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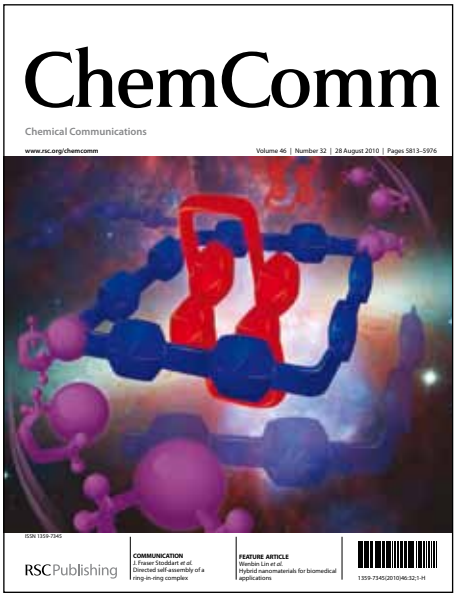


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COMMUNICATION

# An efficient labeling strategy of drug like molecules with functionalized alkyl linkers using CH-activation†

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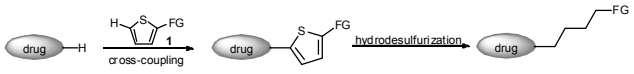
***Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX***

**DOI: 10.1039/b000000x**

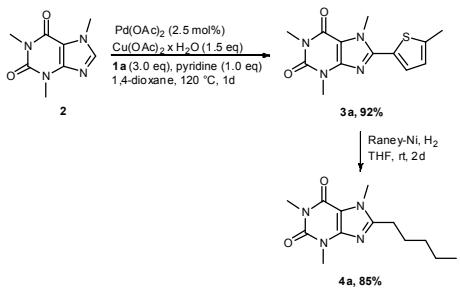
**Heterocyclic drugs can be cross-coupled with functionalized thiophene derivatives under dehydrogenative conditions using Pd-catalysts. Upon reductive desulfurization an alkyl linker is introduced with a functional group at its terminus, which will allow the immobilization of the drug molecule onto a solid support for chemical proteomics.**

Compound-centric chemical proteomics is an emerging method for the identification of a drug's entire protein targets.[1] For any chemical proteomics effort immobilization of the drug molecule under investigation to a solid support is a necessary and challenging requirement as the tethering has to occur at a site without obstructing its biological activity. In the past, tethering has been achieved most of the time by taking advantage of existing functional groups in the drug.[2] Unfortunately, these are very frequently essential for binding to the active site. To address this problem, we have developed a novel linking strategy for heteroaromatic drugs exploiting CH-groups for attachment of an alkyl linker. Despite the considerable progress recently made in CH-activation,[3-5] the cross-coupling between $sp^2$-CH- and $sp^3$-CH-centers has remained an unsolved problem without a general solution.[6] We have developed a two-step procedure, which presents a quite flexible and general access to this compound class. In the first step a biaryl C-C bond between the drug and a substituted thiophene **1** is formed by dehydrogenative cross-coupling (Scheme 1).[5] The second step involves the selective reduction and desulfurization of the thiophene derivative to the corresponding alkyl chain yielding the alkyl-modified drug.[7]




**Scheme 1** General strategy for drug tethering.

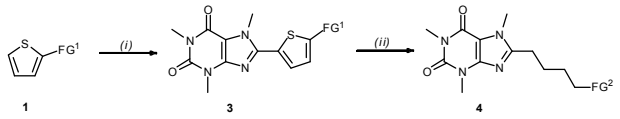
For the proof of concept studies of this two-step strategy, we chose caffeine (**2**) as our model compound, representing a biologically active heterocycle, and explored 2-methylthiophene (**1a**) as a coupling partner (Scheme 2). For the dehydrogenative C-C cross-coupling of caffeine (**2**) with 2-methylthiophene (**1a**) we used the conditions of Xi et al, which delivers the desired product **3a** in 96% yield.[5a] For the subsequent desulfurization and hydrogenation of the thiophene derivative **3a** we screened several conditions. Ultimately, a combination of Raney-Ni (W-2 type)[8] and hydrogen in THF as a solvent turned out to be optimal and delivered 5-pentyl caffeine **4a** in 85% yield. The beneficial effect of THF was surprising to us as the substrate was poorly soluble in it, while with the good solubilizing solvent chloroform no conversion was monitored. Attempts with Pd catalysts[9] supported on charcoal, $Al_2O_3$ or $BaSO_4$ and metal-free versions of the desulfurization[10] with phosphine and radical initiator failed or showed unsatisfying yields.




