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PAPER

One-pot double functionalisation of π-deficient heterocyclic lithium reagents†

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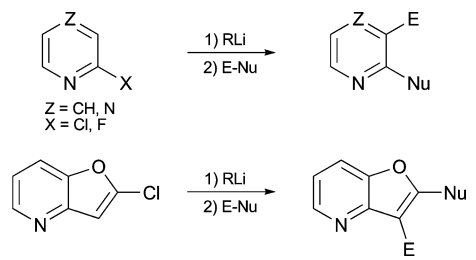
Herein, we report an efficient method for the double functionalisation of lithiated halogenopyridines, -pyrazines or -furopyridines through a convenient one-pot electrophilic trapping/nucleophilic substitution sequence.

Introduction

Over the past few decades, many efforts have been made to develop metalation reactions for the functionalisation of heterocycles.[1] Such reactions are proving to be powerful tools because of the large range of functionalities that can be introduced. Functionalisation by metallation generally proceeds in two main steps : 1) Formation of a carbon-metal bond; 2) Subsequent electrophilic trapping. During the trapping step, some released species can exhibit nucleophilic properties, depending of the nature of the electrophile, and might lead to nucleophilic substitution. To our knowledge, this reactivity is surprisingly considered as a side reaction.[2] In our continuing efforts aimed at developing simple and efficient synthesis of substituted heterocycles,[3–6] we describe here an easy procedure leading to bifunctionalised azaheterocycles. Indeed, by using disulfide and amide derivatives as *E*-Nu trapping reagents (good electrophiles releasing nucleophilic species during the trapping step), the one-pot process combining electrophilic trapping and nucleophilic substitution might be useful to allow the direct preparation of new bifunctional scaffolds (Scheme 1).



Scheme 1 One-pot double functionalisation of π-deficient azaheterocycles.

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† Electronic supplementary information (ESI) available: Copy of GC and NMR spectra of all new compounds. See DOI: 10.1039/c0ob00734j

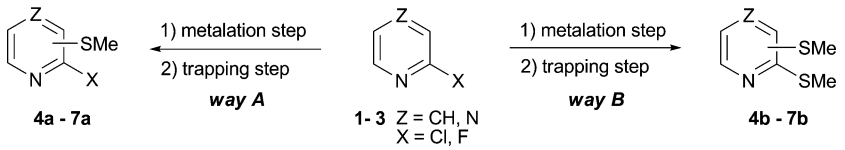
Results and discussion

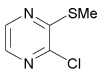
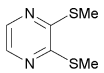
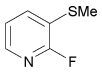
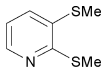
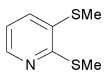
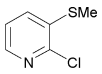
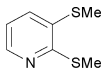
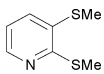
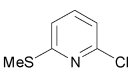
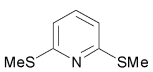
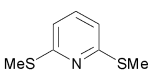
We first studied the action of the most common disulfide : Me_2S_2. Under usual conditions, we succeeded in generating lithiated heterocycles by using LTMP,[7] LDA[8] or [*n*-BuLi/LiDMAE] superbase,[9] leading to halogeno-methylthio-derivatives **4a–7a** in excellent yields (Table 1, **way A**, 82–92%). At low temperature (–78 °C), no nucleophilic substitution of *in situ* formed MeSLi was detected.

With the intention to enhance the nucleophilic potential of MeSLi released during the trapping process, we devoted the most efforts to explore the optimal required conditions to succeed in such a cascade procedure (Table 1, **way B**). Because pyrazine derivatives are well known to be good electrophiles, we began our study with 2-chloropyrazine **1**. After lithiation of **1** with LTMP, 2 eq of Me_2S_2[10] were added at –78 °C for 30 min in THF to quench the lithio-intermediate. After that, we envisionned to warm up the reaction medium in order to reveal the nucleophilicity of MeSLi. Then, the temperature was allowed to warm to 20 °C over a period of 1 h[11] and maintained at 20 °C for 3 h (reaction monitored by GC). The hydrolysis was performed at 20 °C, and the 2,3-bis(methylthio)pyrazine **4b** was consequently obtained in an excellent isolated yield (entry 1, 91%). The proposed mechanism for this double functionalisation process is depicted in Scheme 2. 2-Chloro-3-lithiopyrazine is quenched with Me_2S_2 to form 2-chloro-3-methylthiopyrazine **4a** and MeSLi is released. The nucleophilic attack of MeSLi on the C-2 position leads to a stabilised lithio intermediate and 2,3-bis(methylthio)pyrazine **4b** is obtained after elimination of LiCl.

To extend the scope of this new strategy, we next turned our attention on other substrates. Thus, 2-fluoropyridine **2** appeared as a judicious substrate, because pyridines are known to be less electrophilic than pyrazines. On the other hand, fluorine atom is well known to be a better leaving group in nucleophilic aromatic substitution than the chlorine one. Therefore, 2-fluoropyridine **2** was lithiated with LDA, Me_2S_2 was added according to the **way B** conditions, and the temperature was maintained at 20 °C for 17 h. 2,3-Bis(methylthio)pyridine **5b** was then obtained with a good isolated yield (entry 2, 69%) in presence of **5a** (13%). It is

