[7c] our protocol is effective to induce the annulation of symmetrical aromatic alkynes featuring electronically diverse substituents (**2a-2d)**. Importantly, symmetrical aliphatic alkynes are also suitable reaction partners (80% of **3ae**), and unsymmetrical alkyl-aryl alkyne can also lead to good yields of single regioisomers, as in the case of **3af** (61%). This regioselectivity is consistent with previous related rhodium-promoted heteroannulations,[15] and it mainly stems from the electronic polarization of the alkyne.

Table 2. Cycloadducts obtained from different alkynes.



3ab, 87% **3ac**, 30% **3ad**, 45%

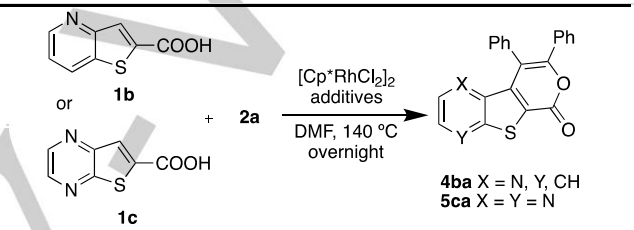
3ae, 80% **3af**, 61%

It was then opportune to analyze if the protocol can be extended to other thiophene fused azacycles that had never been used as cycloaddition partners in processes initiated by C-H activation reactions. Specifically we assessed the reaction with thieno[3,2-*b*]pyridine-2-carboxylic acid (**1b**) and thieno[2,3-*b*]pyrazine-6-carboxylic acid (**1c**). However, using alkyne **2a** as reactant, we only observed traces of the desired adducts (Table 3, entry 1 and 2). Increasing the amount of the Rh complex to 3.5 mol% and using 20 mol% of $AgSbF_6$, the product **4ba** was obtained, albeit in very low yield (entry 3) and only traces of product **5ca** were observed (entry 4).

Surprisingly, when the reactions were performed without $AgSbF_6$ and using 3.5 mol% of $[Cp^*RhCl_2]_2$ the yields of cycloadducts **4ba** and **5ca** increased to 23% (entry 5) and 20% (entry 6), respectively. In this case, the use of $AgSbF_6$ is not beneficial for the reaction, probably because the generation of cationic species might favors a stronger chelation of the substrate with the catalyst that inhibits the reaction.

Thus, it was decided to use 5 mol% of the Rh(III) catalyst in two portions (2x2.5 mol%), but again, only traces of the product were observed (entry 7). Adding the rhodium precatalyst in a single portion the yield of **4ba** was over 30% (entry 8). Indeed, using these conditions, and increasing the amount of catalyst from 5 mol% to 7 mol% we could obtain **4ba** and **5ca** in reasonable yields of 48% and 60%, respectively (entries 9 and 10). It is very probably that the presence of the nitrogen atoms in these heterocyclic systems (**1b** and **1c**), decrease the proportion of reactive species needed for the C-H activation step, and therefore we need higher amounts of the precatalyst.

Table 3. Optimization of the reaction conditions for the synthesis of compounds **4ba** and **5ca**.



Entry	1	$[Cp^*RhCl_2]_2$ (mol%)	Additive (equiv.) + (mol%)	Product Yield (%)
1	**1b**	2.5	Ag_2CO_3 (2) + $AgSbF_6$ (10)	**4ba**, traces
2	**1c**	2.5	Ag_2CO_3 (2) + $AgSbF_6$ (10)	**5ca**, traces
3	**1b**	3.5	Ag_2CO_3 (2) + $AgSbF_6$ (20)	**4ba**, 8
4	**1c**	3.5	Ag_2CO_3 (2) + $AgSbF_6$ (20)	**5ca**, traces
5	**1b**	3.5	Ag_2CO_3 (2)	**4ba**, 23
6	**1c**	3.5	Ag_2CO_3 (2)	**5ca**, 20
7	**1b**	2.5+2.5[a]	Ag_2CO_3 (2)	**4ba**, traces
8	**1b**	5	Ag_2CO_3 (2)	**4ba**, 30
9	**1b**	7	Ag_2CO_3 (2)	**4ba**, 48
10	**1c**	7	Ag_2CO_3 (2)	**5ca**, 60

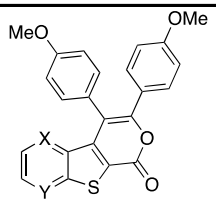
Conditions: **1a** (0.2 mmol), **2a** (0.2 mmol). [a] +2.5 mol% were added after 6h of reaction time.

