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Arylopeptoid oligomers functionalised by combinatorial or sequential on-resin click chemistry using Copper(I)-*N*-heterocyclic carbene catalyst

Ayman Akhdar,^a Sophie Faure^{*b} and Arnaud Gautier^{*b}

Efficient on-resin click chemistry protocol using Copper (I)-*N*-heterocyclic carbene catalyst, a stable source of Cu(I), is developed for post-functionalization of *N*-alkylated aminomethylbenzamide oligomers (arylopeptoids). The accessibility to a panel of polyfunctionalized *N*-substituted aromatic oligoamides by solid-phase synthesis is demonstrated using combinatorial and sequential approaches.

N-alkylated aromatic oligoamides is a class of oligomers still underexplored.¹ Contrary to other aromatic oligoamides relying on hydrogen-bonding networks for their structuration,² the conformational modularity and adaptability of *N*-substituted aromatic oligoamides make them particularly interesting abiotic oligomers for applications in the medical and/or materials field.¹ One major issue for their development is the ability to provide well-defined sequences with high chemical diversity. To this aim, *N*-substituted aminomethylbenzamide oligomers are particularly well adapted and represent particularly promising aromatic oligoamides.³ They were named arylopeptoids⁴ since their backbone can be considered as the peptoid (*N*-substituted glycine oligomer)⁵ backbone in which a phenyl group is inserted (Figure 1). Sequence-defined arylopeptoids are accessible *via* solid-phase submonomer method wherein each residue is created in two steps: acylation/substitution⁶ or acylation/reductive amination.⁷ The submonomer method potentially provides access to highly diverse structures.⁸ Another way to introduce chemical diversity is the post-functionalization of formed oligomers. This strategy is particularly attractive in the context of multivalent display⁹ and has never been studied to access functionalised arylopeptoid oligomers. Therefore, click chemistry and especially the CuAAC reaction which was introduced two decades ago by Kolb, Finn and Sharpless, could be of particular importance as it is modular and high yielding.

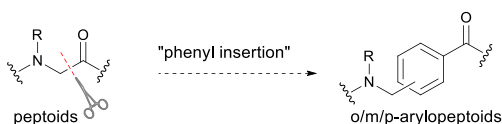


Figure 1 Analogy between peptoid and arylopeptoid oligomeric structures.

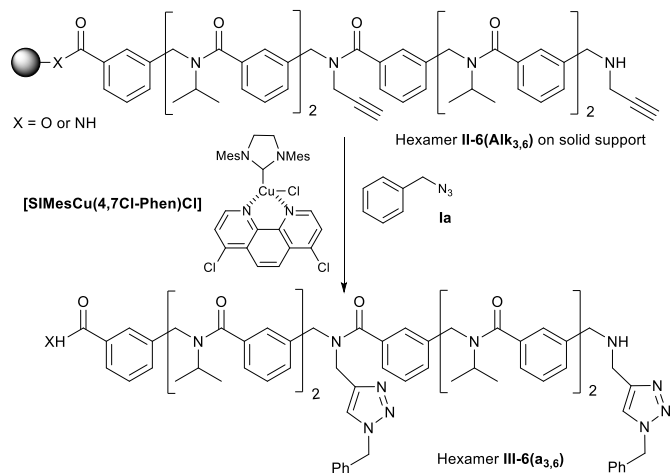
From the point of view of the synthetic chemist, combinatorial synthesis on solid support allows the rapid preparation of large and organized collections of compounds (molecular libraries) which constitute an essential source in drug discovery.¹⁰ Nevertheless, CuAAC on solid support requires sometimes large amount of copper catalyst that is difficult to remove and therefore could contaminate the samples.¹¹ Also, several drawbacks from ascorbic acid has been reported (dehydroascorbate reacts with amines, lysine and arginine).¹² Moreover, some sensible functional groups are damaged by the hydroxy radicals that are produced by the reaction of Cu(I) and oxygen.¹³ Therefore, copper(I)-*N*-heterocyclic carbenes (Cu-NHCs) that are recognized as stable source of Cu(I) offer great opportunities in this field. Indeed, several publications from our group report applications in the peptide field.¹⁴ Here, we report the application of [SiMesCu(4,7 Cl-Phen)Cl] as CuAAC catalyst to the on-resin construction of an arylopeptoid library.