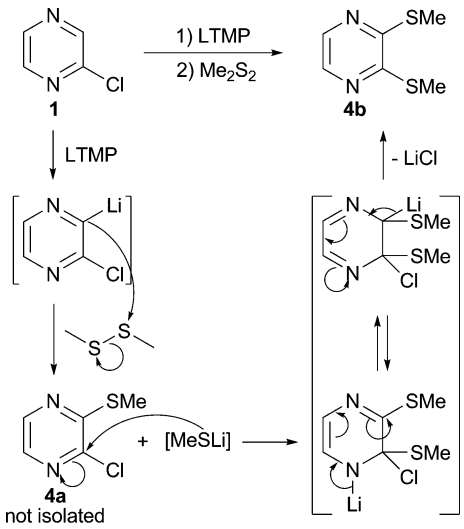
Table 1 One-pot double functionalisation of π-deficient azaheterocycles



Entry	Product **4a–7a**, Yields%[c]	Trapping step ***way A***[a] Me_2S_2 (n eq), T°C	Substrate Metalation step RLi (n eq), T°C, time, solvent	Trapping step ***way B***[b] *i*) *ii*) then T°C, time	Product **4b–7b**, Yields%[c]
1	 **4a**, 90%	3 eq, –78 °C	 **1** LTMP (1.2 eq) -78°C, 30 min, THF	20 °C, 3 h	 **4b**, 91%
2	 **5a**, 82%	3 eq, –70 °C	 **2** LDA (1.2 eq) -70°C, 4 h, THF	20 °C, 17 h	 **5b**, 69%[d]
3	—	—	**2**, LDA (1.5 eq), –70 °C, 4 h, THF	20 °C, 17 h	 **5b**, 90%
4	 **6a**, 90%	3 eq, –78 °C	 **3** LTMP (1.2 eq) -78°C, 1 h 30, THF	reflux, 20 h	 **5b**, 71%[e]
5	—	—	**3**, LTMP (1.5 eq), –78 °C, 1 h 30, THF	reflux, 20 h	 **5b**, 77%
6	 **7a**, 92%	4 eq, –78 °C	**3**, [*n*-BuLi/LiDMAE] (3eq), –78 °C, 1 h, Hexane	reflux, 20 h	 **7b**, 15%[f]
7	—	—	**3**, [*n*-BuLi/LiDMAE] (3eq), –78 °C, 1 h, Hexane	solvent exchange[g] reflux, 20 h	 **7b**, 53%[h]

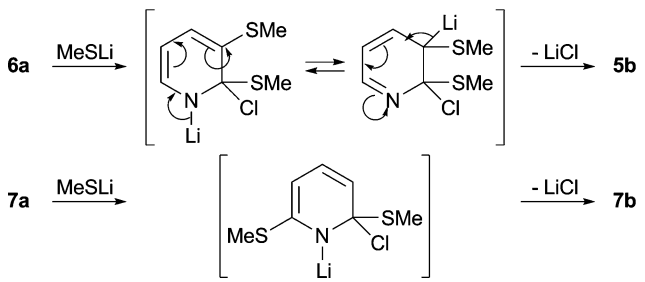
[a] Trapping step conditions (***way A***) : Me_2S_2 (n eq), T°C, 1 h, THF. [b] Trapping step conditions (***way B***) : *i*) Me_2S_2 (2 eq), –78 °C, 30 min, THF *ii*) –78 to 20 °C, 1 h,[11] then T°C, time (h). [c] Isolated yields after centrifugal thin layer chromatography. [d] 13% of **5a** was formed. [e] 18% of **6a** was formed. [f] 75% of **7a** was formed.[12] [g] Evaporation of solvents then THF was added. [h] 36% of **7a** was formed.[12]

to be noted that an extended reaction time (17 h) was necessary to obtain this result (reaction monitored by GC), because of the less electrophilic character of **2** in comparison with **1**. To complete the nucleophilic substitution of the fluorine, a slight excess of LDA (1.5 eq) was used to afford **5b** with an excellent isolated yield (entry 3, 90%). Similar strategy was carried out with 2-chloropyridine **3**. The lithiation on the C-3 position was here conducted with LTMP as precedently presented. After addition of Me_2S_2 as trapping agent according to the **way B** conditions, the mixture was refluxed during 20 h in THF and **5b** was isolated in a good yield (entry 4, 71%) in presence of **6a** (18%). With 1.5 eq of LTMP, **5b** was obtained with an increased yield (entry 5, 77%). The sequence was finally applied to the synthesis of 2,6-bis(methylthio)pyridine **7b**. The lithiation of **3** on the C-6 position was accomplished with the [*n*-BuLi/LiDMAE] superbase, Me_2S_2 was then added according to the **way B** conditions and the mixture was refluxed for 20 h. Only 15% of the desired **7b** was isolated (entry 6), in presence of 75% of 2-chloro-6-methylthiopyridine **7a**.[12] It is well known that the polarity of the solvent plays an important role in the nucleophilic substitution. Actually, metalation with



Scheme 2 Proposed mechanism for the double functionalisation process.

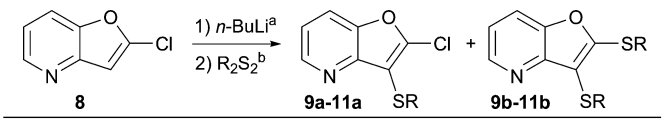
[*n*-BuLi/LiDMAE] superbase occurred in hexane instead of THF in the case of LDA or LTMP. Consequently, we exchanged solvent before to reflux the mixture. Solvents were evaporated and THF was added. After 20 h refluxing in THF, formation of **7b** was observed with an interesting increased result (entry 7, 53%) in presence of **7a** (36%).[12] This lower reactivity of **7a** in relation to nucleophilic addition can be explained by a less stabilised lithio intermediate in comparison with **6a** (Scheme 3).