These conditions were also effective for the reaction with other alkynes (Table 4). As observed for the synthesis of α-pyrones **3**, the product yields are dependent on the electronic characteristics of the groups present in the phenyl substituents of the internal alkynes. Cycloadducts **4bb** and **5cb**, exhibiting electron rich aromatic systems, were obtained in good yields, while alkynes with more electron deficient aryl substituents led to lower conversions and yields. In the reactions using the alkynes **2c** and **2d**, we observed small amounts of secondary,

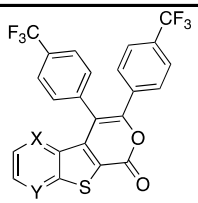
less polar products, resulting from decarboxylation and insertion of two units of alkyne.

Importantly, the annulation process was quite effective with alkynes containing alkyl substituents, and therefore adducts **4be** and **5ce** were obtained in high yields (71-76%). Unsymmetrical alkyne **2f**, equipped with aryl and alkyl substituents, was also an excellent partner for the reaction. Products **4bf** and **5cf** were obtained in high to excellent yields (up to 79%), with totally regioselectivity.

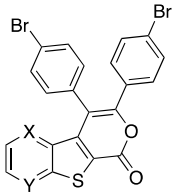
Table 4. Reaction scope with respect to the alkyne.



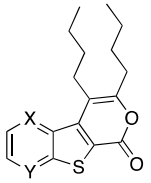
4bb X = N, Y = CH, 55%
5cb, X = Y = N, 54%



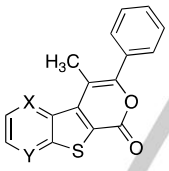
4bc X = N, Y = CH, 28%
5cc, X = Y = N, 21%



4bd X = N, Y = CH, 40%
5cd, X = Y = N, 27%



4be X = N, Y = CH, 76%
5ce, X = Y = N, 71%



4bf X = N, Y = CH, 79%
5cf, X = Y = N, 65%

Conclusion

In this work, we have developed conditions that allow to carry out formal catalytic cycloadditions between alkynes and a variety of challenging thienopyridine and thienopyrazine carboxylic acids. The reactions, initiated by C-H activation processes, provide a one step, atom economical entry to relatively complex α-pyrones fused with *N,S*-heterocycles. These products are of great interest from the pharmacological perspective, and therefore the demonstration that they can be assembled in such a simple manner should accelerate biomedical discoveries based on this type of pharmacophores. As far as our knowledge, this is the first application of a formal (4+2) cycloaddition based on a metal-promoted C-H activation on *N,S*-heterocyclic precursors.

Experimental Section

Experimental Details.

Carboxylic acids **1a** [59944-76-2], **1b** [347187-30-8] and **1c** [59944-79-5] were purchased from Apollo Scientific. Dried *N,N*-dimethylformamide was purchased from Sigma-Aldrich and used without further purification. $[RhCp^*Cl_2]_2$ [12354-85-7], Ag_2CO_3 [534-16-7] and $AgSbF_6$ [26042-64-8] were purchased from Sigma-Aldrich. ^1H, ^{13}C, ^{19}F NMR spectra were recorded on a Bruker Avance III at 400, 100.6 and 376.48 MHz, respectively. The chemical shifts were quoted in parts per million (ppm) referenced to the appropriate non-deuterated solvent peak relative to 0.0 ppm for tetramethylsilane. DEPT θ 135° was used. Heteronuclear correlations ^1H-^{13}C, HMQC and HMBC, were performed to attribute some signals. HRMS was performed by Atmospheric-Pressure Chemical Ionization (APCI) at the CACTUS facility of the University of Santiago de Compostela. Melting points (°C) were determined in a SMP3 Stuart apparatus and are uncorrected. The reactions were monitored by Thin-Layer Chromatography (TLC) using silica gel plates on aluminum. Flash or column chromatography were performed using silica gel. Ether refers to diethyl ether and petroleum ether corresponds to the 40-60 °C boiling fraction.

General procedure for the synthesis of 5,6-disusbtituted-8*H*-pyrano[4',3':4,5]thieno[2,3-*b*]pyridine-8-one (3aa-3af) – Table 1 and 2 - An oven-dried Schlenk tube with a magnetic stirring bar was charged with carboxylic acid **1a** (40.0 mg, 0.223 mmol), internal alkyne (1 equiv.), bis(dichloro(pentamethylcyclopentadienyl)rhodium) (2.5 mol %), silver carbonate (2 equiv.), silver hexafluoroantimonate(V) (10 mol%) and DMF (0.8 mL). The reaction mixture was stirred at 140 °C overnight. After cooling, the mixture was concentrated under vacuum to dryness and the crude obtained was purified by flash/column chromatography using a gradient of solvents from ethyl acetate:hexane or ethyl acetate:petroleum ether 10:90 to ethyl acetate:hexane or ethyl acetate:petroleum ether 40:60, increasing 10% of ethyl acetate each time.