**Scheme 2** Proof of concept with model substrate.

Having demonstrated that our two step strategy (CH-coupling/desulfurization strategy) provides an attractive method for the alkyl modification of heterocyclic compounds, we were encouraged to define the scope and limitations of this method. Driven by our original motivation to provide a tool for chemical proteomics, we first screened various substituted thiophenes **1b-j**, which after hydrogenative desulfurization should produce alkyl linkers with terminal functional groups suitable for immobilization.[11] Results of the C-C cross-coupling and subsequent desulfurization are shown in table 1. To our delight, the protected thiophenes **1f-g** and **1j** gave excellent yields after optimization of the reaction conditions. In contrast all other coupling reactions with nitrile **1b**, nitro **1c** or amino **1e** substrates resulted in low up to moderate yields. The Henry product **1d** underwent aldol cleavage and formed the coupled aldehyde. The carboxylic acid **1h** did not react. The free alcohol **1i** was converted in acceptable 63% yield.

**Table 1** Screening of thiophenes in drug tethering.



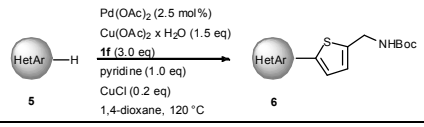

| Entry | FG[1] of **1** | Yield (%) **3b-j** | Yield (%) **4b-j** | FG[2] of **4** |
|---|---|---|---|---|
| 1 | CN **1b** | 50[a] | 3 | $CH_2$-$NH_2$ **4b** |
| 2 | $NO_2$ **1c** | 25 | 2 | $NH_2$ **4c** |
| 3 | CH=CH-$NO_2$ **1d** | -[d] | - | - |
| 4 | $CH_2$-$NH_2$ **1e** | <1% | - | - |
| 5 | $CH_2$-NHBoc **1f** | 99[b] | 83 | $CH_2$-NHBoc **4f** |
| 6 | $CH_2$-NHCbz **1g** | 87[c] | 40 | $CH_2$-$NH_2$ **4b** |
| 7 | COOH **1h** | - | - | - |
| 8 | $CH_2$-OH **1i** | 63 | 40 | $CH_2$-OH **4i** |
| 9 | $CH_2$-OBn **1j** | 89 | 99 | $CH_2$-OH **4i** |

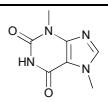
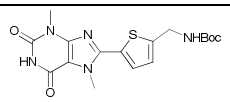
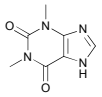
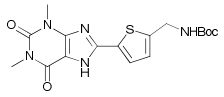
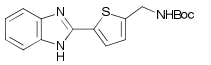
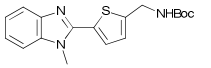
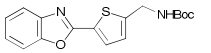
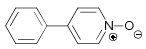
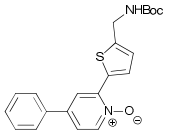
*(i)* Caffeine (1.0 eq), $Pd(OAc)_2$ (2.5 mol%), $Cu(OAc)_2 \times H_2O$ (1.5 eq), **1b-j** (3.0 eq), pyridine (1.0) eq, 1,4-dioxane, 120 °C, 1d; (ii) Raney-Ni, $H_2$, THF, rt. [a]Reaction according to the procedure of Ref [5a]. [b]Addition of 0.2 eq CuCl. [c]Addition of 0.1 eq 1,10-phenanthroline. [d]Aldol cleavage of **1d** occurred. The corresponding cross-coupled aldehyde was formed.