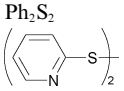
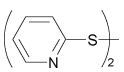


Scheme 3 Stabilisation forms of lithiated intermediates.

Recently, our group has demonstrated a great interest in the functionalisation of furopyridine derivatives by using lithiated bases and metal-catalysed coupling reactions.[5,6] As an extension of this work and of the methodology described in this paper, we focused our attention on 2-chlorofuro[3,2-*b*]pyridine **8**. The lithiation of **8** was carried out with 1.2 eq of *n*-BuLi at –20 °C for 1 h in THF, followed by electrophilic trapping with 2 eq of Me_2S_2 from –20 to 20 °C (20 min) and the temperature was maintained at 20 °C during 40 min. The strategy once more appeared very efficient and 80% of 2,3-bis(methylthio)furo[3,2-*b*]pyridine **9b** was isolated (Table 2, entry 1). The reaction occured very easily and we decided to extend the sequence by using other disulfide *E*-Nu reagents. We chose diphenyldisulfide and bis(pyridin-2-yl)disulfide (Py_2S_2) to examine the versatility of the methodology with less nucleophilic lithium thiolates than MeSLi. In fact, when Ph_2S_2 was used, the nucleophilic substitution step appeared more difficult because the released PhSLi is less nucleophilic than MeSLi. Nevertheless, if the temperature of the trapping step is warmed to 50 °C for 40 min, 85% of the desired 2,3-bis(phenylthio)furo[3,2-*b*]pyridine **10b** was isolated, and only traces of 2-chloro-3-phenylthiofuro[3,2-*b*]pyridine **10a** were detected as a side product (entry 3). In the case of Py_2S_2, the previously reported trapping conditions (Py_2S_2 (2 eq), THF, –20 °C to 20 °C over a period of 20 min, then 20 °C during 40 min) failed to yield efficiently the expected 2,3-bis(pyridin-2-ylthio)furo[3,2-*b*]pyridine **11b** (entry 4, 11%) and the 2-chloro-3-(pyridin-2-ylthio)furo[3,2-*b*]pyridine **11a** was obtained as the main product (entry 4, 65%). Nucleophilicity of PySLi was then enhanced by warming the reaction at 60 °C for 5 h 40. In these conditions, partial degradation of products was observed, nevertheless, **11b** was isolated in a respectable 46% yield (entry 5).

Table 2 Double functionalisation of furo[3,2-*b*]pyridine with various disulfides

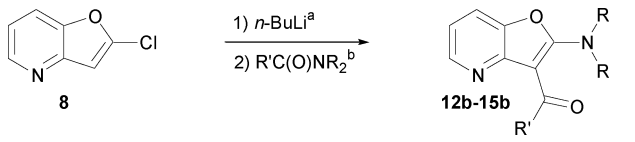


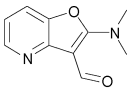
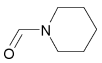
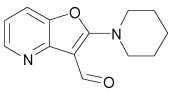
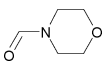
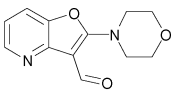
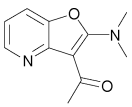
Entry	R_2S_2	Products **9a–11a/9b–11b**	Yields%[c]
1	Me_2S_2	**9a**, -%	**9b**, 80%
2	Ph_2S_2	**10a**, 10%[12]	**10b**, 70%[12]
3[d]	Ph_2S_2	**10a**, traces	**10b**, 85%
4		**11a**, 65%	**11b**, 11%
5[e]		**11a**, -%	**11b**, 46%

[a] *n*-BuLi (1.2 eq), –20 °C, 1 h, THF. [b] R_2S_2 (2 eq), THF, –20 °C to 20 °C (20 min), then 20 °C (40 min), then H_2O. [c] Isolated yields after centrifugal thin layer chromatography. [d] Trapping step conditions : Ph_2S_2 (2 eq), THF, –20 °C to 20 °C (20 min), then 50 °C (40 min), then H_2O. [e] Trapping step conditions : Py_2S_2 (2 eq), THF, –20 °C to 20 °C (20 min), then 60 °C (5 h 40), then H_2O.

We also demonstrated that the procedure was not exclusively specific of the disulfides as the *E*-Nu reagents. In fact we treated 2-chloro-3-lithiofuro[3,2-*b*]pyridine with various amides. 2-Amino-3-formylfuro[3,2-*b*]pyridines **12b–14b** were consequently obtained in good to excellent isolated yields by quenching the lithio intermediate respectively with dimethylformamide, *N*-formylpiperidine and *N*-formylmorpholine (Table 3, entries 1–3, 60–84%). The procedure allowed as well the formation of the 2-(dimethylamino)-3-acetylfuro[3,2-*b*]pyridine **15b** in a very good 77% yield (entry 4) by treating the lithio intermediate with dimethylacetamide. In that specific case, the temperature of the trapping step had to be maintained at –20 °C for only 30 min to avoid deacetylation of **15b** by Me_2NLi in a 1,2-addition process.

Table 3 Double functionalisation of furo[3,2-*b*]pyridine with various amides



Entry	Amide	Product **12b–15b** Yields%[c]
1		 **12b**, 84%
2		 **13b**, 72%
3		 **14b**, 60%
4[d]		 **15b**, 77%

[a] *n*-BuLi (1.2 eq), –20 °C, 1 h, THF. [b] Amide (2 eq), THF, –20 °C to 20 °C (20 min), then 20 °C (40 min), then H_2O. [c] Isolated yields after centrifugal thin layer chromatography. [d] Trapping step conditions : DMA (2 eq), THF, –20 °C (30 min), then H_2O.