To examine the possibility of post-functionalisation of *meta*-arylopeptoid oligomers by 'on support' click chemistry process, we started our investigation by reacting benzyl azide (**1a**) with synthesized resin-bound hexamer **II-6(Alk_{3,6})** containing four isopropylamine and two propargylamine side chains (Scheme 1; see ‡ for the nomenclature). This model reaction was studied on four different resins; three polystyrene-based resins: 2-chlorotrityl chloride, Rink Acid and Rink Amide, and one (polyethylene glycol)-based resin: trityl-OH ChemMatrix[®]. The Rink amide resin providing oligomers with a primary amide in C-terminal (X = NH) and the others leading to oligomers with an acid function (X = O).

First, the hexamer **II-6(Alk_{3,6})** was prepared on the various resins using published protocols (ESI for details).⁶ We used [SiMesCu(4,7Cl-Phen)Cl]^{‡‡} in a mixture of methanol and dichloromethane (2/8) to keep a good swelling of the resin in presence of a proton source that is essential for the catalysis. In these conditions, the outcome is strongly dependant of the type of resin. A total lack of reactivity was observed using 2-chlorotrityl resin with 20 mol-% catalyst or more as demonstrate by the recovery of the hexamer **II-6(Alk_{3,6})** in 95% yield after cleavage. In addition, the colour of the solution stays reddish, even after 24h, suggesting that the catalyst is not destroyed. Using trityl-OH ChemMatrix[®] resin (20 mol-% catalyst), a total conversion to **III-6(a_{3,6})** takes place at room temperature after 16h.

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Scheme 1. Model reaction to study the on-resin click chemistry process

However, HPLC-mass spectroscopy proved that the products consist in a mixture of mono- and double-clicked compounds in a ratio 7/3. Increasing the temperature to 50°C allows to obtain a total conversion of the two propargyl groups after 2h. Regardless the temperature, in all cases a 50% purity measured by HPLC was observed after cleavage, hampering the use of the trityl-OH ChemMatrix® as solid support. Using Rink acid resin and performing the CuAAC reaction at 50°C during 3h, we were pleased to obtain full conversion and acceptable crude HPLC purity (>70%) for III-6(a_{3,6}) (X = O) but in low yields (ranging from 20 to 50%). We also noticed that the reaction colour turns rapidly from red to greenish, suggesting a fast destruction of the catalyst and the production of copper(II). By analysis of the reaction mixture and the washing solvent, we found that partial cleavage of the aryloleptoid oligomer occurred during the click step, explaining low yields obtained. Decreasing the temperature to RT doesn't improve the results (80% conversion after 18h but cleavage from the resin still occurring). Thus, we concluded that a partial cleavage occurs (either due to the Lewis acidity of Cu^I or the small amount of HCl realized in the media by the catalyst) competitively with the CuAAC reaction. From these first tests, the CuAAC reaction using copper(I)-N-heterocyclic carbene [SIMesCu(4,7Cl-Phen)Cl] proved to be difficult to efficiently access functionalised aryloleptoid oligomers with a C-terminal acid group. By contrast, using Rink Amide resin, we were delighted to find a lack of cleavage, a total conversion to III-6(a_{3,6}) featuring a C-terminal primary amide (X = NH) with good reproducibility, crude purity (84%) and yield (85%) after 5 hours at room temperature using 20 mol-% catalyst (Figure 2). Importantly, the solution stays reddish, suggesting a good stability of the catalyst. At 50°C, we were also able to decrease the reaction time to 1 h without alteration of yield and purity and reach the same results using only 1 mol-% of catalyst after 7 h. For comparison, the more classical conditions¹⁵ using CuI catalyst (5 mol%) in presence of ascorbic acid (8 mol-%) and Hünig base (15 mol-%) in DMF/piperidine (7/3) at 50°C affords a low conversion (30%) to an equimolar mixture of mono- and bis-triazole after 3h.

