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CSIRO PUBLISHING

Aust. J. Chem. **2011**, *64*, 166–173

www.publish.csiro.au/journals/ajc

Investigations into Competitive Cycloaddition/Cyclization or Elimination from 1,1-Dimethyl-propargylcarbamates of Anilines

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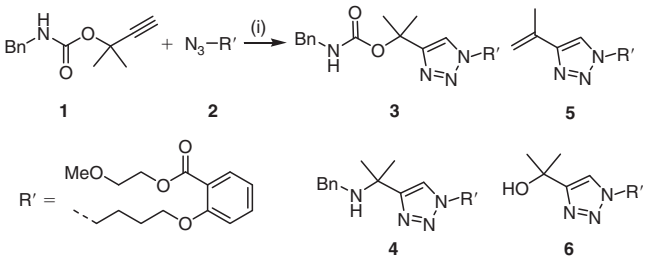
The copper-catalyzed reaction of 1,1-dimethyl-*O*-propargyl aniline carbamates was studied and revealed the unexpected formation of oxazolidin-2-ones and alkylamines. An in-depth study of the reaction conditions showed that the formation of these products was highly dependent on the solvent, copper catalyst and aniline substituents. The reaction can be oriented towards oxazolidinones in pyridine and alkylamines in ethanol, whereas cycloaddition can be achieved in dry tetrahydrofuran.

Manuscript received: 16 September 2010.
Manuscript accepted: 18 October 2010.

Introduction

The easy preparation of a large variety of propargyl alcohols has made them convenient intermediates to access functional propargylic compounds of greater value. Several preparations of propargylamines from the corresponding alcohols have been described. Propargyl alcohols were directly converted to propargylamines in a three-step synthesis[1] or in a single step under rhenium catalysis.[2] Propargylic fluorides have been synthesized from propargyl alcohols as intermediates to five-membered heteroaromatic compounds.[3] *O*-Propargylcarbamates were studied some decades ago as potential anticancer compounds[4] and were recently involved in fungicide preparation[5] and their cycloaddition with nitrile oxides reported.[6] Specific deprotection of propargylic carbonate with tetrathiomolybdate in the presence of propagylic carbamates was described.[7] Several copper-catalyzed reactions involving propargylcarbamates are available.[8–10] Finally, propargylic compounds are now commonly used in the popular Huisgen [3 + 2] cycloaddition of terminal alkynes and azides, the so-called click chemistry (also referred to as CuAAC: Cu-catalyzed azide–alkyne cycloaddition).[11] Propargylcarbamates have been used in such cycloadditions in different ways with unsubstituted *O*-propargylcarbamate,[12] and *N*-propargyl[13] and *N*-disubstituted propargylcarbamate.[14,15] Interested in the possibility of preparing carbamate **1** to be reacted with azide **2** in the copper-catalyzed Huisgen cycloaddition[16] (Scheme 1), we observed different reaction products, illustrating the above-mentioned versatile reactivity of propargylic derivatives. We found that the cycloadduct **3** could be obtained in good yields



1 **2** **3** **5** **4** **6**

Scheme 1. (i) Copper catalyst, solvent, see text.

with CuI as the catalyst and pyridine as the solvent. Under the classical Sharpless conditions (^{t}BuOH/H_2O, $CuSO_4 \cdot 5H_2O$, sodium ascorbate), three other products **4**, **5** and **6** were formed after cycloaddition. The propargylamine **4** resulted from a new and interesting rearrangement of the triazolyl carbamate, the alkene **5** was produced by elimination from the carbamate, and the alcohol **6** was obtained as a hydrolysis product. All these compounds were expected to be formed from the cycloaddition reaction, the carbamate **1** alone being found stable under all the tested conditions. The reaction was studied with the nucleophilic benzylamine and the formation of several compounds mainly attributed to a solvent effect having some influence on the intermediate copper complex stability and reactivity.

It was envisioned to extend this study to the cycloaddition of less nucleophilic aromatic amines like anilines. In order to evaluate the influence of substituents on the aniline ring and their possible effects on the ratio in rearranged products to

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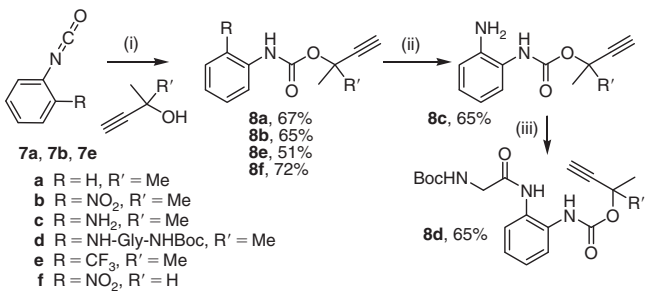


Scheme 2. (i) Heptane, reflux, NEt_3 catalyst, 3 h; (ii) $SnCl_2 \cdot xH_2O$, EtOH, reflux, 1 h; (iii) BOC-Gly-COOH, TBTU, HOBt, DIPEA, acetonitrile, 1 day.

3, **4**, **5** or **6** *ortho*-substituted aniline carbamates were prepared bearing either electron-donating or withdrawing groups. In the present work are described our efforts to prepare several triazolyl aniline carbamates. We report herein the unexpected solvent- and substituent-dependent reactivity of these carbamates under copper catalysis with a mechanistic proposal.

Results and Discussion

Several substituted aniline carbamates **8** were prepared (Scheme 2) to monitor the substituent effect of the aniline ring (R) and propargyl alcohols (R′). The nitroformiate strategy previously described by us[16] for benzylamine carbamates was not found suitable for the less nucleophilic anilines. Carbamates **8a**, **8b** were finally obtained in good yields by reacting phenylisocyanates **7** with 2-methyl-but-1-yn-2-ol in refluxing heptane and a catalytic amount of triethylamine as described by Thorne.[17] Phenylisocyanate **7a** provided carbamate **8a** as an example of an unsubstituted phenyl ring, whereas isocyanates **7b**, **7e** gave two examples of carbamates **8b**, **8e** with an electron-withdrawing group. In order to have an example of a carbamate with an electron-donating group, **8b** was reduced to **8c** ($SnCl_2 \cdot xH_2O$, EtOH, reflux).[18] The amide **8d** was prepared as another example of withdrawing group from **8c**, under peptide-coupling conditions (TBTU (tetrafluoroborate *O*-(benzotriazol-1-yl-1,1,3,3-tetramethyl)-uronium), HOBt (*N*-hydroxybenzotriazole), DIPEA (diisopropylethylamine), ACN (acetonitrile)). Unfortunately, only the additional carbamate **8f** could be prepared as an example of the diversely substituted propargyl moiety.