Reduction of these cross-coupling products **3** with Raney-Nickel gave similar results. Free amino groups inhibited the reaction and just traces of product **4** were formed. Substrates **3b-c**, where the functional groups would under the conditions of desulfurization be simultaneously converted to the terminal free amines **4b-c**, also resulted in low conversion. Gratifyingly, the *N*-Boc-protected substrate **3f** was reduced in very good overall yield of 82% for the two-step procedure. Final deprotection under acidic conditions with TFA furnishes the corresponding caffeine pentylamine **4b** quantitatively. Similiarly, Cbz-protected substrate **3g** was also an excellent substrate for dehydrogenative coupling, but delivered directly the free amine **4b** upon hydrogenation, although in lower yields. The benzyl-protected, cross-coupled alcohol **3j** was converted to 5-hydroxypentyl caffeine **4i** in excellent 99% yield. This nearly quantitative conversion could be achieved in a stepwise reduction of **3j** via hydrodesulfurization first, followed by deprotection of the benzyl group by Raney-Nickel. With the benzyl-protected thiophenemethanol **1j** we were able to accomplish caffeine linkage within two steps in 88% overall yield.

Having established a route for introducing $NH_2$- resp OH-functionalized linkers with caffeine (**2**) as substrate, we were interested to make inroads to explore the scope and limitations of this strategy by investigating other substrates embodying priviliged heterocyclic scaffolds (Table 2). We screened imidazol-type heterocycles with and without free NH-groups **5a-d**, indole, quinoline, *N*-oxide **5f** and benzoxazole **5e** to convert them with our most attractive thiophene derivative (*N*-Boc-protected thiophene **1f**) under the optimized reaction conditions. Unfortunately, reactivity of these substrates was rather low and required considerable optimization. Again free NH- or $NH_2$-groups turned out to be detrimental for coupling yields. Indole and quinoline derivatives did not react so far. While there are not yet universal conditions for dehydrogenative coupling of thiophenes **1** with a broad range of coupling partners available, we do feel that considering the rapid progress in the field of CH-activation that with considerable efforts in optimization for each substrate it might be possible to find suitable conditions for most of them. For now we could successfully demonstrate our approach for theobromine (**5a**), *N*-methylbenzimidazole (**5d**) and pyridine-*N*-oxide **5f**.

**Table 2** Cross-coupling of various heteroarenes with *N*-Boc-protected thiophene **1f**.




| Entry | Heteroarene | Product | Yield (%) |
|---|---|---|---|
| 1 |  **5a*** |  **6a** | 66 |
| 2 |  **5b** |  **6b** | - |
| 3 |  **5c** |  **6c** | - |
| 4 |  **5d** |  **6d** | 50 |
| 5 |  **5e** |  **6e** | 6 |
| 6 |  **5f**** |  **6f** | 51 |

*__6a__ was further desulfurized and deprotected to yield the tethered theobromine **8a** in 58%. **Cross-coupling proceeded without CuCl.

In summary, we have successfully established an efficient route for the attachment of linker groups to tether heteroaromatic drugs to a solid support using a so far unprecedented way of formal $C(sp^2)$-$C(sp^3)$ coupling, which is performed in two steps: involving first dehydrogenative cross-coupling using double CH-activation followed by desulfurization and hydrogenation in one step resulting in the corresponding alkyl chain with a functional group at its terminus. After optimization with caffeine (**2**) as substrate we achieved an excellent overall yield of 81% using Boc-protected thiophene amine **1f** and 88% using benzyl-protected thiophene methanol **1j**. From a panel of several privileged *N*-heterocyclic substrates **5** several are accepted but need further optimization steps to reach excellent yields. This method so far is limited to *N*-heterocycles favoring imidazole type

arenes. We are very optimistic that with the ongoing progress in dehydrogenative CH-coupling and CH-activation our two step method using the reductive desulfurization of thiophenes will become a broadly useable tool for attaching functionalized $sp^3$-chains to arenes and heteroarenes.

This research was supported by the PLACEBO (Platform for Chemical Biology) project as part of the Austrian Genome Project GEN-AU funded by the Forschungsförderungs-gesellschaft (FFG) und Bundesministerium für Wissenschaft und Forschung (BMWF). Lisa Offner, Christian Pichler and Katharina Plasch are gratefully acknowledged for skillful assistance in the lab.

## Notes and references

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