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Click to learn, learn to click: undergraduate synthetic organic chemistry experiments

Alejandro Lopez-Ruiz[1] · Mariano Ortega-Muñoz[1,2] · Francisco Santoyo-Gonzalez[1,2] · Alicia Megia-Fernandez[1,2]

Abstract

The optimization of an undergraduate experiment for Organic Chemistry students is described to explore the concept of click chemistry. The preparation of a terminal fluorescent alkyne and an organic azide is reported consisting of simple steps. These are employed in the Cu(I)-catalyzed azide-alkyne cycloaddition to obtain a novel molecule containing a triazole ring whose characterization allows the students to practice a variety of techniques: NMR (^{1}H, ^{13}C, COSY and HSQC), melting point, thin layer chromatography, IR, fluorescence spectroscopy and mass spectrometry to confirm the structure of their obtained product. An alternative methodology in a one-pot reaction is also explored and a full laboratory manual provided.

Keywords Click chemistry · Cycloaddition · One-pot · Laboratory practice

Introduction

With the award of The Nobel Prize in Chemistry 2022 to Carolyn R. Bertozzi, Morten Meldal, and K. Barry Sharpless, click chemistry (Kolb et al. 2001) has been recognized as one of the most relevant chemical reactions in the twenty-first century. In words of the Nobel Committee, "Click chemistry and bioorthogonal reactions have taken chemistry into the era of functionalism. This is bringing the greatest benefit to humankind."

The starting point for this reaction could be set on the development of 1,3-dipolar cycloadditions (Huisgen 1963) by Rolf Huisgen (Breugst and Reissig 2020; Giese et al. 2020), which had huge impact on the development of organic chemistry (Houk and Reissig 2019; Houk 2010; Seeman and Restrepo 2020) making the 1,3-dipolar cycloadditions the most general tool to synthesize five-membered heterocycles. The thermal Huisgen reaction between alkynes and azides to form a triazole reached a new era with the Cu(I) catalyzed

reaction, independently reported by Meldal (Tornøe et al. 2002) and Sharpless (Rostovtsev et al. 2002), which selectively afforded the 1,4-regioisomer (Fig. 1). This highly efficient CuAAC reaction has gain huge interest across a range of disciplines, including material science and medicinal chemistry and bioconjugation (Thirumurugan et al. 2013; Goals and Matyjaszewski 2010; Binder and Sachsenhofer 2007). In addition, the click chemistry versatility broadened with the Cu-free reaction developed by Bertozzi (Agard et al. 2004) employing cyclooctyne as an activated alkyne in the strain-promoted azide-alkyne cycloaddition (SPAAC), which occurs under physiological conditions in the absence of auxiliary reagents allowing the chemical modification of living cells. Despite that, two decades later the exposure of undergraduate students to the concept of click chemistry and its practice is still scarce, with a very small number of examples found in literature with the focus on an educational setting (Hansen et al. 2005; Mendes and Schoffstall 2011; Ison 2012; Lipshutz et al. 2013). Some of the advantages of this reaction, such as being modular, wide in scope, high-yielding, lack of by-products, highly regioselective, with atom economy, requiring simple reaction conditions, readily available starting materials, benign solvents and simple product isolation, make it an ideal option to build a set of practical sessions around this concept. Hands-on learning exploring this reaction deeper in the laboratory can help the students to become familiar with this contemporary chemistry, in addition to practising a number of organic chemistry

✉ Alicia Megia-Fernandez
amegia@ugr.es

1 Departamento de Química Orgánica, Facultad de Ciencias, Unidad de Excelencia de Química Aplicada a Biomedicina y Medioambiente (UEQ), Avda. Fuente Nueva S/N, 18071 Granada, Spain