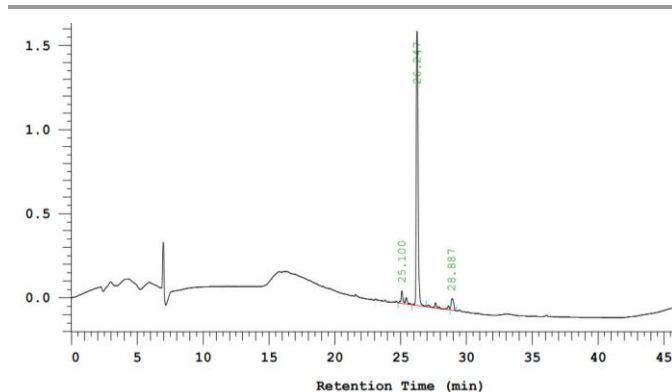
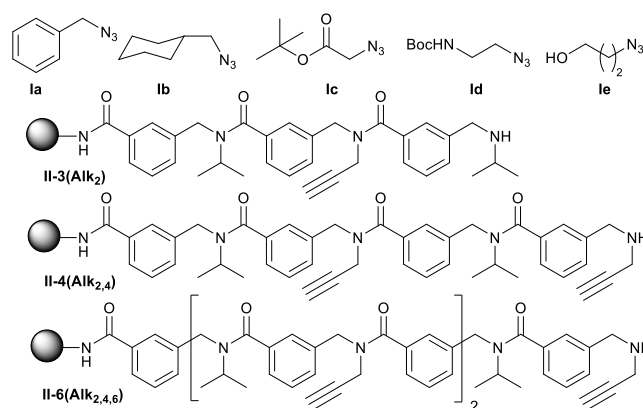


Figure 2. HPLC chromatogram at 220 nm of crude III-6(a_{3,6}).

In view of these results, to continue this work we decided to use only Rink Amide resin-bound oligomers and to perform on support CuAAC reaction with 5 mol-% of [SIMesCu(4,7Cl-Phen)Cl] as catalyst at 50°C in presence of four equivalents of azides per alkyne. Using these optimized conditions, a set of functionalized azides (**Ia-e**) were tested on II-3(Alk₂), II-4(Alk_{2,4}) and II-6(Alk_{2,4,6}) resin-bound oligomers (Scheme 2). The collection of azides contains benzyl (**Ia**), cyclohexyl (**Ib**), *tert*-butyl carboxylic ester (**Ic**), Boc-protected amine (**Id**), and alcohol (**Ie**) groups.



Scheme 2. Collection of azides and resin-bound starting materials.

We were glad to obtain good yields and purities regardless the number and the position(s) of the alkyne(s) (table 1). In all cases, a total conversion was observed by LCMS associated with good crude purities. Therefore, a large range of functionalized triazoles could be introduced efficiently at different positions of the aryloleptoids.