According to the Hammett constants, the carbamate N–H bond acidity may be related to the electron-withdrawing character of the phenyl substituent, and should be correlated with higher ^{1}H NMR chemical shifts. These chemical shifts were measured in $CDCl_3$ and were as follows: 6.41, 6.54, 6.89, 8.52 and 9.81 ppm for, respectively, **8c** (R = NH_2), **8a** (R = H), **8e** (R = CF_3), **8d** (R = NHCOR′) and **8b** (R = NO_2). Compared with the theoretical Hammet's σ_p values,[19] an extremely large chemical shift is observed for the nitro compound **8b** (9.81 ppm). This can be explained by the strong electron-withdrawing property of the nitro group and by intramolecular hydrogen bonding as described by Ringdahl for some propargyl nitroanilines. In such cases, the formation of a six-membered ring by hydrogen bonding between the nitro group in the *ortho* position and the carbamate hydrogen is highly favoured (Fig. 1).[20] The chemical shift of the carbamate proton in the amide **8d** was, surprisingly, observed at higher fields than the equivalent proton in the CF_3 analogue. This was explained by hydrogen bonding between the amide carbonyl and carbamate hydrogen in **8d** (Fig. 1), forming a favoured

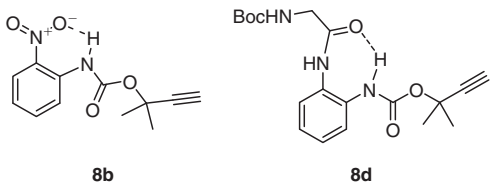
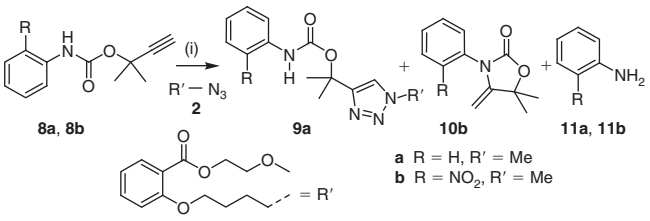


Fig. 1. Hypotheses of intramolecular hydrogen bonding for **8b** and **8d**.



Scheme 3. (i) CuI 5 mol-%, pyridine, 24 h, 20°C.

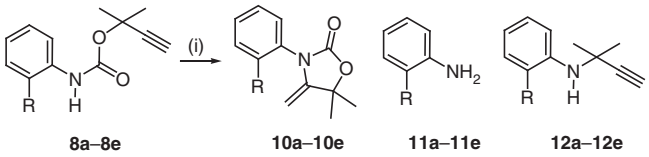
seven-membered ring. For the CF_3 derivative **8e**, hydrogen bonding is not possible and only the electron-withdrawing effect affects the chemical shift, lowered compared with the amide **8d**. As expected, the H- and NH_2-substituted products **8a** and **8c** exhibited the smallest chemical shifts.

Having successfully prepared the desired propargyl carbamates **8**, Huisgen cycloaddition was investigated with the azide **2** under the conditions we had developed earlier (pyridine, CuI) to avoid the formation of undesired products.[11] Starting with carbamate **8a**, the cycloadduct **9a** was obtained in only 19% yield. The free aniline **11a** (Scheme 3) and the elimination product **5a** (Scheme 1) were obtained as side products. Compared with the cycloaddition with benzylaminecarbamate **1**, these new results were clearly associated with the presence of the aniline ring. It can be postulated that the more nucleophilic benzylamine gave stronger carbamate bonds compared with the corresponding aniline carbamate **9a** owing to higher electron density. Under the mild basic conditions used with pyridine, the elimination is thus easier for **9a** than for **1**. This type of elimination catalyzed by pyridine was observed during the tosylation of alcohol **6**, which directly gave the alkene **5**.[16] Unexpectedly, the nitro derivative **8b** gave the oxazolidinone **10b** as a major product and the free 2-nitroaniline **11b** as a side product without any trace of the desired cycloadduct **9b**.

The synthesis of 4-methylene-oxazolidin-2-one has previously been described and *O*-propargylic carbamates have thus received much attention for the preparation of antibacterial 1,3-oxazolidin-2-one.[21] Several syntheses of oxazolidinones from propargylic alcohols are known. They can be reacted with an amine and carbon dioxide under pressure with a phosphine as a catalyst,[22] or with aryl isocyanates under strong base catalysis (sodium acetate,[23] sodium methoxide[24]) or boiling pyridine.[25] Alternatively, propargyl carbamates can be used as starting material in boiling pyridine.[12] Recently, an efficient method was developed to only convert non-substituted and monosubstituted propargyl carbamates to 4-methylene oxazolidin-2-one, using LiOH catalysis at room temperature.[26] The synthesis of oxazolidinones from *N*-propargylcarbamates under gold catalysis has been reported.[27] Only a few examples of copper-catalyzed reactions can be found in the literature, mostly applied to unsubstituted and 1-monosubstituted propargylcarbamates. CuCl was used with ionic liquids[28] or with 10% potassium *tert*-butylate at reflux in toluene or THF,[29] but in the

Table 1. Catalyst effect on the ratio of formation of compounds 10:11 and unreacted carbamates 8 in pyridine
Compound **12** was not observed in this series of experiments

Entry	R	Catalyst [mol-%]	**10**:**11**:**8**
1	H	–	0:0:100
2	NO_2	–	0:0:100
3	H	CuI, 20	0:100:0
4	NO_2	CuI, 20	63:37:0
5	H	CuI, 5	0:100:0
6	NO_2	CuI, 5	72:28:0
7	NO_2	CuI, 1	72:28:0
8	NO_2	CuCl, 10	53:47:0
9	NO_2	$CuSO_4 \cdot 5H_2O$, 10; sodium ascorbate, 20	77:23:0



Scheme 4. (i) Copper catalyst, solvent, room temperature, overnight; see Tables 1, 2 and 3.

latter case, CuCl was not critical. Mechanistic studies were proposed with deuterated *N*-tosyl propargyl carbamates.[30] The present work describes unprecedented conditions affording oxazolidinones instead of the expected Huisgen cycloaddition from propargylcarbamates of anilines bearing an electron-withdrawing group. According to the literature mentioned above and the proposed mechanism for gold catalysis,[27] the more acidic the carbamate N–H bond, the easier its deprotonation, even with mild bases. This process can lead to intramolecular cyclization if the alkyne bond is activated by chelating the metal (copper, gold). In this respect, the nitrocarbamate **8b** is more prone to deprotonation than the unsubstituted aniline compound **8a**. Another point of interest in this work is the use of 1,1-dimethylcarbamates, compared with literature data where mainly unsubstituted or 1-monosubstituted carbamates were used, particularly with a copper catalyst. This disubstitution introduced another difficulty owing to the possible formation of dimethylallene from carbamates **8** or an elimination product like **5** (Scheme 1) when cycloaddition is favoured.