2 Instituto de Biotecnología, Universidad de Granada, Granada, Spain

Fig. 1 Cu(I)-catalysed cycloaddition of azides and alkynes (CuAAC) to afford 1,4-disubstituted-1*H*-1,2,3-triazoles is the centrepiece of click chemistry
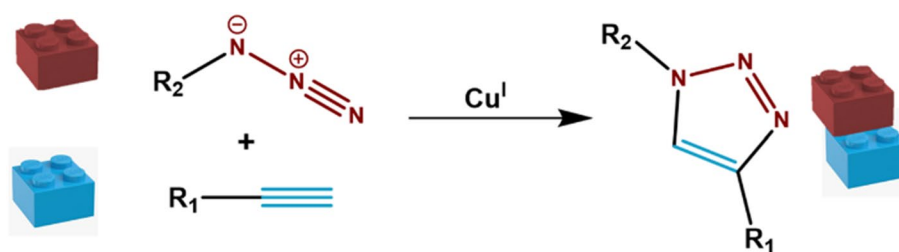
techniques for the synthesis and characterization of new compounds. With that aim, the design of a few consecutive practical sessions based on the click reaction have been explored and the results and implications for the students are discussed in this article, as well as providing the laboratory manual and set of data for the full characterization of the novel triazole formed.

Experimental

Material and methods

TLCs were performed on Silica Gel 60 F254 aluminium sheets. Reagents used for developing plates include potassium permanganate (1% w/v) and UV light. Flash column chromatography was performed on Silica Gel (230–400 mesh, ASTM). Melting points were obtained in a Gallenkamp instrument and are not corrected. IR spectra were recorded using a Mattson FTIR instrument, model Satellite. The NMR ^{1}H and ^{13}C spectra were recorded at room temperature on a BRUKER Nanobay Avance III HD (400 MHz). Chemical shifts are reported on the δ scale in ppm and are referenced to residual non-deuterated solvent resonances. Coupling constant values are given in Hz. ESI HR-MS spectra were obtained with a Waters spectrometer (SYNAP G2). Fluorescence spectra was recorded with a Hitachi F-2000 fluorescence spectrophotometer. UV–Vis absorbance spectra was obtained with a Specord 200 plus spectrophotometer.

Synthesis of 7-hydroxy-4-methylcoumarin (3) (Teizo and Koichi 2001)

In a round bottom flask resorcinol (**1**) (2.400 g, 21.8 mmol, 1 eq) was added together with ethyl acetoacetate (**2**) (2.5 ml, 21.8 mmol, 1 eq) and *p*-toluenesulfonic acid (*p*TSA, 178 mg, 1.0 mmol, 0.05 eq). The reaction was heated at 100 °C under magnetic stirring until the appearance of a precipitate (5–10 min). The reaction was allowed to cool to room temperature followed by the addition of ethanol:water (1:1, 10 ml). The final mixture was filtered under vacuum to obtain **3** (2.456 g, 64%) as a white solid. M.p. 187–189 °C. IR (film): ν 3487, 3436, 1671, 1607, 1395, 1276, 1077, 842 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40 (d, *J* = 8.6 Hz,

1H), 6.76 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.73 (d, *J* = 2.3 Hz, 1H), 6.02 (s, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 162.7, 161.1, 155.1, 153.9, 125.9, 113.4, 112.8, 110.7, 102.9, 18.7.

Synthesis of 4-methyl-7-propargyloxycoumarin (5)

In a round bottom flask **3** (300 mg, 1.7 mmol, 1 eq) was added together with K$_2$CO$_3$ (300 mg, 2.17 mmol, 1.3 eq) and acetone (8.5 ml). To the mixture propargyl bromide (**4**) was slowly added (1.2, 2.0 or 3.0 eq). The reaction mixture was heated under reflux (120, 90 or 60 min for 1.2, 2.0 or 3.0 eq respectively). After allowing to cool, water (8 ml) was added. The acetone was evaporated under vacuum and the remaining aqueous phase was extracted with ethyl acetate (40 ml), washing with water (2 × 30 ml) and drying with anhydrous sodium sulfate. After filtration, the solvent was eliminated under vacuum and the residue purified by column chromatography (EtOAc:hexane 1:1), obtaining the compound **5** (83, 78 and 52% for 1.2, 2.0 or 3.0 eq respectively) as a white solid, with the data matching those reported previously in literature (Yadav et al. 2018). M.p. 130–132 °C. IR (film): ν 3302, 2922, 1716, 1606, 1389, 1280, 1017, 845 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.51 (d, *J* = 9.5 Hz, 1H), 6.94–6.89 (m, 2H), 6.14 (s, 1H), 4.75 (d, *J* = 2.4 Hz, 2H), 2.57 (t, *J* = 2.4 Hz, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 161.3, 160.5, 155.2, 152.5, 125.8, 114.4, 112.9, 112.6, 102.3, 77.6, 76.6, 56.3, 18.8. HRMS (ESI) *m/z*: calcd for C$_{13}$H$_{11}$O$_3$ [M + H]$^+$, 215.0708; found, 215.0697.