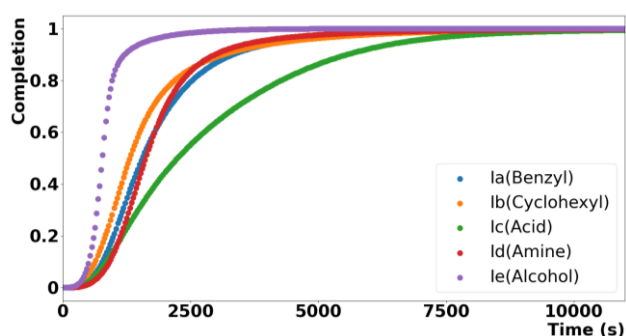
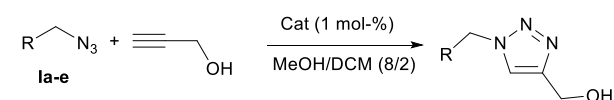
Table 1: Clicked aryloleptoid from II-3(Alk₂), II-4(Alk_{2,4}) and II-6(Alk_{2,4,6})

Aryloleptoid	Isolated yield (%)	Isolated purity (%) ^a
III-3(a ₂)	98	98
III-3(b ₂)	85	85
III-3(c ₂)	97	96
III-3(d ₂)	85	97
III-3(e ₂)	90	99
III-4(a _{2,4})	85	87
III-4(b _{2,4})	75	95
III-4(c _{2,4})	85	81
III-4(d _{2,4})	77	95

III-4(e _{2,4})	98	97
III-6(a _{2,4,6})	78	88
III-6(b _{2,4,6})	76	91
III-6(c _{2,4,6})	67	95
III-6(d _{2,4,6})	70	93
III-6(e _{2,4,6})	82	98

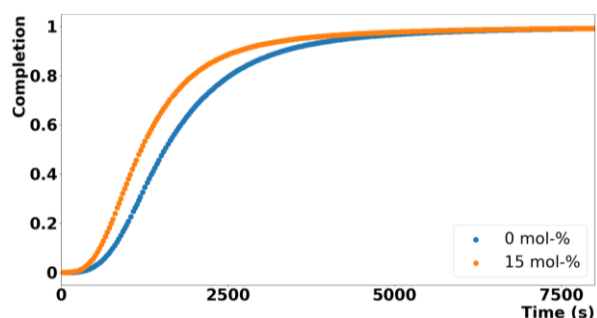
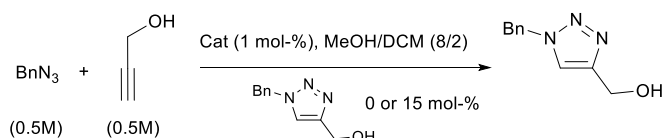
^a Purity determined by analytical HPLC.

In order to increase the chemical diversity, we have explored the possibility to build a small combinatorial library. A major issue in this field is to obtain a homogeneous distribution of the products. Therefore, we estimate the relative reaction rate of the different azides **1a-e** in solution toward propargyl alcohol, as depicted in Scheme 3, using microcalorimetry.



Scheme 3. Completion vs time for azides **1a-e** in solution.

Interestingly, the completion versus time curves present all a sigmoid shape, the alcohol **1e** being the more reactive and the protected acid **1c** the less. This shape is consistent with the one obtained when the reaction presents a non-classical kinetics, due to either a slow generation of the active catalyst or an activation by the product.



Scheme 4. Completion vs time in presence of 0 or 15 mol-% of added product

To determine if the reaction is activated by the product, we compared the reaction of benzyl azide with propargyl alcohol in solution in absence or presence of a small amount of triazole product (15 mol-%, Scheme 4). The addition of 15 mol-% of the product produces a decrease of the inductive period and an increase of rate,

typical of an activation by the product. This observation is important to build our combinatorial library because it suggests that a reaction can be accelerated by the product of another one that occurs faster and simultaneously. Therefore, the products repartition will not reflect the rates anymore. This was confirmed by measuring the amount of each product after reaction the amine **1d** and alcohol **1e** with the supported **II-4(Alk_{2,4})** using 5 mol-% of catalyst (Figure 3).