In order to find reaction conditions where competitive cyclization or cyloaddition could be monitored, the carbamates **8a**, **8b** were reacted alone in pyridine with the different copper salts involved in both reactions, i.e. CuI, CuCl and $CuSO_4$ (Table 1, Scheme 4). If cyclization and elimination do not both occur, and provided that the copper–alkyne insertion is realized, it should be possible to have cycloaddition with azide **2**. The influence of catalyst quantity was also evaluated. After reaction, the solvent was removed under vacuum and the crude mixture was analyzed by ^{1}H NMR in $CDCl_3$ to calculate the conversion based on the characteristic peaks of the 2-methylene-oxazolidin-2-one (exo methylene signals at ~4 ppm), starting material (terminal alkyne signal at ~2.5 ppm) and the released amine. Compounds **8a**, **8b** in pyridine without catalyst gave no reaction, underlining the essential role of the copper salts (Table 1, entries 1, 2). A 20% molar amount of CuI produced a complete release of the aniline **11a** from **8a**, whereas the carbamate **8b** gave the cyclized product **10b** with the nitroaniline **11b** (Table 1, entries 3, 4). The reduction of the molar quantity of CuI catalyst to 5 and 1% (Table 1, entries 5–7) gave improved, similar yields of oxazolidinone **10b**, with again aniline **11b**. For carbamate **8a**, the complete release of aniline was always observed. The replacement of CuI by a $CuSO_4$/sodium ascorbate combination led to the formation of oxazolidinone **10b** from carbamate **8b** with good conversion. CuCl was found less selective (Table 1, entries 8, 9). Although $CuSO_4$ and CuI gave equivalent results, CuI was selected as the catalyst for further studies, in order to remove water traces which could potentially favour side reactions as previously observed.[16]

Table 2. Solvent effect on the ratio of products 10:11:12 and unreacted carbamates 8

Entry	R	Catalyst [mol-%]	Solvent	**10**:**11**:**12**:**8**
1	H	CuI, 20	DMF	0:100:0:0
2	H	CuI, 20	Pyridine	0:100:0:0
3	NO_2	CuI, 20	DMF	0:100:0:0
4	NO_2	CuI, 5	DMF	0:100:0:0
5	NO_2	CuI, 5	Et_3N	1:99:0:0
6	NO_2	CuI, 5	Acetonitrile	7:93:0:0
7	NO_2	CuI, 5	Pyridine[A]	86:14:0:0
8	NO_2	CuI, 5	Pyridine	72:28:0:0
9	NO_2	CuI, 5	EtOH	2:33:36:26
10	NO_2	CuI, 5	THF/H_2O	0:0:0:100

[A]Pyridine was freshly distilled over KOH.

The role of the solvent was investigated with carbamates **8a**, **8b**. At 20 mol-% CuI, pyridine or DMF again gave complete release of aniline **11a** from carbamate **8a** (Table 2, entries 1, 2). DMF was also able to promote complete release of aniline **8b** at 5 or 20 mol-% CuI (Table 2, entries 3, 4), which was observed, but incomplete, in pyridine (Table 1, entry 4). The key intermediate **8b** was reacted in other solvents. NEt_3 and CH_3CN promoted the release of aniline **8b**, as did DMF, even at 5 mol-% CuI (Table 2, entries 5, 6). Pyridine appeared to be the best solvent for the cyclization to oxazolidinone **11b**. We also checked the reactivity of our described propargyl benzylamine carbamate **1** with CuI in different solvents and confirmed that no reaction occurred in pyridine or ethanol but decomposition in DMF gave quantitatively the corresponding symmetric dibenzylurea, probably resulting from the release of the free benzylamine, which attacked another molecule of carbamate **1**.

A particular feature of these reactions is the release of aniline. Comparing cyclization and amine release, a proton source is required in the latter case to equilibrate the reaction with the transfer of two protons (one for the aniline, one for the allene). Hattori et al.[24] showed in propargylamine syntheses that proton[1] exchange should occur from the reaction mixture and $CuSO_4 \cdot 5H_2O$ is thus a possible source. This is not possible for CuI in pyridine, except if one considers the presence of water traces in the solvent or the catalyst. The standard 99.5+% pure pyridine was then distilled over KOH, and a ratio increase to 86:14 of oxazolidinone **10b**:**11b** was effectively obtained (Table 2, entry 7). The very low quantity of catalyst required for the cyclization with CuI and the mild reaction conditions could make this procedure very attractive compared with others using strong bases that are not suitable for all starting materials. Finally, polar protic solvent conditions were evaluated. In the case of EtOH, the unexpected *N*-propargylaniline **12b** was obtained as the major product (Table 2, entry 9) in modest and variable yields, with free aniline **11b**, starting material **8b** and a

Table 3. Aniline substituent effect on the reactivity of carbamates 8 in pyridine, with 5 mol-% CuI
n.d., not determined

Entry	R	**10**:**11**:**12**:**8** Isolated yields in parentheses are in mol-%
1	NO_2	72:28:0:0
2	NO_2[A]	84 (67[B]):16:0:0
3	NHCOGlyBoc[A]	n.d. (67[B]):n.d.:n.d.:n.d.
4	H[A]	0:100:0:0
5	NH_2[A]	0:0:0:100
6	CF_3[A]	n.d. (46[B]):n.d.:n.d.:n.d.