Conclusions

In summary, we have developed a new efficient double functionalisation of various π-deficient heterocycles *via* a one-pot cascade process combining electrophilic trapping of lithio intermediate and subsequent nucleophilic substitution. The sequence is not dependent of the lithiated agent (*n*-BuLi, LDA, LTMP, or [*n*-BuLi/LiDMAE] were used) and is applicable with several *E*-Nu reagents. By this way, bifunctionalised pyrazine, pyridines or furo[3,2-*b*]pyridines have been efficiently and directly obtained in only one pot procedure (46–91%).

Experimental section

General. ^{1}H and ^{13}C NMR spectra were recorded at 250 and 63 MHz respectively with $CDCl_3$ as solvent and TMS as internal standard (for ^{1}H NMR). HRMS spectra were recorded on a BRUKER micrOTOF-Q spectrometer. GC-MS were recorded on a SHIMADZU GCMS-QP2010 spectrometer. Melting temperatures were measured on a Totoli apparatus and are uncorrected. Centrifugal thin-layer chromatography purification was performed with Chromatotron®.

Reagents. All reagents were commercially available and were purified by distillation when necessary. *n*-BuLi was used as a commercial 1.6 M solution in hexanes. 2-(Dimethylamino)ethanol (DMAE) was distilled and stored over molecular sieves before use. Di*iso*propylamine was distilled on sodium before use. Hexane and THF were distilled and stored on sodium wire before use. Centrifugal thin-layer chromatography purifications were performed on silica gel (Merck silica gel 60 PF_{254} containing gypsum).

Procedure for the preparation of LTMP. To a solution of 2,2,6,6-tetramethylpiperidine (542 mg, 3.84 mmol, 1.0 eq) in THF (10 mL) was added dropwise *n*-BuLi (2.4 mL, 3.84 mmol, 1.0 eq) at –20 °C, under argon atmosphere. After stirring for 30 min at 0 °C, LTMP is ready to be used.

Procedure for the preparation of LDA. To a solution of di*iso*propylamine (388 mg, 3.84 mmol, 1.0 eq) in THF (10 mL) was added dropwise *n*-BuLi (2.4 mL, 3.84 mmol, 1.0 eq) at –20 °C, under argon atmosphere. After stirring for 30 min at 0 °C, LDA is ready to be used.

Procedure for the preparation of [*n*-BuLi/LiDMAE] superbase. To a solution of DMAE (712 mg, 8.0 mmol, 1.0 eq) in anhydrous hexane (5 mL) at –20 °C was added dropwise *n*-BuLi (10 mL, 1.6 M in hexanes, 16.0 mmol, 2.0 eq) under argon atmosphere. After 15 min at 0 °C, [*n*-BuLi/LiDMAE] superbase is ready to be used.

Lithiation sequences using the "way A" trapping conditions : preparation of derivatives 4a–7a

2-Chloro-3-methylthiopyrazine (4a). To a solution of LTMP (3.84 mmol, 1.2 eq) prepared as previously described in THF (10 mL) was added dropwise 2-chloropyrazine **1** (366 mg, 3.20 mmol, 1.0 eq) at –78 °C in THF (5 mL), under argon atmosphere. After 30 min of stirring at –78 °C, dimethyldisulfide (903 mg, 9.60 mmol, 3.0 eq) was added in THF (5 mL) at –78 °C. After the mixture was stirred for 1 h at –78 °C, the hydrolysis was performed with H_2O (10 mL) at –78 °C. The aqueous layer was then extracted twice with AcOEt (10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by centrifugal thin-layer chromatography with cyclohexane/AcOEt : 10/0 to 9/1 as eluent and led to the expected derivative **4a** (462 mg, 90%) as a white powder; mp 44–46 °C; ^{1}H NMR δ_H 2.54 (s, 3H), 7.99 (d, J = 2.6 Hz, 1H), 8.30 (d, J = 2.6 Hz, 1H); ^{13}C NMR δ_C 13.6, 137.6, 141.8, 146.5, 157.3; MS (EI) m/z 162 (37), 160 ([M]$^+$, 100), 127 (41), 125 (59), 79 (34); ESI-HRMS calcd for $C_5H_6ClN_2S$ (M+H)$^+$: 160.9935, found: 160.9933.

2-Fluoro-3-methylthiopyridine (5a). To a solution of LDA (3.84 mmol, 1.2 eq) prepared as previously described in THF (10 mL) was added dropwise 2-fluoropyridine **2** (310 mg, 3.20 mmol, 1.0 eq) at –70 °C in THF (5 mL), under argon atmosphere. After 4 h of stirring at –70 °C, dimethyldisulfide (903 mg, 9.60 mmol, 3.0 eq) was added in THF (5 mL) at –70 °C. After the mixture was stirred for 1 h at –70 °C, the hydrolysis was performed with H_2O (10 mL) at –70 °C. The aqueous layer was then extracted twice with AcOEt (10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by centrifugal thin-layer chromatography with cyclohexane/AcOEt : 9/1 to 8/2 as eluent and led to the expected derivative **5a** (375 mg, 82%) as a yellow liquid; ^{1}H NMR δ_H 2.47 (s, 3H), 7.10–7.18 (m, 1H), 7.56–7.65 (m, 1H), 7.94–7.99 (m, 1H); ^{13}C NMR δ_C 14.9 (d, J = 1.9 Hz), 121.9 (d, J = 4.3 Hz), 137.6 (d, J = 4.0 Hz), 143.4 (d, J = 14.0 Hz), 158.3, 162.0; MS

(EI) *m/z* 143 ([M]$^+$, 100), 128 (23), 101 (25); ESI-HRMS calcd for C_6H_7FNS (M+H)$^+$: 144.0278, found: 144.0262.