5,6-diphenyl-8*H*-pyrano[4',3':4,5]thieno[2,3-*b*]pyridin-8-one (3aa): Compound **3aa** was isolated using ethyl acetate:hexane 40:60 as a beige solid (68 mg, 86%), m.p. 259-261 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.91 (d, *J* = 8.4 Hz, 1H, 4-H), 7.13 (broad d, *J* = 5.6 Hz, 1H, 3-H), 7.21-7.31 (m, 3H, 3xArH), 7.38-7.40 (m, 4H, 4xArH), 7.49-7.57 (m, 3H, 3xArH), 8.72 (large s, 1H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 116.0 (C), 120.1 (4-CH), 123.0 (C), 128.0 (2×CH), 129.2 (3xCH), 129.4 (CH), 129.5 (2xCH), 129.6 (C), 130.0 (2×CH), 132.1 (C), 134.0 (C), 134.3 (3-CH), 141.4 (C), 150.0 (2-CH), 154.5 (C), 158.3 (C), 164.6 (C) ppm. HRMS (APCI, $[M+H]^+$) calculated for $C_{22}H_{14}NO_2S$: 356.0740, found: 356.0739.

5,6-bis(4-methoxyphenyl)-8*H*-pyrano[4',3':4,5]thieno[2,3-*b*]pyridin-8-one (3ab): Compound **3ab** was isolated using ethyl acetate:hexane 20:80 as a beige solid (81.0 mg, 87%), m.p. 189-191 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.78 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.76 (d, *J* = 8.8 Hz, 2H, 2xArH), 7.02-7.07 (m, 3H, 4-H and 2xArH), 7.15 (dd, *J* = 8.4 and 4.4, 1H, 3-H), 7.28 (d, *J* = 8.8 Hz, 2H, 2xArH), 7.34 (d, *J* = 8.8 Hz, 2H, 2xArH), 8.66 (broad dd, *J* = 4.4 and 0.8 Hz, 1H, 2-H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 55.2 (OCH_3), 55.4 (OCH_3), 113.5 (2×CH), 114.6 (C), 115.1 (2×CH), 120.0 (3-CH), 122.1 (C), 125.0 (C), 126.0 (C), 130.0 (C), 130.6 (2×CH), 132.0 (2×CH), 135.0 (4-CH), 142.1 (C), 149.4 (2-CH), 155.0 (C), 158.4 (C), 160.0 (C), 160.3 (C), 164.0 (C) ppm. HRMS (APCI, $[M+H]^+$) calculated for $C_{24}H_{18}NO_4S$: 416.0951, found: 416.0955.

5,6-bis(4-(trifluoromethyl)phenyl)-8*H*-pyrano[4',3':4,5]thieno[2,3-*b*]pyridin-8-one (3ac): Compound **3ac** was isolated using ethyl acetate:hexane 20:80 as a beige solid (33.0 mg, 30%), m.p. 258-260 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.86 (dd, *J* = 8.4 and 1.2 Hz, 1H, 4-H), 7.15 (dd, *J* = 8.4 and 4.4 Hz, 1H, 3-H), 7.45 (d, *J* = 8.4 Hz, 2H, 2xArH), 7.52 (d, *J* = 8.4 Hz, 2H, 2xArH), 7.56 (d, *J* = 8.0 Hz, 2H, 2xArH), 7.82 (d, *J* = 8.0 Hz, 2H, 2xArH), 8.71 (dd, *J* = 4.4 and 1.2, 1H, 2-H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 116.0 (C), 120.2 (3-CH),

123.5 (q, *J* = 272.0 Hz, CF_3), 123.6 (q, *J* = 272.0 Hz, CF_3), 124.0 (C), 125.3 (q, *J* = 3.0 Hz, 2×CH), 126.7 (q, *J* = 3.0 Hz, 2×CH), 128.4 (C), 129.5 (2×CH), 131.4 (2×CH), 131.5 (q, *J* = 33 Hz, *C*-CF_3), 131.8 (q, *J* = 33 Hz, *C*-CF_3), 133.2 (4-CH), 135.1 (C), 137.3 (C), 140.0 (C), 151.0 (2-CH), 153.0 (C), 158.0 (C), 165.0 (C) ppm. ^{19}F NMR (376.48 MHz, $CDCl_3$): δ = -63.0 (s), -62.6 (s) ppm. HRMS (APCI, $[M+H]^+$) calculated for $C_{24}H_{12}F_6NO_2S$: 492.0487, found: 492.0491**.**