[A]Pyridine was freshly distilled over KOH.
[B]Isolated yields.

small amount of oxazolidinone **10b**. The variable yields could be explained by the poor solubility of the substrate and catalyst in ethanol and by the probable volatility of propargylamine **11b**. The rearrangement leading to the alkylamine was previously observed with benzylamine carbamate **1**, but after cycloaddition. To our knowledge, the rearrangement of propargylic carbamates of anilines to propagylic anilines has not been described previously. The combination of THF and H_2O as solvent gave no reaction, suggesting that the cycloaddition of nitrocarbamate **8b** with **2** should occur without side reactions under these conditions, if the copper–alkyne insertion is obtained.

The aniline substituent effect was investigated with carbamates **8c**–**8e**, reacted with 5 mol-% CuI in pyridine, at room temperature overnight (Table 3). Results from carbamates **8a**, **8b** are replicated from Table 2 for simplicity (Table 3, entries 1, 2, 4) with a 67% isolated yield for **8b**. The less acidic character of the carbamate N–H bond in the amino derivative **8c** was associated with no reaction whereas the amide **8d** also gave oxazolidinone **10d** in 67% isolated yield. Additional hydrogen bonding between the hydrogen atom of the carbamate group and the *ortho* substituent for **8b**, **8d** may also increase acidity, as observed from ^{1}H NMR experiments.

The effect of the propargyl substituents on position 1 for the nitroaniline carbamate was determined for the carbamate **8f** and gave a 52:48 ratio for compounds **10f**:**11f**, from which **10f** was isolated in 46% yield. This should be compared with the 84:16 ratio obtained for **10b**:**11b**. The latter result seems to indicate that our procedure may be convenient for the synthesis of oxazolidinones from 1,1-disubstituted N–H acidic propargylcarbamates. In the case of **10f**, the isolated compound showed more complex ^{1}H NMR signals than its dimethyl counterpart **10b**. This was attributed to the possible existence of two inseparable atropoisomers (Fig. 2), where a *trans* and *cis* relation may exist between the methyl group and the nitrophenyl ring. The *ortho* positioning of the nitro group and the presence of the carbonyl and methylene groups should block these two isomers in two different particular conformations. To a lesser extent, this atropoisomerism was also detected for the dimethylnitro **10b**, trifluoromethyl **10e** and amide **10d** analogues. Molecular modelling was performed[31] and showed that in both isomers, the nitro group tends to be orientated toward the methylene group, the *cis* isomer being slightly more stable, probably giving the lowest electronic interactions between oxygen and nitrogen atoms. An equivalent atropoisomerism was found in the literature for oxazoline.[32]

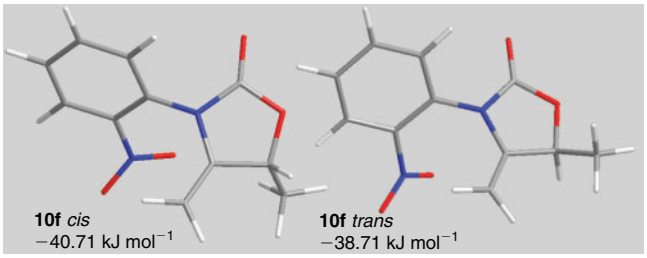
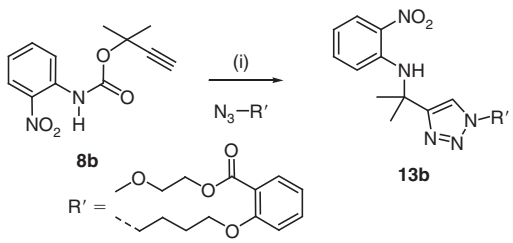


Fig. 2. Hypothesis for two blocked atropoisomers of **10f** with calculated relative stabilities [kJ mol^{-1}].

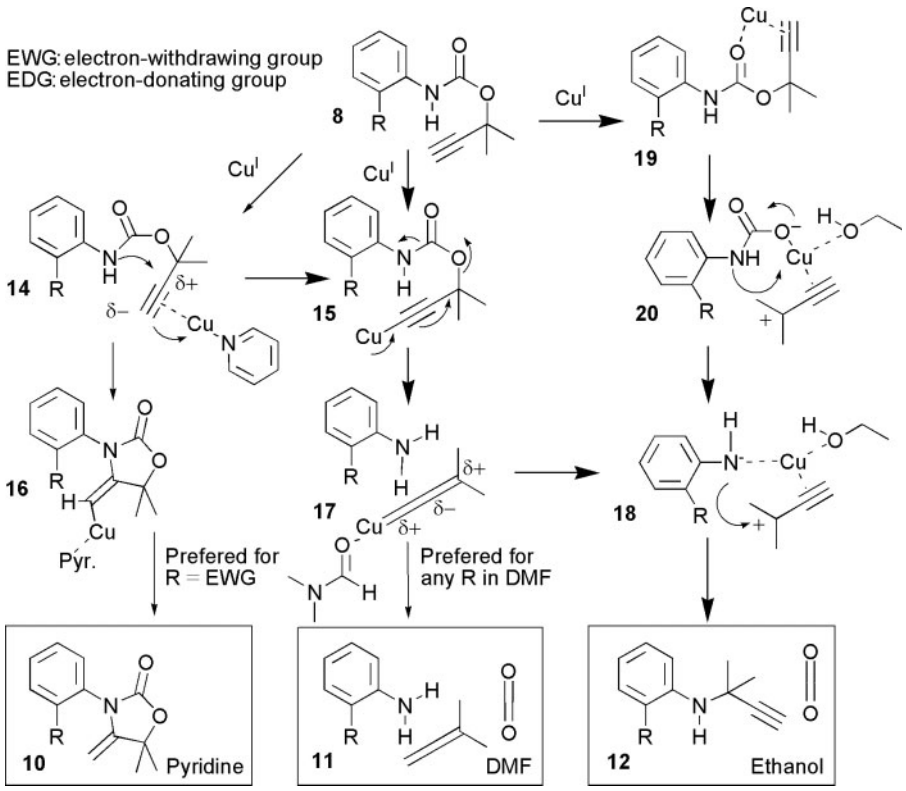


Scheme 5. (i) CuI 5 mol-%, THF, room temperature, overnight.

The use of THF/H_2O as solvent (Table 2, entry 10) gave no reaction for **8b** and thus these conditions were evaluated for the cycloaddition of **8b** with the azide **2** (Scheme 5). In the presence of 5 mol-% CuI in dry THF, the rearranged dimethyltriazolylmethylaniline **13b** was obtained in a moderate 31% yield, as previously observed for carbamate **1** (Scheme 1).