Synthesis of 2-azido-1-phenylethanone (7)

In a round bottom flask 2-bromo-1-phenylethanone (**6**) (300 mg, 1.51 mmol, 1.0 eq) and NaN$_3$ (245 mg, 3.77 mmol, 2.5 eq) in acetone (15 ml) were heated at reflux for 1 h. After that the acetone was evaporated under vacuum. The crude was dissolved in EtOAc (40 ml) and washed with saturated NaHCO$_3$ (30 ml) and water (30 ml). The organic phase was dried with anhydrous Na$_2$SO$_4$ and after filtration the solvent was evaporated under vacuum to obtain **7** (209 mg, 86%) as a brown oil. IR (film): ν 2910, 2097, 1693, 1215, 754, 687 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.91 (d, *J* = 7.4 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 4.55

(s, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 193.3, 134.4, 134.2, 129.0, 128.0, 54.9. Spectroscopic data matches those reported previously in literature by Edegger et al. 2006.

Synthesis of triazole by click reaction between azide and alkyne

In a round bottom flask the following reagents were added: alkyne **5** (80 mg, 0.35 mmol, 1 eq), azide **7** (57 mg, 0.35 mmol, 1 eq), sodium ascorbate (NaAsc) (7 mg, 0.035 mmol, 0.1 eq.), CuSO$_4$·5H$_2$O (5 mg, 0.018 mmol, 0.05 eq) and *t*BuOH:water (10:1, 11 ml). The reaction was stirred and heated under reflux for 15 min. Once at room temperature, water (10 ml) was added and the reaction crude extracted with EtOAc (20 ml). The organic phase was dried with anhydrous Na$_2$SO$_4$, filtered and evaporated under vacuum to afford compound **8** (120 mg, 93%) as a yellow solid. M.p. 184–186 °C. IR (film): ν 2923, 2852, 1705, 1614, 1392, 1230, 1145, 1070 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.27 (s, 1H), 8.08 (d, $J = 7.0$ Hz, 2H), 7.74 (t, $J = 7.4$ Hz, 1H), 7.68 (d, $J = 8.8$ Hz, 1H), 7.60 (t, $J = 7.8$ Hz, 2H), 7.16 (d, $J = 2.5$ Hz, 1H), 7.05 (dd, $J = 8.8$, 2.5 Hz, 1H), 6.23 (s, 2H), 6.20 (d, $J = 1.3$ Hz, 1H), 5.34 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d$_6$) δ 192.1, 161.1, 160.2, 154.7, 153.4, 141.9, 134.3, 134.1, 129.0, 128.2, 126.6, 126.5, 113.4, 112.6, 111.3, 101.6, 61.7, 56.0, 18.1. HRMS (ESI) *m/z*: calcd for C$_{21}$H$_{18}$N$_3$O$_4$ [M + H]$^+$, 376.1297; found, 376.1282.