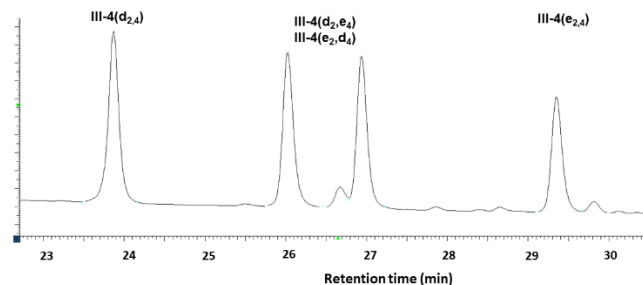


Figure 3. HPLC chromatogram at 220 nm showing repartition of products **III-4-(e,d)(2,4)**.

After cleavage, we observe the presence of the four products (identified by LC-MS) in comparable amount determined by HPLC (28, 25, 24 and 19% area), demonstrating that no strong preference occurs. Therefore, couples of azides from the pool **1a-e** were selected for building the combinatorial libraries from resin-bound tetramer **II-4(Alk_{2,4})** and hexamer **II-6(Alk_{2,4,6})** containing two and three alkynes respectively. The combination should afford n^m possible compounds (where n : number of azides and m : number of alkynes), thus four and eight different oligomers are expected. As shown in Table 2, total conversions were observed with good isolated yields and purities. For entries 1-5, as expected, a mixture of four aryloptoids were obtained, containing two identical triazoles and two positional isomeric compounds identified by LC-MS. For entries 6-10, HPLC separable signals were obtained. However, difficult separation was sometime obtained giving peaks overlapping. Figure 4 depicts the eight diversely functionalised aryloptoids **III-6(a,c)(2,4,6)** (entry 7). The first and last peaks were identified as **III-6(c_{2,4,6})** and **III-6(a_{2,4,6})** respectively (comparison with authentic samples, Table 1). The regioisomers containing two acids/one benzyl or two benzyl/one acid respectively were identified (LC-MS and HPLC) as two distinct subsets (retention times of 41-43 and 47-50 minutes, respectively).

Table 2. Combinatorial CuAAC on resin-bound **II-4(Alk_{2,4})** or **II-6(Alk_{2,4,6})**

Entry	Products ^a	Isolated yield (%)	Purity (%) ^b
1	III-4(a,b)(2,4)	76	90
2	III-4(a,d)(2,4)	92	97
3	III-4(b,d)(2,4)	99	95
4	III-4(c,d)(2,4)	68	96
5	III-4(d,e)(2,4)	85	84
6	III-6(b,c)(2,4,6)	82	97
7	III-6(a,c)(2,4,6)	68	98
8	III-6(b,d)(2,4,6)	82	95
9	III-6(a,d)(2,4,6)	80	98
10	III-6(d,e)(2,4,6)	81	99

^a Double bracket notation refers for all positional isomers. [†] ^b Purity determined by analytical HPLC.

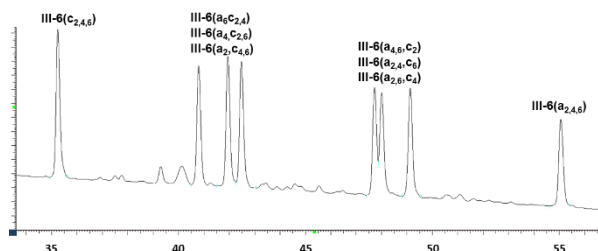
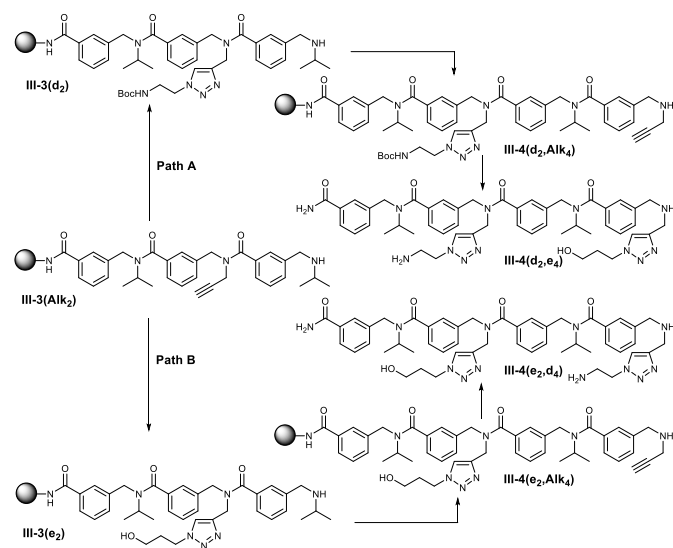