In order to propose some rationale for the observed results, the mechanistic aspects of this work were investigated. As mentioned above, propargylic derivatives are prone to allene formation, a reaction that is also catalyzed by copper reagents.[33] Unfortunately, we were not able to detect such compounds. The selection of the solvent is important for the formation of solvent–copper–alkyne complexes[34,35] and a first terminal alkyne copper(I) insertion is generally proposed. The access to oxazolidinones **10** was rationalized[25,36] by the formation of the intermediate alkyne complex **14** (Scheme 6).

The deprotonation of compounds **8b**, **8d**, **8e** by the base gave an anion able to attack the internal alkyne carbon atom, affording oxazolidinone via the complex **16**. Stronger bases than pyridine have been reported, like KOH, for the preparation of oxazolidinones for unsubstituted aniline derivatives. In our case, pyridine is sufficient to deprotonate the acidic aniline derivatives bearing an electron-withdrawing group, as observed for gold catalysis in NEt_3 with *N*-tosylpropargylcarbamates. Carbamates **8** being stable in pyridine with no catalyst, the copper salt appeared critical to activate the alkyne bond. Direct insertion of the copper ion as in complex **15** was proposed for the copper-catalyzed Huisgen cycloaddition. This is not totally in agreement with the mechanism proposed by Murahashi[8] and Nishibayashi,[10] where complexes like **15** are involved in propargylic amine formation. In such an intermediate **15**, the terminal copper complex can give allenylidene complex **17** by decarboxylation of the carbamate. This was apparently the major process in DMF, where free amines were obtained in all cases. The released amine can then be isolated (DMF) or re-attack the carbocation **18** obtained from complex **17**. An important aspect in this proposed mechanism is the driving force making the poorly nucleophilic aniline **8b** attack the carbocation **18** in conditions where no base or temperature are



Scheme 6.

involved. The intermediate carbocation **18** may also be trapped by the solvent in the case of EtOH, but the resulting ether was not detected in the reaction. We previously proposed a reversed chelation to explain an equivalent rearrangement.[16] Thus the intermediate **19** could give **20**, where the amine is maintained near the reactive site by chelating the copper atom. After carbamate decarboxylation, the amine can attack the carbocation to give **12**. The possible participation of the nitro group for **8b** ($R = NO_2$) can be suggested to stabilize complex **14** or **20** but was not determined. The presence of the two methyl groups induces steric hindrance,[37] probably facilitating the internal rearrangements. One should note that oxazolidinones are essentially prepared from either unsubstituted or only 1-monosubstituted propargylcarbamates. However, 1,1-disubstituted propargylamines are not often described. Thus the preparation of compound **10** or **12** from 1,1-disubstituted propargylcarbamates brings additional possibilities to this chemistry.

Conclusion

Copper-catalyzed reactions involving propargylic anilines carbamates revealed unexpected reactivity of these derivatives associated with the acidity of the carbamate N–H bond. Electron-withdrawing substituents on the aniline ring of these carbamates favoured deprotonation, leading to oxazolidinones under very mild conditions with a small amount of copper catalyst. When no substituent or electron-donating groups are present on the aniline ring, the release of aniline may be favoured, a process that can be potentially exploited for the design of new protective groups. The expected Huisgen cycloaddition was obtained when tetrahydrofuran was used as the solvent, with a subsequent in situ rearrangement to alkylaniline in moderate yields. Our results indicated that the conversion of propargylcarbamates to the interesting triazolylalkylanilines should occur after the carbamate cycloaddition, followed by rearrangement with CO_2 loss. This suggested that conditions may be found where such carbamates can be isolated. A possible atropoisomerism has been detected in *ortho*-substituted phenyl oxazolidinones **8b**, **8d**–**8f** that was not reported earlier. These results highlighted the important impact of the solvent and substituent on the aniline ring of aniline propargylcarbamates, providing new insight into the reactivity of these compounds. Work is in progress to optimize the cycloaddition reaction observed in THF to develop access to triazolylanilines.

Experimental

General

CH_2Cl_2 was distilled over P_2O_5, THF was distilled over sodium/benzophenone under a nitrogen atmosphere. Pyridine was distilled over KOH under a nitrogen atmosphere. Silica (35–70-μm) was used for flash chromatography and preparative TLC. TLC was performed on aluminium plates coated with silica gel (Merck silica gel 60 F254, thickness 0.2 mm). Visualization was accomplished by UV light and the stains used were ninhydrin and phosphomolybdic acid solutions. All reactions were conducted under a nitrogen atmosphere, and solutions were concentrated under reduced pressure using a rotary evaporator. Melting points were recorded on a Büchi B-545 and are uncorrected. ^{1}H NMR spectra were recorded on Bruker Ultrashield Plus 400 (400 MHz). The chemical shifts are reporter in δ [ppm] relative to chloroform ($CDCl_3$, 7.26 ppm), acetone ([D6] acetone, 2.05 ppm) and tetramethylsilane (TMS, 0.00 ppm) as internal standards. The spectra were analysed by first order; the coupling constants (J) are reported in Hertz [Hz] and refer to apparent multiplicities and not true coupling constants: s,

singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bm, broad multiplet; dd, double doublet; dt, double triplet; ddd, double double doublet. ^{13}C NMR spectra were recorded on a Bruker Ultrashield Plus 400 (100.6 MHz). The chemical shifts are reported in δ [ppm] relative to chloroform ($CDCl_3$, 77 ppm), acetone ([D6]acetone, 29.84 ppm) and tetramethylsilane (TMS, 0.00 ppm) as internal standards. 2D-NMR spectra (COSY (Correlation spectroscopy), HETCORR (Heteronuclear correlation), HSQCed (Heteronuclear Single Quantum Coherence)) were recorded on a Bruker Ultrashield Plus 400 (400 MHz). HRMS (High Resolution Mass Spectra) were performed at the Centre Régional de Mesures Physiques de l'Ouest (CRMPO), Rennes, France. Abbreviations used: PS (petroleum spirit), EA (ethyl acetate), THF (tetrahydrofuran), DCM (dichloromethane), DIPEA (diisopropylethylamine), HOBt, TBTU.