2-Chloro-3-methylthiopyridine (6a). To a solution of LTMP (3.84 mmol, 1.2 eq) prepared as previously described in THF (10 mL) was added dropwise 2-chloropyridine **3** (363 mg, 3.20 mmol, 1.0 eq) at −78 °C in THF (5 mL), under argon atmosphere. After 1 h 30 of stirring at −78 °C, dimethyldisulfide (903 mg, 9.60 mmol, 3.0 eq) was added in THF (5 mL) at −78 °C. After the mixture was stirred for 1 h at −78 °C, the hydrolysis was performed with H_2O (10 mL) at −78 °C. The aqueous layer was then extracted twice with AcOEt (10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by centrifugal thin-layer chromatography with cyclohexane/AcOEt : 9/1 to 8/2 as eluent and led to the expected derivative **6a** (459 mg, 90%) as an orange solid; mp, ^{1}H NMR, ^{13}C NMR and MS are in conformity with literature;[4,13] ESI-HRMS calcd for C_6H_7ClNS (M+H)$^+$: 159.9982, found: 159.9994.

2-Chloro-6-methylthiopyridine (7a). **7a** was prepared according to the procedure described in the literature.[9]

Lithiation sequences using the "way B" trapping conditions : preparation of derivatives 4b–7b

2,3-Bis(methylthio)pyrazine (4b). To a solution of LTMP (3.84 mmol, 1.2 eq) prepared as previously described in THF (10 mL) was added dropwise 2-chloropyrazine **1** (366 mg, 3.20 mmol, 1.0 eq) at −78 °C in THF (5 mL), under argon atmosphere. After 30 min of stirring at −78 °C, dimethyldisulfide (602 mg, 6.40 mmol, 2.0 eq) was added in THF (5 mL) at −78 °C. After the mixture was stirred for 30 min at −78 °C, the temperature was allowed to warm to 20 °C over a period of 1 h (for a good reproducibility, 35 min from −78 °C to 0 °C and 25 min from 0 °C to 20 °C). The temperature was then maintained at 20 °C during 3 h before that the hydrolysis was performed with H_2O (10 mL) at 20 °C. The aqueous layer was then extracted twice with AcOEt (10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by centrifugal thin-layer chromatography with cyclohexane/AcOEt : 10/0 to 9/1 as eluent and led to the expected derivative **4b** (501 mg, 91%) as a white powder; mp 88–90 °C; ^{1}H NMR δ_H 2.59 (s, 6H), 8.06 (s, 2H); ^{13}C NMR δ_C 13.2 (2C), 138.1 (2C), 154.7 (2C); MS (EI) *m/z* 172 ([M]$^+$, 80), 157 (100), 142 (25); ESI-HRMS calcd for $C_6H_9N_2S_2$ (M+H)$^+$: 173.0202, found: 173.0195.

2,3-Bis(methylthio)pyridine (5b) starting from 2-fluoropyridine (2). To a solution of LDA (4.80 mmol, 1.5 eq) prepared as previously described in THF (10 mL) was added dropwise 2-fluoropyridine **2** (310 mg, 3.20 mmol, 1.0 eq) at −70 °C in THF (5 mL), under argon atmosphere. After 4 h of stirring at −70 °C, dimethyldisulfide (602 mg, 6.40 mmol, 2.0 eq) was added in THF (5 mL) at −70 °C. After the mixture was stirred for 30 min at −70 °C, the temperature was allowed to warm to 20 °C over a period of 1 h (for a good reproducibility, 35 min from −70 °C to 0 °C and 25 min from 0 °C to 20 °C). The temperature was then maintained at 20 °C during 17 h before that the hydrolysis was performed with H_2O (10 mL) at 20 °C. The aqueous layer was then extracted twice with AcOEt (10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by centrifugal thin-layer chromatography with cyclohexane/AcOEt : 9/1 to 8/2 as eluent and led to the expected derivative **5b** (492 mg, 90%) as an orange liquid; ^{1}H NMR δ_H 2.46 (s, 3H), 2.58 (s, 3H), 6.96 (dd, J = 4.8 Hz, J' = 7.7 Hz, 1H), 7.41 (dd, J = 1.6 Hz, J' = 7.7 Hz, 1H), 8.27 (dd, J = 1.6 Hz, J' = 4.8 Hz, 1H); ^{13}C NMR δ_C 13.7, 16.1, 119.3, 132.5, 134.0, 146.0, 158.7; MS (EI) *m/z* 171 ([M]$^+$, 45), 156 (100), 124 (25), 79 (34); ESI-HRMS calcd for $C_7H_{10}NS_2$ (M+H)$^+$: 172.0249, found: 172.0259.

2,3-Bis(methylthio)pyridine (5b) starting from 2-chloropyridine (3). To a solution of LTMP (4.80 mmol, 1.5 eq) prepared as previously described in THF (10 mL) was added dropwise 2-chloropyridine **3** (363 mg, 3.20 mmol, 1.0 eq) at −78 °C in THF (5 mL), under argon atmosphere. After 1 h 30 min of stirring at −78 °C, dimethyldisulfide (602 mg, 6.40 mmol, 2.0 eq) was added in THF (5 mL) at −78 °C. After the mixture was stirred for 30 min at −78 °C, the temperature was allowed to warm to 20 °C over a period of 1 h (for a good reproducibility, 35 min from −78 °C to 0 °C and 25 min from 0 °C to 20 °C). The temperature was then refluxed during 20 h before that the hydrolysis was performed with H_2O (10 mL) at 20 °C. The aqueous layer was then extracted twice with AcOEt (10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by centrifugal thin-layer chromatography with cyclohexane/AcOEt : 9/1 to 8/2 as eluent and led to the expected derivative **5b** (421 mg, 77%).