Sequential one-pot click reaction: In a round bottom flask, 2-bromo-1-phenylethanone **6** (176 mg, 0.9 mmol, 1 eq) was added together with NaN$_3$ (58 mg, 0.9 mmol, 1 eq) and a mixture *t*BuOH:H$_2$O (10:1, 25 ml). The mixture was heated under reflux for 1 h. Then alkyne **5** (200 mg, 0.9 mmol, 1 eq), sodium ascorbate (18 mg, 0.09 mmol, 0.1 eq) and CuSO$_4$·5H$_2$O (11 mg, 0.05 mmol, 0.05 eq) were added and the reaction mixture stirred for 90 min at reflux. Once cooled down to room temperature, water (15 ml) was added and the reaction crude extracted with EtOAc (20 ml). The organic phase was dried with anhydrous Na$_2$SO$_4$ and after filtration the solvent was evaporated under vacuum. The crude was purified by column chromatography (EtOAc:Hexane 1:1→EtOAc) to obtain compound **8** (206 mg, 61%).

Multicomponent one-pot formation of triazole

In a round bottom flask the following reagents were added: 2-bromo-1-phenylethanone **6** (264 mg, 1.3 mmol, 1 eq), the alkyne **5** (300 mg, 1.3 mmol, 1 eq), NaN$_3$ (86 mg, 1.3 mmol, 1 eq), sodium ascorbate (26 mg, 0.13 mmol, 0.1 eq) and CuSO$_4$·5H$_2$O (17 mg, 0.07 mmol, 0.05 eq), in a mixture of *t*BuOH:water (10:1, 25 ml). After heating at reflux for 3 h, and cooling down to room temperature, water (15 ml) was added and it was extracted with EtOAc (20 ml). The organic

phase was dried with anhydrous Na$_2$SO$_4$ and after filtration the solvent was evaporated under vacuum. The crude was purified by column chromatography (EtOAc:Hexane 1:1→EtOAc) to obtain compound **8** (374 mg, 74%).

Health and safety considerations

Personal protective equipment i.e. safety goggles, lab coat and gloves should be worn at all times and chemicals and solvents handled in a ventilated chemical fume hood. The use of organic azides in undergraduate experiments has been previously reported (Hansen et al. 2005; Ison 2012) but caution should be exercised when using azides. Working with inorganic azides, as a general rule acids, halogenated solvents, and metals should be strictly avoided (Treitler and Leung 2022). Both organic and inorganic azides can be heat and shock sensitive (Bräse et al. 2005; Bräse and Banert 2010). Sodium azide is toxic and its mixing with acid must be avoided as hydrazoic acid is highly toxic. Any azide waste should be handled separately and never disposed down the drain. Safe disposal by oxidation using NaNO$_2$ is recommended (see protocol on Lunn and Lawler 2002). Organic azides are especially sensitive to violent decomposition by light, heat, friction, or pressure. Those following the rule of C to N ratio ≥ 3 [(C$_{atoms}$ + O$_{atoms}$)/N$_{atoms} \geq 3$] are considered stable for handling. Azides should not be manipulated using metal utensils (e.g. metal spatulas) and halogenated solvents, especially dichloromethane, must never be used in reactions with azides. 2-Bromo-1-phenylethanone can cause skin corrosion. Resorcinol is toxic. Copper sulfate is hazardous (skin and eye irritation). Students should become familiar with the safety data sheets of the chemicals to be used, and an introduction to COSHH (Control of Substances Hazardous to Health) assessment to identify hazard and assessing risk is highly desirable. Waste disposal is also considered in the lab manual supplied for the students.

Results and discussion

Design of a laboratory session to put click chemistry into practice

With the aim of providing the students with a general overview of the click chemistry concept a practical session has been designed. The designed synthetic route to obtain the alkyne and the azide is shown in Scheme 1.