2-Methylbut-3-yn-2-yl Phenylcarbamate ***8a***

To a solution of 2-methyl-but-3-yn-2-ol (0.58 mL, 5.61 mmol, 2 equiv.) in heptane (30 mL) was added NEt_3 (0.391 mL, 2.81 mmol, 1 equiv.). The solution was refluxed and phenylisocyanate was added (0.304 mL, 2.81 mmol, 1 equiv.). After refluxing for 2 h, the solution was cooled to room temperature, dissolved in Et_2O and washed with 1 M $KHSO_4$ and brine, dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified (flash chromatography on silica gel, PE/EA 9:1) and the collected fractions evaporated under reduced pressure to afford **8a** as a white solid (0.391 g, 1.88 mmol, 67%). δ_H (400 MHz, $CDCl_3$) 7.37 (d, 2H, *J* 7.9), 7.26 (m, 2H), 7.03 (m, 1H), 6.54 (s, 1H), 2.56 (s, 1H), 1.73 (s, 6H). δ_C (100 MHz, $CDCl_3$) 151.6, 137.8, 129.0, 123.4, 118.6, 84.9, 72.4, 72.2, 29.2. *m/z* (HRMS) 226.0846. $C_{12}H_{13}NO_2Na$ requires $[M + Na]^+$ 226.08440.

2-Methylbut-3-yn-2-yl 2-Nitrophenylcarbamate ***8b***

To a solution of 2-methyl-but-3-yn-2-ol (1.16 mL, 11.12 mmol, 1 equiv.) in toluene (50 mL) in a two-necked flask under a nitrogen atmosphere was added NEt_3 (0.313 mL, 2.24 mmol, 0.2 equiv.). The solution was heated until reflux and a solution of 2-nitrophenylisocyanate (1.0 g, 6.09 mmol, 0.54 equiv.) in THF (few mL) was added. After 1 h, a precipitate was observed. The solution was cooled to room temperature, diluted with Et_2O and washed several times with water and brine. The organic phase was dried over $MgSO_4$ and concentrated under vacuum. The crude material was purified (flash chromatography on silica gel, PE/EA 9:1) affording **8b** as a yellow powder (0.983 g, 65% yield), mp 108°C. The product can be easily crystallized from a mixture of PE/EA. R_f (PS/EA 85:15) 0.72. δ_H (400 MHz, $CDCl_3$) 9.81 (s, 1H), 8.61 (d, 1H, *J* 8.6), 8.20 (d, 1H, *J* 8.5), 7.62 (dd, 1H, *J* 7.6), 7.13 (dd, 1H, *J* 7.5, 8.2), 2.62 (s, 1H), 1.78 (s, 6H). δ_C (100 MHz, $CDCl_3$) 151.3, 136.1, 135.9, 135.4, 125.9, 122.3, 120.8, 84.4, 73.2, 72.9, 29.1. *m/z* (HRMS) 271.0696 (0 ppm). $C_{12}H_{12}N_2O_4Na$ requires $[M + Na]^+$ 271.06948.

2-Methylbut-3-yn-2-yl 2-Aminophenylcarbamate ***8c***

To a solution of 2-methylbut-3-yn-2-yl 2-nitrophenylcarbamate (0.500 g, 2.01 mmol, 1 equiv.) in absolute ethanol (50 mL) was added $SnCl_2$ hydrate (0.802 g, 4.23 mmol, 2.1 equiv.). The solution was refluxed for 2 h. While refluxing, the colour of the solution changed from yellow to deep red. The solution was then cooled to room temperature, diluted in EA and washed subsequently with water, saturated $NaHCO_3$ and brine. The organic phase was collected, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The crude mixture was then purified by flash chromatography, affording the amino carbamate **8c** (0.279 g, 64%) as a brownish solid. R_f (EP/EA 1:1) 0.79. δ_H (400 MHz, $CDCl_3$) 7.33 (bd, 1H, *J* 6.4), 7.01 (dt, 1H, *J* 1.4, 7.7), 6.79 (m, 2H), 6.41 (s, 1H), 3.32 (bs, 2H), 2.57 (s, 1H), 1.75 (s, 1H). δ_C (100 MHz, $CDCl_3$) 152.7, 139.5, 126.3, 124.6, 124.5, 119.9, 117.9, 84.9, 72.4, 72.4, 29.2. *m/z* (HRMS) 241.0952 (0 ppm). $C_{12}H_{14}N_2O_2Na$ requires $[M + Na]^+$ 241.09530.

*2-Methylbut-3-yn-2-yl 2-(*N*-Boc-glycinamido) phenylcarbamate* ***8d***

To a solution of butyloxycarbonyl (BOC)-glycine (0.279 g, 1.59 mmol, 1.5 equiv.) in DCM (20 mL) at 0°C were added TBTU (0.512 g, 1.59 mmol, 1.5 equiv.), HOBt (0.244 g, 1.59 mmol, 1.5 equiv.) and DIPEA (0.53 mL, 3.19 mmol, 3 equiv.). The reaction was left at 0°C for 30 min and then 2-methyl-but-3-yn-2-yl 2-aminophenylcarbamate (0.232 g, 1.06 mmol, 1 equiv.) was added. After overnight stirring, the reaction was diluted in EA and washed subsequently with 1 M $KHSO_4$, saturated $NaHCO_3$ and brine. The organic phases were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica, affording **8d** (0.215 g, 54%) as a viscous oil. R_f (EP/EA 60:40) 0.23. δ_H (400 MHz, $CDCl_3$) 8.52 (s, 1H), 7.61 (d, 1H, *J* 7.9), 7.38 (d, 1H, *J* 7.5), 7.32 (s, 1H), 7.21 (dt, 1H, *J* 1.3, 7.9), 7.13 (dt, 1H, *J* 1.4, 7.7), 5.39 (t, 1H, *J* 5.0), 3.92 (d, 2H, *J* 5.7), 2.62 (s, 1H), 1.76 (s, 6H), 1.49 (s, 9H). δ_C (100 MHz, $CDCl_3$) 168.6, 161.2, 152.9, 130.8, 128.8, 126.7, 125.4, 124.2, 124.2, 84.9, 77.2, 72.6, 72.6, 45.0, 29.2, 28.3. *m/z* (HRMS) 398.1689 (1 ppm). $C_{19}H_{25}N_3O_5Na$ requires $[M + Na]^+$ 398.16854.