2,6-Bis(methylthio)pyridine (7b). To a solution of [*n*-BuLi/LiDMAE] superbase (8.00 mmol, 3.0 eq) prepared as previously described in hexane (5 mL) was added dropwise 2-chloropyridine **3** (303 mg, 2.67 mmol, 1.0 eq) at −78 °C in hexane (5 mL), under argon atmosphere. After 1 h of stirring at −78 °C, dimethyldisulfide (1004 mg, 10.68 mmol, 4.0 eq) was added in THF (10 mL) at −78 °C. After the mixture was stirred for 30 min at −78 °C, the temperature was allowed to warm to 20 °C over a period of 1 h (for a good reproducibility, 35 min from −78 °C to 0 °C and 25 min from 0 °C to 20 °C). The solvents are then removed under reduced pressure (vacuum line), and THF (20 mL) was added under argon atmosphere. The temperature was then refluxed during 20 h before that the hydrolysis was performed with H_2O (10 mL) at 20 °C. The aqueous layer was then extracted twice with AcOEt (10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by centrifugal thin-layer chromatography with cyclohexane/AcOEt : 10/0 to 9/1 as eluent and led to the expected derivative **7b** in mixture with **7a** (398 mg, 53 + 36%, NMR yields) as a yellow liquid; ^{1}H-NMR δ_H 2.58 (s, 6H), 6.86 (d, J = 7.8 Hz, 2H), 7.27 (t, J = 7.8 Hz, 1H); ^{13}C NMR δ_C 12.3 (2C), 115.7 (2C), 134.7, 158.4 (2C); MS (EI) *m/z* 171 ([M]$^+$, 100), 137 (63), 110 (25).

2-Chlorofuro[3,2-*b*]pyridine (8). To a solution of furo[3,2-*b*]pyridine[5] (1.43 g, 12.0 mmol, 1.0 eq) in THF (100 mL) was added dropwise *n*-BuLi (11.25 mL, 18.0 mmol, 1.5 eq) at −78 °C, under argon atmosphere. After 1 h of stirring at −78 °C, hexachloroethane (5.69 g, 24.0 mmol, 2.0 eq) was added in THF (50 mL) at −95 °C. After the mixture was stirred for 1 h at −95 °C, the hydrolysis was performed with H_2O (100 mL) at −95 °C. The aqueous layer was then extracted twice with AcOEt (100 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by chromatography on silica gel with cyclohexane/AcOEt : 10/0 to 8/2 as eluent and led to the expected derivative **8** (1.29 g, 70%) as a yellow solid; mp[14] 44–50 °C; ^{1}H

NMR δ_H 6.83 (d, J = 0.8 Hz, 1H), 7.21 (dd, J = 4.9 Hz, J' = 8.4 Hz, 1H), 7.68 (ddd, J = 0.8 Hz, J' = 1.2 Hz, J'' = 8.4 Hz, 1H), 8.51 (dd, J = 1.2 Hz, J' = 4.9 Hz, 1H); ^{13}C NMR δ_C 105.0, 117.8, 119.2, 146.4, 146.5, 147.7, 147.9; MS (EI) m/z 155 (33), 153 ([M]$^+$, 100), 127 (28), 125 (74), 90 (81), 63 (59); ESI-HRMS calcd for C_7H_5ClNO (M+H)$^+$: 154.0054, found: 154.0056. It is to be noted that 2,3-dichlorofuro[3,2-*b*]pyridine is formed during the reaction but is easily removed by chromatography. **8** is quite unstable and has to be stored carefully.

General procedure for the double functionalisation of furo[3,2-*b*]pyridine : preparation of derivatives 9b–15b and 11a. To a solution of 2-chlorofuro[3,2-*b*]pyridine **8** (123 mg, 0.80 mmol, 1.0 eq) in THF (10 mL) was added dropwise *n*-BuLi (0.6 mL, 0.96 mmol, 1.2 eq) at –20 °C, under argon atmosphere. After 1 h of stirring at –20 °C, the appropriate *E*-Nu reagent (1.6 mmol, 2.0 eq) was added in THF (5 mL) at –20 °C. The temperature was allowed to warm to 20 °C over a period of 20 min and was next maintained at 20 °C during 40 min before that the hydrolysis was performed with H_2O (10 mL) at 20 °C. The aqueous layer was then extracted twice with AcOEt (10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by centrifugal thin-layer chromatography.

2,3-Bis(methylthio)furo[3,2-*b*]pyridine (9b). The product was prepared according to the general method described herein with dimethyldisulfide (151 mg, 1.6 mmol, 2.0 eq) as the *E*-Nu reagent. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt : 9/1 to 8/2 as eluent and led to the expected derivative **9b** (135 mg, 80%) as a yellow oil; ^{1}H NMR δ_H 2.53 (s, 3H), 2.65 (s, 3H), 7.16 (dd, J = 4.8 Hz, J' = 8.3 Hz, 1H), 7.65 (dd, J = 1.3 Hz, J' = 8.3 Hz, 1H), 8.53 (dd, J = 1.3 Hz, J' = 4.8 Hz, 1H); ^{13}C NMR δ_C 15.4, 17.5, 113.7, 117.4, 118.6, 146.1, 148.6, 148.8, 158.1; MS (EI) m/z 211 ([M]$^+$, 100), 196 (88), 178 (81); ESI-HRMS calcd for $C_9H_{10}NOS_2$ (M+H)$^+$: 212.0198, found: 212.0205.