5,6-bis(4-bromophenyl)-8H-pyrano[4',3':4,5]thieno[2,3-b]pyridin-8-one (3ad); Compound **3ad** was isolated using ethyl acetate:hexane 30:70 as a beige solid (52.0 mg, 45%), m.p. 232-234 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (broad d, *J* = 8.4 Hz, 1H, 4-H), 7.18-7.23 (m, 3H), 7.26 (d, *J* = 8.0 Hz, 2H, 2xArH), 7.41 (d, *J* = 8.8 Hz, 2H, 2xArH), 7.68 (d, *J* = 8.0 Hz, 2H, 2xArH), 8.70 (dd, *J* = 4.4 and 1.6 Hz, 1H, 2-H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 115.1 (C), 120.2 (3-CH), 123.5 (C), 124.0 (C), 124.3 (C), 129.0 (C), 130.6 (2xCH), 130.7 (C), 131.5 (2xCH), 132.45 (2xCH), 132.47 (C), 133.1 (2xCH), 134.0 (4-CH), 140.5 (C), 150.0 (2-CH), 154.0 (C), 158.0 (C), 164.0 (C) ppm. HRMS (APCI, $[M+H]^+$) calculated for $C_{22}H_{12}{}^{79}Br_2NO_2S$: 511.8950, found: 511.8951.

5,6-dibutyl-8*H*-pyrano[4',3':4,5]thieno[2,3-*b*]pyridin-8-one (3ae): Compound 3ae was isolated using ethyl acetate:hexane 30:70 as a beige solid (57.0 mg, 80%), m.p. 102-104 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.2 Hz, 3H, CH_3), 1.02 (t, *J* = 7.2 Hz, 3H, CH_3), 1.41-1.78 (m, 8H), 2.66-2.70 (m, 2H, CH_2), 2.87-2.91 (m, 2H, CH_2), 7.51 (dd, *J* = 8.4 and 4.4 Hz, 1H, 3-H), 8.47 (broad d, *J* = 8.4 Hz, 1H, 4-H), 8.77 (dd, *J* = 4.4 and 1.2 Hz, 2-H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 13.8 (CH_3), 13.9 (CH_3), 22.5 (CH_2), 22.6 (CH_2), 27.0 (CH_2), 30.2 (CH_2), 30.3 (CH_2), 32.0 (CH_2), 113.4 (C), 120.3 (3-CH), 123.0 (C), 129.0 (C), 134.0 (4-CH), 141.2 (C), 149.5 (2-CH), 158.2 (C), 159.0 (C), 164.0 (C) ppm. HRMS (APCI, $[M+H]^+$) calculated for $C_{18}H_{22}NO_2S$: 316.1366, found: 316.1363.

5-methyl-6-phenyl-8*H*-pyrano[4',3':4,5]thieno[2,3-*b*]pyridin-8-one (3af): Compound **3af** was isolated using ether:petroleum ether 80:20 as a pale yellow solid (40.0 mg, 61%), m.p. 256-258 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.67 (s, 3H, CH_3), 7.47-7.54 (m, 4H, 3-H and 3xArH), 7.60-7.63 (m, 2H, 2xArH), 8.67 (dd, *J* = 8.4 and 1.6, 1H, 4-H), 8.80 (dd, *J* = 4.4 and 1.6 Hz, 1H, 2-H) ppm. The regioisomer 3af was assigned using nOe (see SI). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 16.0 (CH_3), 110.0 (C), 120.2 (3-CH), 123.4 (C), 128.5 (2×CH), 129.5 (C), 129.6 (2×CH), 129.8 (CH), 132.3 (C), 133.9 (4-CH), 142.0 (C), 150.3 (2-CH), 155.0 (C), 159.0 (C), 165.0 (C) ppm. HRMS (APCI, $[M+H]^+$) calculated for $C_{17}H_{12}NO_2S$: 294.0583, found: 294.0581.