Figure 4. 220 nm HPLC chromatogram at 200 nm of **III-6(a,c)(2,4,6)**.

This points out the problem of the identification of a specific compound from a mixture of regioisomers. Therefore, a sequential approach was developed to access oligomers with various triazoles at well-defined positions. Thus, the oligomer should continue to grow-up on the solid support after click reaction. We performed a back synthesis of **III-4(d₂,e₄)** and **III-4(e₂,d₄)** (Figure 3) and all the regioisomers of **III-6(a,c)(2,4,6)** appearing between 40-50 minutes (Figure 4). For the tetramers, two synthetic pathways were explored (scheme 5). Path A starts with **III-3(Alk₂)** which was clicked with **Id**. We were pleased to see that elongation occurs efficiently to afford **III-4(d₂,Alk₄)**. Final post-functionalization using **1e** affords the expected product (82 % yield, 92% HPLC purity). Path B describes the synthesis of the second regioisomer which occurs by i) cycloaddition with **1e**, ii) elongation, iii) CuAAC with **Id** and iv) cleavage. **III-4(e₂,d₄)** was obtained in 79% isolated yield (87% HPLC purity) for 11 steps. Interestingly, elongation occurs on the alcohol **III-3(e₂)** without any side reactions (*i.e.* esterification).



Scheme 5. Back synthesis of **III-4(d₂,e₄)** and **III-4(e₂,d₄)**.

Following identical strategies (see ESI), hexamers **III-6(a₂,c₄,e₆)**, **III-6(a₄,c₂,e₆)** and **III-6(a₆,c₂,e₄)** for first subset (Figure 4) were synthesized in 84, 93 and 67% isolated yield respectively (85, 97 and 87% HPLC purity); the second subset **III-6(a₄,e₂,c₆)**, **III-6(a₂,e₄,c₆)** and **III-6(a₂,c₄,e₆)** being isolated in 83, 84 and 90% yield respectively (92, 92.5 and 83% HPLC purity). This combination of sequential post-functionalization by click and growing sequence allows an efficient back synthesis of each of the mixture components allowing each peak displayed in schemes 5 and 6 to be attributed using the pure samples (table S1 in ESI).

In conclusion, we report for the first time the use of Cu(I)-NHC for poly-functionalisation by CuAAC reaction on resin. This efficient and mild process performed on rink amide resin-bound oligomers with a panel of azides was applied to access a small library of functionalized *meta*-aryloleptoid trimers, tetramers and hexamers. To increase the chemical diversity, a combinatorial approach was efficiently developed. Finally, a sequential approach has enabled the synthesis of specific oligomers containing various triazole groups at well-defined positions demonstrating the versatility of this on support click chemistry process using [SiMesCu(4,7Cl-Phen)Cl] as catalyst.

Notes and references

‡: **I** stand for azides, **II** for resin-bound aryloleptoid oligomers containing alkyne(s) and **III** for aryloleptoid oligomers containing triazole(s). A single bracket notation stands for a single regioisomer, *i.e.* **III-3(a₂)** refers to a trimer containing a benzyl triazole at position 2. Notation with two brackets refers to a mixture of compounds from combinatorial library, first bracket stands for the triazole's substituents and the second for the positions.

‡‡: SiMes: 1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene; 4,7Cl-Phen : 4,7-dichloro-1,10-phenanthroline.

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