2,3-Bis(phenylthio)furo[3,2-*b*]pyridine (10b). To a solution of 2-chlorofuro[3,2-*b*]pyridine **8** (123 mg, 0.80 mmol, 1.0 eq) in THF (10 mL) was added dropwise *n*-BuLi (0.6 mL, 0.96 mmol, 1.2 eq) at –20 °C, under argon atmosphere. After 1 h of stirring at –20 °C, diphenyldisulfide (349 mg, 1.6 mmol, 2.0 eq) was added in THF (5 mL) at –20 °C. The temperature was allowed to warm to 20 °C over a period of 20 min and was next warm at 50 °C during 40 min before that the hydrolysis was performed with H_2O (10 mL) at 20 °C. The aqueous layer was then extracted twice with AcOEt (10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by centrifugal thin-layer chromatography with cyclohexane/AcOEt : 9/1 to 8/2 as eluent and led to the expected derivative **10b** (228 mg, 85%) as a yellow gummy; ^{1}H NMR δ_H 7.10–7.22 (m, 4H), 7.25–7.31 (m, 5H), 7.40–7.45 (m, 2H), 7.64 (dd, J = 1.3 Hz, J' = 8.3 Hz, 1H), 8.55 (dd, J = 1.3 Hz, J' = 4.8 Hz, 1H); ^{13}C NMR δ_C 115.4, 118.3, 119.9, 126.3, 128.3, 128.5, 129.0, 129.4, 130.8, 132.0, 135.3, 147.0, 147.6, 149.3, 158.9; MS (EI) m/z 335 ([M]$^+$, 100), 302 (25), 226 (71), 198 (50), 154 (28); ESI-HRMS calcd for $C_{19}H_{14}NOS_2$ (M+H)$^+$: 336.0511, found: 336.0513.

2-Chloro-3-(pyridin-2-ylthio)furo[3,2-*b*]pyridine (11a). The product was prepared according to the general method described herein with bis(pyridin-2-yl)disulfide (352 mg, 1.6 mmol, 2.0 eq) as the *E*-Nu reagent. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt : 5/5 to 2/8 as eluent and led to the expected derivative **11a** (137 mg, 65%) as a white powder; mp 121–123 °C; ^{1}H NMR δ_H 6.96–7.10 (m, 2H), 7.30 (dd, J = 4.3 Hz, J' = 8.1 Hz, 1H), 7.47 (dd, J = 7.3 Hz, J' = 7.3 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 8.35 (d, J = 3.8 Hz, 1H), 8.59 (d, J = 4.3 Hz, 1H); ^{13}C NMR δ_C 106.6, 118.4, 120.0, 120.4, 120.8, 136.8, 147.1, 147.3, 147.5, 149.7, 151.7, 157.4; MS (EI) m/z 227 ([M–35]$^+$, 100); ESI-HRMS calcd for $C_{12}H_8ClN_2OS$ (M+H)$^+$: 263.0040, found: 263.0049.

2,3-Bis(pyridin-2-ylthio)furo[3,2-*b*]pyridine (11b). To a solution of 2-chlorofuro[3,2-*b*]pyridine **8** (123 mg, 0.80 mmol, 1.0 eq) in THF (10 mL) was added dropwise *n*-BuLi (0.6 mL, 0.96 mmol, 1.2 eq) at –20 °C, under argon atmosphere. After 1 h of stirring at –20 °C, bis(pyridin-2-yl)disulfide (352 mg, 1.6 mmol, 2.0 eq) was added in THF (5 mL) at –20 °C. The temperature was allowed to warm to 20 °C over a period of 20 min and was next warm at 60 °C during 5 h 40 min before that the hydrolysis was performed with H_2O (10 mL) at 20 °C. The aqueous layer was then extracted twice with AcOEt (10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by centrifugal thin-layer chromatography with cyclohexane/AcOEt : 5/5 to 2/8 as eluent and led to the expected derivative **11b** (124 mg, 46%) as an orange solid; mp 86–89 °C; ^{1}H NMR δ_H 6.96 (ddd, J = 1.0 Hz, J' = 4.9 Hz, J'' = 7.3 Hz, 1H), 7.04–7.16 (m, 2H), 7.22 (dd, J = 0.8 Hz, J' = 8.0 Hz, 1H), 7.28–7.70 (m, 3H), 7.83 (dd, J = 1.2 Hz, J' = 8.4 Hz, 1H), 8.27–8.34 (m, 1H), 8.36–8.44 (m, 1H), 8.64 (dd, J = 1.2 Hz, J' = 4.7 Hz, 1H); ^{13}C NMR δ_C 113.2, 117.9, 119.0, 120.3, 120.7, 121.4, 121.5, 123.1, 134.0, 136.6, 137.2, 147.2, 149.5, 150.0, 156.2, 156.4, 157.7; MS (EI) m/z 227 ([M–110]$^+$, 100); ESI-HRMS calcd for $C_{17}H_{12}N_3OS_2$ (M+H)$^+$: 338.0416, found: 338.0429.