General procedure for the synthesis of 8,9-disusbtituted-6*H*-pyrano[4',3':4,5]thieno[3,2-*b*]pyridin-6-one (4ba-4bf) and 8,9-bis(4-methoxyphenyl)-6*H*-pyrano[4',3':4,5]thieno[2,3-*b*]pyrazin-6-one (5ca-5cf) – Table 3 and 4- An oven-dried Schlenk tube with a magnetic stirring bar was charged with carboxylic acid **1b** (0.223 mmol) or carboxylic acid **1c** (0.222 mmol), internal alkyne (1 equiv.) bis(dichloro(pentamethylcyclopentadienyl)rhodium) (7 mol %), silver carbonate (2 equiv.) and DMF (0.8 mL). The reaction mixture was stirred at 140 °C overnight. After cooling, the mixture was concentrated under vacuum to dryness and the crude obtained was purified by flash/column chromatography using a gradient of solvents from ethyl acetate:hexane or ethyl acetate:petroleum ether 10:90 to ethyl acetate:hexane or ethyl acetate:petroleum ether 40:60, increasing 10% of ethyl acetate each time, to isolate the product.

8,9-diphenyl-6*H*-pyrano[4',3':4,5]thieno[3,2-*b*]pyridin-6-one (4ba): Compound **4ba** was isolated using ethyl acetate:hexane 20:80 as a beige solid (38.0 mg, 48%), m.p. 237-239 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20-7.29 (m, 3H), 7.33-7.41 (m, 8H, 7×ArH and 3-H), 8.27 (dd, *J* = 8.4 and 1.6 Hz, 1H, 4-H), 8.51 (dd, *J* = 4.4 and 1.6 Hz, 1H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 117.0 (C), 122.0 (3-CH), 126.0 (C), 127.9 (3×CH), 128.0 (2×CH), 129.1 (CH), 129.5 (2×CH), 131.1 (4-CH), 131.5 (2×CH), 132.5 (C), 133.3 (C), 138.2 (C), 142.3 (C), 148.0 (2-CH), 151.0 (C), 155.0 (C), 159.0 (C) ppm. HRMS (APCI, $[M+H]^+$) calculated for $C_{22}H_{14}NO_2S$: 356.0740, found: 356.0738.

8,9-bis(4-methoxyphenyl)-6*H*-pyrano[4',3':4,5]thieno[3,2-*b*]pyridin-6-one (4bb): Compound **4bb** was isolated using ethyl acetate:petroleum ether 40:60 as a yellow solid (51.0 mg, 55%), m.p. 167-169 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.79 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.75 (d, *J* = 8.8 Hz, 2H, 2xArH), 6.93 (d, *J* = 8.8 Hz, 2H, 2xArH), 7.25 (d, *J* = 8.8 Hz, 2H, 2xArH), 7.30-7.35 (m, 3H, 2×ArH and 3-H), 8.25 (dd, *J* = 8.4 and 1.6, 1H, 4-H), 8.53 (dd, *J* = 4.4 and 1.6 Hz, 1H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.18 (OCH_3), 55.20 (OCH_3), 113.4 (2×CH), 113.5 (2×CH), 115.5 (C), 122.0 (3-CH), 124.7 (C), 125.1 (C), 126.0 (C), 131.0 (2×CH), 131.04 (4-CH), 133.0 (2×CH), 138.2 (C), 143.0 (C), 148.0 (2-CH), 151.2 (C), 155.0 (C), 159.1 (C), 159.2 (C), 160.0 (C) ppm. HRMS (APCI, $[M+H]^+$) calculated for $C_{24}H_{18}NO_4S$: 416.0951, found: 416.0954.

8,9-bis(4-(trifluoromethyl)phenyl)-6*H*-pyrano[4',3':4,5]thieno[3,2-*b*]pyridin-6-one (4bc): Compound **4bc** was isolated using ethyl acetate:hexane 20:80 as a yellow solid (31.0 mg, 28%), m.p. 200-202 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (dd, *J* = 8.4 and 4.4 Hz, 1H, 3-H), 7.45-7.53 (m, 6H, 6xArH), 7.66 (d, *J* = 8.0 Hz, 2H, 2xArH), 8.30 (dd, *J* = 8.4 and 1.6 Hz, 1H, 4-H), 8.49 (dd, *J* = 4.4 and 1.6 Hz, 1H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 116.5 (C), 122.1 (3-CH), 123.6 (q, *J* = 272.0 Hz, CF_3), 124.1 (q, *J* = 272.0 Hz, CF_3), 125.1-125.2 (m, 4xCH), 126.5 (C), 129.8 (2xCH), 130.5 (q, *J* = 33 Hz, *C*-CF_3), 131.2 (q, *J* = 33 Hz, *C*-CF_3), 131.23 (4-CH), 132.0 (2xCH), 135.5 (C), 136.6 (C), 138.2 (C), 141.2 (C), 148.1 (2-CH), 151.0 (C), 153.3 (C), 158.2 (C) ppm. ^{19}F NMR (376.48 MHz, $CDCl_3$): δ = -63.0 (s), -62.4 (s) ppm. HRMS (APCI, $[M+H]^+$) calculated for $C_{24}H_{12}F_6NO_2S$: 492.0487, found: 492.0488.