For the alkyne, we chose the synthesis of coumarin from resorcinol, which involves the reaction of a phenol with a β-ketoester in the presence of an acid condensing agent (Pechmann reaction). Starting from resorcinol (**1**), the coumarin **3** is formed by reaction with ethyl acetoacetate and a catalytic amount of *p*-toluenesulfonic acid. Work up is very

Scheme 1 Synthesis of alkyne **5** and azide **7** counterparts used in the click reaction
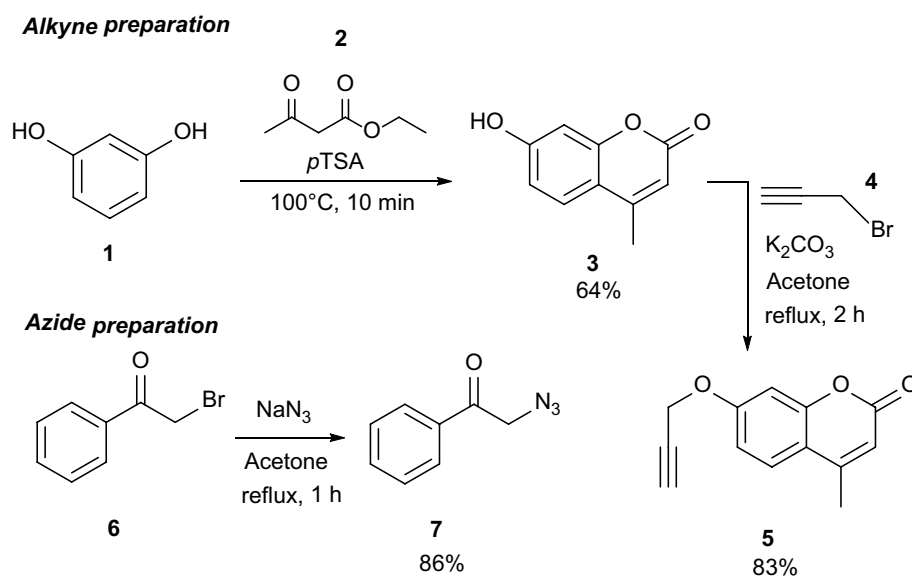
convenient for a practical session as the product precipitated as a white solid in a short time and was isolated by filtration. After that, *O*-alkylation of the phenol with propargyl bromide in basic medium afforded the alkyne **5** to be used as the first coupling partner in the click reaction. A set of three different conditions varying reaction time and equivalents of propargyl bromide were evaluated: 120, 90 or 60 min for 1.2, 2.0 or 3.0 eq respectively were tested, affording the product with 83, 78 and 52% respectively. Comparing these results, increasing the amount of propargyl bromide did not replace what time can achieve in this reaction, therefore 90 min and 2.0 equivalents is chosen from a practical point of view.

The choice of azide was based on a straightforward preparation using simple and commercially available starting materials such as sodium azide and 2-bromo-1-phenylethanone. The nucleophilic substitution afforded organic azide **7** in one step after a simple work up consisting of liquid–liquid extraction with a very good yield (86%) and purity.

Once obtained the alkyne and the azide, the click reaction (Scheme 2) was tested using the catalytic system CuSO$_4$ / sodium ascorbate, where the Cu(II) is reduced in situ to Cu(I), and a mixture of *t*BuOH:H$_2$O (10:1) was excellent to dissolve both azide and alkyne. At room temperature a conversion of approximately 50% was estimated by TLC after 6 h. At reflux the reaction needed only 15 min for full conversion.

The work up step was also optimized: two different work-ups were tried in order to isolate the formed triazole. In the first one, water (10 ml) was added followed by conc. NH$_3$ (1 ml) in order to precipitate the product. Filtration under vacuum afforded compound **8** with 76% yield and good purity without additional steps of chromatographic purification. An alternative work up involved liquid–liquid extraction with ethyl acetate obtaining in this case compound **8** with 93% yield. The compound was characterized by NMR (^{1}H, ^{13}C, DEPT, HSQC, COSY), IR, UV–Vis and mass spectrometry.

Techniques for monitoring and characterization

The monitoring of the click reaction can help the students to practice TLC and different staining, as the compounds are UV-active and can be seen on the lamp and/or stained with potassium permanganate solution. Besides helping in monitoring the reaction and consumption of reagents, TLC in each step can be helpful to estimate the purity of the prepared compounds.