2-(Dimethylamino)-3-formylfuro[3,2-*b*]pyridine (12b). The product was prepared according to the general method described herein with dimethylformamide (117 mg, 1.6 mmol, 2.0 eq) as the *E*-Nu reagent. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt : 5/5 to 0/10 as eluent and led to the expected derivative **12b** (128 mg, 84%) as a beige powder; mp 113–115 °C; ^{1}H NMR δ_H 3.45 (s, 6H), 6.98 (dd, J = 5.1 Hz, J' = 8.1 Hz, 1H), 7.39 (dd, J = 1.3 Hz, J' = 8.1 Hz, 1H), 8.35 (dd, J = 1.3 Hz, J' = 5.1 Hz, 1H), 10.15 (s, 1H); ^{13}C NMR δ_C 40.5 (2C), 95.2, 115.3, 116.5, 142.1, 145.6, 150.2, 163.4, 181.4; IR (KBr) ν 1629 (br); MS (EI) m/z 190 ([M]$^+$, 44), 162 (25), 147 (100); ESI-HRMS calcd for $C_{10}H_{11}N_2O_2$ (M+H)$^+$: 191.0815, found: 191.0822.

2-(Piperidin-1-yl)-3-formylfuro[3,2-*b*]pyridine (13b). The product was prepared according to the general method described herein with *N*-formylpiperidine (181 mg, 1.6 mmol, 2.0 eq) as the *E*-Nu reagent. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt : 7/3 to 5/5 as eluent and led to the expected derivative **13b** (132 mg, 72%) as an orange solid; mp 63–65 °C; ^{1}H NMR δ_H 1.74–1.76 (m, 6H), 3.93–3.96 (m, 4H), 6.97 (dd, J = 5.1 Hz, J' = 8.1 Hz, 1H), 7.37 (dd, J = 1.3 Hz, J' = 8.1 Hz, 1H), 8.31 (dd, J = 1.3 Hz, J' = 5.1 Hz, 1H), 10.13 (s, 1H); ^{13}C NMR δ_C 24.1, 26.1 (2C),

49.4 (2C), 94.5, 115.2, 116.4, 141.8, 145.4, 150.4, 161.8, 181.2; IR (KBr) ν 1667 (br); MS (EI) *m/z* 230 ([M]$^+$, 33), 202 (25), 147 (18), 134 (100); ESI-HRMS calcd for $C_{13}H_{15}N_2O_2$ (M+H)$^+$: 231.1128, found: 231.1136.

2-(Morpholin-4-yl)-3-formylfuro[3,2-*b*]pyridine (14b). The product was prepared according to the general method described herein with *N*-formylmorpholine (184 mg, 1.6 mmol, 2.0 eq) as the *E*-Nu reagent. Purification by centrifugal thin-layer chromatography was performed with cyclohexane/AcOEt : 5/5 to 0/10 as eluent and led to the expected derivative **14b** (112 mg, 60%) as an orange powder; mp 94–96 °C; ^{1}H NMR δ_H 3.87 (t, J = 5.1 Hz, 4H), 4.06 (t, J = 5.1 Hz, 4H), 7.02 (dd, J = 5.0 Hz, J' = 8.1 Hz, 1H), 7.42 (dd, J = 1.3 Hz, J' = 8.1 Hz, 1H), 8.35 (dd, J = 1.3 Hz, J' = 5.0 Hz, 1H), 10.14 (s, 1H); ^{13}C NMR δ_C 48.2 (2C), 66.6 (2C), 95.1, 115.6, 116.9, 141.8, 145.7, 149.9, 161.6, 181.7; IR (KBr) ν 1659 (br); MS (EI) *m/z* 232 ([M]$^+$, 75), 201 (58), 174 (41), 147 (100), 133 (43), 119 (33), 91 (40); ESI-HRMS calcd for $C_{12}H_{13}N_2O_3$ (M+H)$^+$: 233.0921, found: 233.0922.

2-(Dimethylamino)-3-acetylfuro[3,2-*b*]pyridine (15b). To a solution of 2-chlorofuro[3,2-*b*]pyridine **8** (123 mg, 0.80 mmol, 1.0 eq) in THF (10 mL) was added dropwise *n*-BuLi (0.6 mL, 0.96 mmol, 1.2 eq) at –20 °C, under argon atmosphere. After 1 h of stirring at –20 °C, dimethylacetamide (139 mg, 1.6 mmol, 2.0 eq) was added in THF (5 mL) at –20 °C. The temperature was then maintained at –20 °C during 30 min before that the hydrolysis was performed with H_2O (10 mL) at –20 °C. The aqueous layer was then extracted twice with AcOEt (10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by centrifugal thin-layer chromatography with cyclohexane/AcOEt : 7/3 to 5/5 as eluent and led to the expected derivative **15b** (126 mg, 77%) as a yellow powder; mp 66–68 °C; ^{1}H NMR δ_H 2.84 (s, 3H), 3.25 (s, 6H), 6.95 (dd, J = 5.0 Hz, J' = 8.0 Hz, 1H), 7.39 (dd, J = 1.3 Hz, J' = 8.0 Hz, 1H), 8.36 (dd, J = 1.3 Hz, J' = 5.0 Hz, 1H); ^{13}C NMR δ_C 31.1, 40.8 (2C), 96.4, 115.1, 115.9, 142.2, 144.9, 149.1, 164.9, 192.3; IR (KBr) ν 1648 (br); MS (EI) *m/z* 204 ([M]$^+$, 85), 189 (100), 175 (20), 161 (33), 133 (40), 119 (19); ESI-HRMS calcd for $C_{11}H_{13}N_2O_2$ (M+H)$^+$: 205.0972, found: 205.0983.

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