8,9-bis(4-bromophenyl)-6*H*-pyrano[4',3':4,5]thieno[3,2-*b*]pyridin-6-one (4bd): Compound **4bd** was isolated using ethyl acetate:hexane 20:80 as a pale yellow solid (46.0 mg, 40%), m.p. 206-208 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19-7.24 (m, 4H), 7.36-7.42 (m, 3H, 2xArH and 3-H), 7.52 (d, *J* = 8.4 Hz, 2H, 2xArH), 8.28 (dd, *J* = 8.2 and 1.6 Hz, 1H, 4-H), 8.54 (dd, *J* = 4.4 and 1.6 Hz, 1H, 2-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 116.0 (C), 122.0 (3-CH), 122.4 (C), 124.0 (C), 126.0 (C), 131.0 (2xCH), 131.1 (C), 131.2 (4-CH), 131.39 (2xCH), 131.41 (2xCH), 132.0 (C), 133.1 (2xCH), 138.2 (C), 142.0 (C), 148.0 (2-CH), 151.0 (C), 154.0 (C), 158.5 (C) ppm. HRMS (APCI, $[M+H]^+$) calculated for $C_{22}H_{12}{}^{79}Br_2NO_2S$: 511.8950, found: 511.8940.

8,9-dibutyl-6*H*-pyrano[4',3':4,5]thieno[3,2-*b*]pyridin-6-one (4be): Compound **4be was** isolated using ethyl acetate:hexane 10:90 as a beige solid (54.0 mg, 76%), m.p. 100-102 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96-1.01 (m, 6H, 2xCH_3), 1.44-1.75 (m, 8H, 4xCH_2, including H_2O of the $CDCl_3$), 2.69-2.73 (m, 2H, CH_2), 3.25-3.29 (m, 2H, CH_2), 7.45 (dd, *J* = 8.4 and 4.4 Hz, 1H, 3-H), 8.28 (dd, *J* = 8.4 and 1.6 Hz, 1H, 4-H), 8.84 (dd, *J* = 4.4 and 1.6 Hz, 1H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.9 (CH_3), 14.0 (CH_3), 22.5 (CH_2), 22.7 (CH_2), 25.4 (CH_2), 30.0 (**(**CH_2), 30.3 (CH_2), 32.9 (CH_2), 115.0 (C), 122.0 (3-CH), 125.0 (C), 131.2 (4-CH), 138.0 (C), 143.0 (C), 148.0 (2-CH), 151.4 (C), 158.0 (C), 160.0 (C) ppm. HRMS (APCI, $[M+H]^+$) calculated for $C_{18}H_{22}NO_2S$: 316.1366, found: 316.1365.

9-methyl-8-phenyl-6*H*-pyrano[4',3':4,5]thieno[3,2-*b*]pyridin-6-one (4bf): Compound **4bf** was isolated using ethyl acetate:petroleum 30:70 as a pale yellow solid (52.0 mg, 79%), m.p. 219-221 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.87 (s, 3H, CH_3), 7.48-7.54 (m, 4H, 3xArH and 3-H), 7.66 (dd, *J* = 7.6 and 1.6 Hz, 2H, 2xArH), 8.33 (dd, *J* = 8.4 and 1.6 Hz, 1H, 4-H), 8.88 (dd, *J* = 4.4 and 1.6 Hz, 1H, 2-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.6 (CH_3), 111.2 (C), 122.0 (3-CH), 126.0 (C), 128.3 (2×CH), 130.0 (3×CH), 131.4 (4-CH), 133.0 (C), 138.2 (C), 143.3 (C), 148.0 (2-CH), 152.1 (C), 154.4 (C), 159.2 (C) ppm. HRMS (APCI, $[M+H]^+$) calculated for $C_{17}H_{12}NO_2S$: 294.0583, found: 294.0586.