2-Methylbut-3-yn-2-yl 2-(Trifluoromethyl) phenylcarbamate ***8e***

To a solution of 2-methyl-but-3-yn-2-ol (1.16 mL, 11.88 mmol, 1 equiv.) in heptane (20 mL) was added triethylamine (0.32 mL, 2.37 mmol, 0.2 equiv.). The solution was heated until refluxing and 2-trifluoromethyl phenylisocyanate (1.79 mL, 11.88 mmol, 1 equiv.) was added. The solution was refluxed for 2 h under stirring. After cooling to room temperature, the reaction mixture was extracted with diethyl ether and washed with saturated NaCl. The organic phase was dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was separated by flash chromatography, affording **8e** as a white solid (1.640 g, 6.04 mmol, 51%), mp 50°C. δ_H (400 MHz, $CDCl_3$) 8.21 (d, 1H, *J* 8.4), 7.57 (d, 1H, *J* 8.3), 7.53 (t, 1H, *J* 7.9), 7.16 (t, 1H, *J* 7.7), 6.89 (s, 1H), 2.60 (s, 1H), 1.76 (s, 6H). δ_C (100 MHz, $CDCl_3$) 151.5, 135.7, 132.9, 126.0, 125.5, 123.3, 122.8, 122.3, 84.6, 72.9, 72.6, 29.2. δ_F (376 MHz, $CDCl_3$) −60.69. *m/z* (HRMS) 294.0714 (1 ppm). $C_{13}H_{12}NO_2F_3Na$ requires $[M + Na]^+$ 294.07123.

But-3-yn-2-yl 2-Nitrophenylcarbamate ***8f***

To a solution of but-3-yn-2-ol (0.56 mL, 7.13 mmol, 1 equiv.) in heptane (40 mL) in a two-necked flask under nitrogen was added triethylamine (0.99 mL, 7.13 mmol, 1 equiv.). The mixture was heated until refluxing and 2-nitrophenylisocyanate (1.17 g, 7.13 mmol, 1 equiv.) diluted in a few mL THF was added. The reaction was stirred for 2 h. After cooling, the mixture was diluted in diethyl ether and washed with brine. The organic phase was dried over $MgSO_4$, filtered and the solvent evaporated using a rotary evaporator. The crude solid was then purified by gradient flash chromatography with PS/EA 95:5 to

70:30, affording **8f** as a yellow solid (1.209 g, 5.16 mmol, 72%), mp 78°C. δ_H (400 MHz, $CDCl_3$) 9.90 (s, 1H), 8.58 (dd, 1H, *J* 1.3, 8.6), 8.21 (dd, 1H, *J* 1.5, 8.5), 7.64 (ddd, 1H, *J* 1.6, 7.1, 8.5), 7.15 (ddd, 1H, *J* 1.3, 7.2, 8.5), 5.48 (dq, 1H, *J* 2.1, 6.7), 2.53 (d, 1H, *J* 2.1), 1.60 (d, 3H, *J* 6.7). δ_C (100 MHz, $CDCl_3$) 152.0, 136.2, 135.9, 135.1, 125.9, 122.6, 120.8, 81.7, 73.6, 61.9, 21.3. *m/z* (HRMS) 257.034 (0 ppm). $C_{11}H_{10}N_2O_4Na$ requires $[M + Na]^+$ 257.0538.

General Procedure for the Catalyzed Cyclization of Propargyl Carbamates ***10***

In solvent (4 mL) were added the propargyl carbamate (100 mg) and a catalytic amount of copper catalyst (1, 5, 10 or 20 mol-%). The mixture was stirred overnight at room temperature. After reaction, the solvent was removed under vacuum and the crude mixture was analysed by ^1H NMR in $CDCl_3$ to calculate the conversion based on the integration of the characteristic peaks of the 2-methylene oxazolidin-2-one (methylene protons, doublets ~4 ppm), starting material (alkyne proton, singlet ~2.5 ppm) and released amine (NH_2 ~6 ppm, aromatic protons). Every cyclized new compound was purified by either preparative TLC or flash chromatography on silica gel, allowing calculation of the isolated yield.

5,5-Dimethyl-4-methylene-3-(2-nitrophenyl)oxazolidin-2-one ***10b***

Obtained as a yellow solid, mp 92°C. δ_H (400 MHz, $CDCl_3$) 8.16 (dd, 1H, *J* 1.5, 8.2), 7.77 (dt, 1H, *J* 1.5, 7.7), 7.62 (ddd, 1H, *J* 1.4, 7.6, 8.2), 7.51 (dd, 1H, *J* 1.3, 7.9), 4.06 (d, 1H, *J* 3.4), 3.90 (d, 1H, *J* 3.4), 1.68 (s, 3H), 1.66 (s, 3H). δ_C (100 MHz, $CDCl_3$) 153.8, 150.9, 145.8, 134.5, 131.2, 130.0, 127.7, 126.2, 83.9, 81.1, 27.9, 27.8. *m/z* (HRMS) 271.0690 (0 ppm). $C_{12}H_{12}N_2O_4Na$ requires $[M + Na]^+$ 271.06893.

tert-*Butyl 2-(2-(5,5-Dimethyl-4-methylene-2-oxooxazolidin-3-yl)phenylamino)-2-oxoethylcarbamate* ***10d***

Obtained as a colourless viscous oil. δ_H (400 MHz, $CDCl_3$) 8.45 (s, 1H), 8.05–8.03 (m, 1H), 7.42–7.38 (m, 1H), 7.22–7.21 (m, 2H), 5.26 (bs, 1H), 4.04 (d, 1H, *J* 3.1), 3.94 (dd, 1H, *J* 5.0, 17.5, AB system, Gly CH_2, broad signal), 3.90 (d, 1H, *J* 3.0), 3.73 (dd, 1H, *J* 5.7, 17.1, AB system, Gly CH_2), 1.66 (s, 3H), 1.61 (s, 3H), 1.44 (s, 9H). δ_C (100 MHz, $CDCl_3$) 168.2, 156.1, 154.9, 150.6, 134.5, 129.9, 128.4, 125.7, 124.5, 124.5, 83.7, 82.4, 80.5, 45.2, 28.3, 28.3, 27.9. *m/z* (HRMS) 398.1684 (1 ppm). $C_{19}H_{25}N_3O_5Na$ requires $[M + Na]^+$ 398.16864.