8,9-diphenyl-6*H*-pyrano[4',3':4,5]thieno[2,3-*b*]pyrazin-6-one (5ca): Compound **5ca** was isolated using ethyl acetate:hexane 20:80 as a beige solid (48.0 mg, 60%), m.p. 221-223 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23-7.41 (m, 10H, 10xArH), 8.50 (d, *J* = 2.0 Hz, 1H, HetArH), 8.59 (d, *J* = 2.0 Hz, 1H, HetArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 116.2 (C), 125.3 (C), 128.0 (2×CH), 128.2 (CH), 128.3 (2×CH), 129.4 (CH), 129.5 (2×CH), 131.3 (2×CH), 132.2 (C), 133.0 (C), 140.3 (C), 142.3 (HetAr-CH), 143.4 (HetAr-CH), 146.0 (C), 155.4 (C), 158.4 (C), 159.2 (C) ppm. HRMS (APCI, $[M+H]^+$) calculated for $C_{21}H_{13}N_2O_2S$: 357.0692, found: 357.0690.

8,9-bis(4-methoxyphenyl)-6*H*-pyrano[4',3':4,5]thieno[2,3-*b*]pyrazin-6-one (5cb): Compound **5cb** was isolated using ethyl acetate:petroleum ether 30:70 as a yellow solid (50.0 mg, 54%), m.p. 186-188 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.76 (d, *J* = 8.8 Hz, 2H, 2xArH), 6.94 (d, *J* = 8.8 Hz, 2H, 2xArH), 7.23 (d, *J* = 8.8 Hz, 2H, 2xArH), 7.33 (d, *J* = 8.8 Hz, 2H, 2xArH), 8.52 (d, *J* = 2.0 Hz, 1H, HetArH), 8.58 (d, *J* = 2.0 Hz, 1H, HetArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.21 (OCH_3), 55.24 (OCH_3), 113.5 (2×CH), 113.8 (2×CH), 115.0 (C), 124.4 (C), 124.7 (C), 125.1 (C), 131.0 (2×CH), 132.5 (2×CH), 141.0 (C), 142.2 (CH), 143.3 (CH), 146.0 (C), 155.4 (C), 158.6 (C), 159.2 (C), 159.4 (C), 160.3 (C) ppm. HRMS (APCI, $[M+H]^+$) calculated for $C_{23}H_{17}N_2O_4S$: 417.0904, found: 417.0906.

8,9-bis(4-(trifluoromethyl)phenyl)-6*H*-pyrano[4',3':4,5]thieno[2,3-*b*]pyrazin-6-one (5cc): Compound **5cc** was isolated using ethyl acetate:hexane 20:80 as a pale yellow solid (23.0 mg, 21%), m.p. 193-195 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46-7.55 (m, 6H, 6xArH), 7.68 (d, *J* = 7.8 Hz, 2H, 2xArH), 8.50 (d, *J* = 2.4 Hz, 1H, HetArH), 8.63 (d, *J* = 2.4 Hz, 1H, HetArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 116.0 (C), 123.5 (q, *J* = 272.0 Hz, CF_3), 124.0 (q, *J* = 272.0 Hz, CF_3), 125.2 (q, *J* = 3.7 Hz, 2xCH), 125.5 (q, *J* = 3.7 Hz, 2xCH), 126.3 (C), 130.0 (2xCH), 131.0 (q, *J* = 33.0 Hz, *C*-CF_3), 131.5 (q, *J* = 33.0 Hz, *C*-CF_3), 131.7 (2xCH), 135.1 (C), 136.1 (C), 139.2 (C), 142.5 (CH), 144.0 (CH), 145.1 (C), 154.0 (C), 158.0 (C), 159.2 ppm. ^{19}F NMR (376.48 MHz, $CDCl_3$): δ = -63.0 (s), -62.5 (s) ppm. HRMS (APCI, $[M+H]^+$) calculated for $C_{23}H_{11}F_6N_2O_2S$: 493.0440, found: 493.0445.

8,9-bis(4-bromophenyl)-6*H*-pyrano[4',3':4,5]thieno[2,3-*b*]pyrazin-6-one (5cd): Compound **5cd** was isolated using ethyl acetate:hexane 20:80 as a yellow solid (31.0 mg, 27%), m.p. 183-185 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.8 Hz, 2H, 2xArH), 7.23 (d, *J* = 8.8 Hz, 2H, 2xArH), 7.41 (d, *J* = 8.8 Hz, 2H, 2xArH), 7.54 (d, *J* = 8.8 Hz, 2H, 2xArH), 8.54 (d, *J* = 2.4 Hz, 1H, HetArH), 8.62 (d, *J* = 2.4 Hz, 1H, HetArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 115.3 (C), 123.0 (C), 124.4 (C), 126.0 (C), 130.8 (C), 130.9 (2xCH), 131.4 (C), 131.5 (2xCH), 131.7 (2xCH), 133.0 (2xCH), 140.0 (C), 142.4 (CH), 143.6 (CH), 145.3 (C), 154.3 (C), 158.0 (C), 159.2 (C). HRMS (APCI, $[M+H]^+$) calculated for $C_{21}H_{11}{}^{79}Br_2N_2O_2S$: 512.8903, found: 512.8908.

8,9-dibutyl-6*H*-pyrano[4',3':4,5]thieno[2,3-*b*]pyrazin-6-one (5ce): Compound **5ce** was isolated using ethyl acetate:hexane 10:90 as a beige solid (50.0 mg, 71%), m.p. 91-93 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.2 Hz, 6H, 2×CH_3), 1.42-1.58 (m, 6H, 3xCH_2), 1.73-1.77 (m, 2H, CH_2), 2.68-2.72 (m, 2H, CH_2), 3.15-3.19 (m, 2H, CH_2), 8.68 (d, *J* = 2.0 Hz, 1H, HetArH), 8.82 (d, *J* = 2.0 Hz, 1H, HetArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.8 (CH_3), 13.9 (CH_3), 22.5 (CH_2), 22.6 (CH_2), 25.5 (CH_2), 30.0 (CH_2), 30.2 (CH_2), 33.0 (CH_2), 114.4 (C), 125.0 (C), 141.0 (C), 142.2 (CH), 143.3 (CH), 146.0 (C), 159.0 (C), 159.1 (C), 159.2 (C) ppm. HRMS (APCI, $[M+H]^+$) calculated for $C_{17}H_{21}N_2O_2S$: 317.1318, found: 317.1315.

9-methyl-8-phenyl-6*H*-pyrano[4',3':4,5]thieno[2,3-*b*]pyrazin-6-one (5cf): Compound **5cf** was isolated using ethyl acetate:petroleum ether 30:70 as a yellow solid (43.0 mg, 65%), m.p. 192-194 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.82 (s, 3H, CH_3), 7.49-7.55 (m, 3H, 3xArH), 7.64-7.67 (m, 2H, 2xArH), 8.73 (d, *J* = 2.0 Hz, 1H, HetArH), 8.85 (d, *J* = 2.0 Hz, 1H, HetArH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.4 (CH_3), 111.0 (C), 125.5 (C), 128.4 (2×CH), 129.5 (2×CH), 130.0 (CH), 132.2 (C), 141.2 (C), 142.3 (CH), 143.6 (CH), 146.5 (C), 155.0 (C), 159.0 (C), 159.3 (C) ppm. HRMS (APCI, $[M+H]^+$) calculated for $C_{16}H_{11}N_2O_2S$: 295.0536, found: 295.0534.

Acknowledgements

To Fundação para a Ciência e Tecnologia (FCT)–Portugal financially supports CQUM (UID/QUI/686/2020), also financed by European Regional Development Fund (ERDF), COMPETE2020 and Portugal2020, the PTNMR network also supported by Portugal2020 and the PhD grant of J.M.R. (SFRH/BD/115844/2016) also financed by ESF (European Social Fund – North Portugal Regional Operational Programme) and HCOP (Human Capital Operational Programme). To COST Action CA15106 – C-H Activation in Organic Synthesis (CHAOS) – including a Short-Term Scientific Mission (STSM) grant attributed to J.M.R. to work in CiQUS.

We also thank Spanish grants SAF2016-76689-R, PID2019-108624RB-I00, PID2019-110385GB-I00 and FPI fellowship BES-2017- 079784 to B.C., the Consellería de Cultura, Educación e Ordenación Universitaria (ED431C 2017/19, 2015-CP082 and Centro Singular de Investigación de Galicia accreditation 2019-2022, ED431G 2019/03, the European Regional Development Fund (ERDF), and the European Research Council (Advanced Grant No. 340055).

Keywords: Annulation • C-H Activation • *N*,*S*-heterocycles • Rhodium catalysis • Tricyclic α-pyrones

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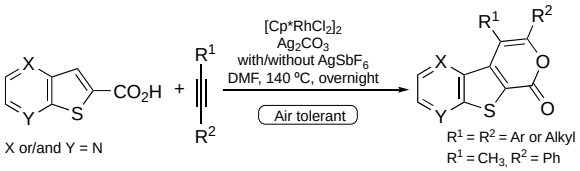

Formal Rh(III)-catalyzed (4+2) cycloadditions of *N*,*S*-heterocycles bearing carboxylic acid substituents with alkynes, triggered by C-H activation, are described. The reaction works with different symmetrical and unsymmetrical alkynes, producing appealing tricyclic α-pyrones with potential pharmaceutical interest, in a straightforward manner.