5,5-Dimethyl-4-methylene-3-(2-(trifluoromethyl)phenyl) oxazolidin-2-one ***10e***

Obtained as a white solid. δ_H (400 MHz, $CDCl_3$) 7.82 (d, 1H, *J* 7.3), 7.71 (dt, 1H, *J* 1.0, 7.7), 7.60 (t, 1H, *J* 7.7), 7.37 (d, 1H, *J* 7.8), 4.05 (d, 1H, *J* 3.1), 3.69 (d, 1H, *J* 3.1), 1.65 (s, 3H), 1.64 (s, 3H). δ_C (100 MHz, $CDCl_3$) 154.2, 152.8, 133.6, 131.8, 131.5, 130.0, 127.9, 127.9, 124.3, 83.5, 81.8, 28.2, 27.5. δ_F (376 MHz, $CDCl_3$) −61.45. *m/z* (HRMS) 294.0710 (1 ppm). $C_{13}H_{12}NO_2F_3Na$ requires $[M + Na]^+$ 294.07123.

5-Methyl-4-methylene-3-(2-nitrophenyl)oxazolidin-2-one ***10f***

Obtained as a yellow powder. δ_H (400 MHz, $CDCl_3$) 8.15 (td, 1H, *J* 1.8, 8.2), 7.77 (tt, 1H, *J* 1.5, 7.8), 7.62 (tt, 1H, *J* 1.5, 7.5), 7.50 (ddd, 1H, *J* 1.4, 2.5, 7.9), 5.32 (m, 1H), 4.10 (m, 1H), 3.97 (m, 1H), 1.64 (m, 3H). The complex mutiplicity of the CH endocyclic proton, the methylene protons and the methyl protons are due to ^4J and ^5J couplings. δ_C (100 MHz, $CDCl_3$) 154.6, 146.7, 134.7, 131.3, 131.1, 130.2, 127.5, 126.3, 82.0, 76.2, 20.9. *m/z* (HRMS) 257.034 (0 ppm). $C_{11}H_{10}N_2O_4Na$ requires $[M + Na]^+$ 257.0538.

*2-Methoxyethyl 2-(4-(4-(2-(Phenylcarbamoyloxy) propan-2-yl)-1*H*-1,2,3-triazol-1-yl)butoxy)benzoate* ***9a***

To a solution of 2-methylbut-3-yn-2-yl phenylcarbamate (0.208 g, 1 mmol, 1 equiv.) and **2** (0.323 g, 1 mmol, 1 equiv.) in pyridine (5 mL) was added copper iodide (38 mg, 0.2 mmol, 0.2 equiv.). The solution was stirred overnight and pyridine was then evaporated under reduced pressure. The crude mixture was separated by flash chromatography over silica gel, affording the clicked carbamate **9a** as a yellowish viscous oil (99 mg, 19% yield). δ_H (400 MHz, [D6]acetone) 8.57 (s, 1H), 7.99 (s, 1H), 7.72 (dd, 1H, *J* 1.7, 7.7), 7.49 (m, 3H), 7.24 (m, 2H), 7.08 (dd, 1H, *J* 0.6, 8.5), 6.98 (m, 2H), 4.51 (t, 2H, *J* 7.1), 4.38 (m, 2H), 4.08 (t, 2H, *J* 6.0), 3.65 (m, 2H), 3.32 (s, 3H), 2.17 (m, 2H), 1.85 (s, 6H), 1.80 (m, 2H). δ_C (100 MHz, [D6]acetone) 167.8, 160.1, 154.1, 153.3, 141.4, 135.2, 132.9, 130.5, 124.1, 123.3, 122.7, 121.9, 120.0, 115.2, 78.3, 72.1, 69.7, 65.4, 59.8, 51.2, 29.0, 28.8, 27.8. *m/z* (HRMS) 519.2210 (1 ppm). $C_{26}H_{32}N_4O_6Na$ requires $[M + Na]^+$ 519.22195.

*2-Methoxyethyl 2-(4-(4-(2-(2-Nitrophenylcarbamoyloxy) propan-2-yl)-1*H*-1,2,3-triazol-1-yl)butoxy)benzoate* ***13b***

To a solution of 2-methylbut-3-yn-2-yl 2-nitrophenylcarbamate (0.134 g, 0.54 mmol, 1 equiv.) and 2-methoxyethyl 2-(4-azidobutoxy)benzoate (0.165 g, 0.54 mmol, 1 equiv.) in freshly distilled THF (4 mL) was added copper iodide (20 mg, 0.108 mmol, 0.2 equiv.). The mixture was stirred at room temperature overnight. The mixture was diluted in EA and washed with saturated NH_4Cl, and the organic phase was dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude residue was then purified by flash chromatography, affording the clicked propargylamine **13b** (83.2 mg, 0.167 mmol, 31%) as a yellow oil. δ_H (400 MHz, [D6]acetone) 8.47 (s, 1H), 7.95 (dd, 1H, *J* 1.6, 8.6), 7.84 (s, 1H), 7.59 (dd, 1H, *J* 1.8, 7.7), 7.35 (ddd, 1H, *J* 1.8, 7.4, 8.5), 7.12 (ddd, 1H, *J* 1.5, 7.0, 8.6), 6.93 (d, 1H, *J* 8.4), 6.86 (dt, 1H, *J* 0.9, 7.6), 6.54 (dd, 1H, *J* 1.0, 8.8), 6.48 (ddd, 1H, *J* 1.1, 6.9, 8.3), 4.37 (t, 2H, *J* 7.0), 4.21 (m, 2H), 3.92 (t, 2H, *J* 6.0), 3.51 (m, 2H), 3.18 (s, 3H), 2.01 (m, 2H), 1.70 (s, 6H), 1.61 (qd, 2H, *J* 6.1, 12.4). δ_C (100 MHz, [D6]acetone) 166.7, 159.1, 153.1, 144.7, 136.0, 134.2, 133.7, 132.0, 127.4, 122.3 121.7, 120.9, 117.5, 116.3, 114.2, 71.1, 68.7, 64.4, 58.8, 53.0, 50.4, 29.8, 27.7, 26.7. *m/z* (HRMS) 520.2167 (0 ppm). $C_{25}H_{31}N_5O_6Na$ requires $[M + Na]^+$ 520.21665.

Acknowledgements

The authors thank CNRS and Agence National de la Recherche (ANR-08-PCVI-030, grant to R.D., F.C.) for financial support.

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