As expected, the triazole compound increased in polarity compared with the precursors azide and alkyne and showed the smallest R$_f$ value (0.18 for the triazole **8**, 0.54 for the azide and 0.44 for the alkyne, Fig. 2). The students can obtain their own values in order to practice their TLC skills.

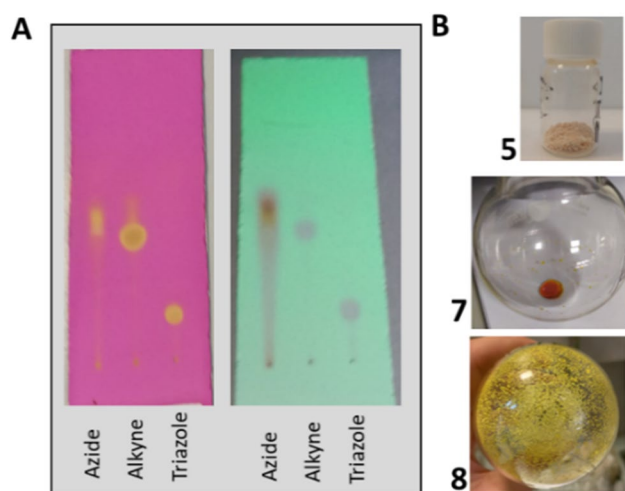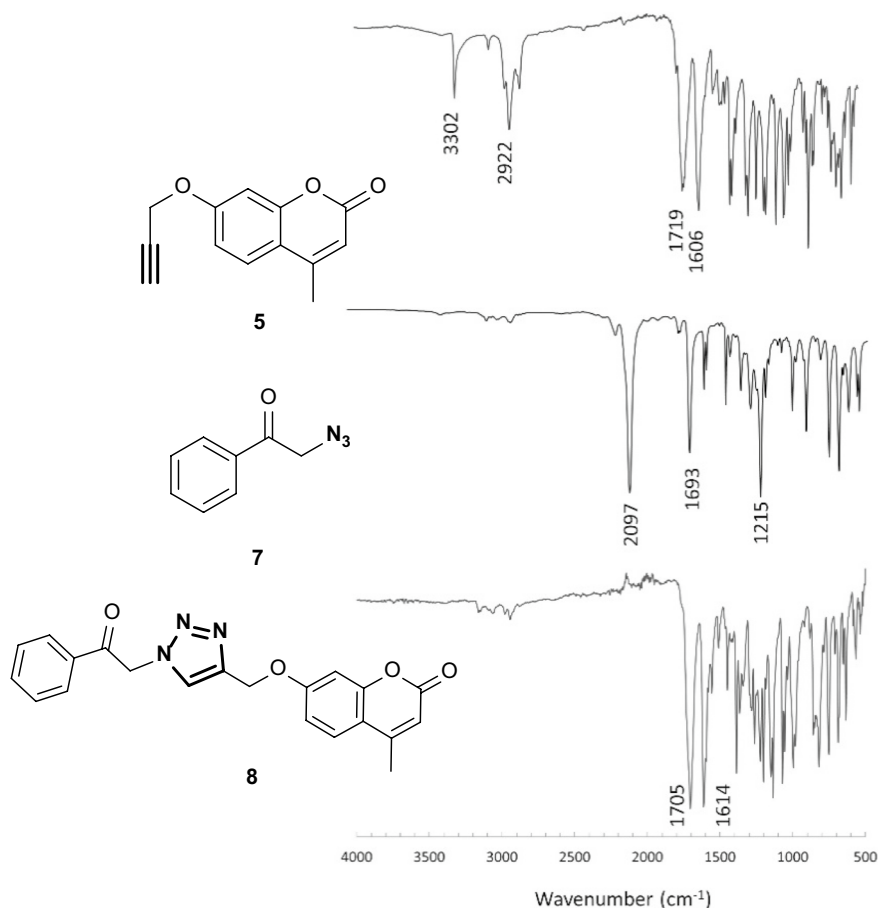**Scheme 2** Click reaction catalyzed by Cu(I) to obtain triazole **8**
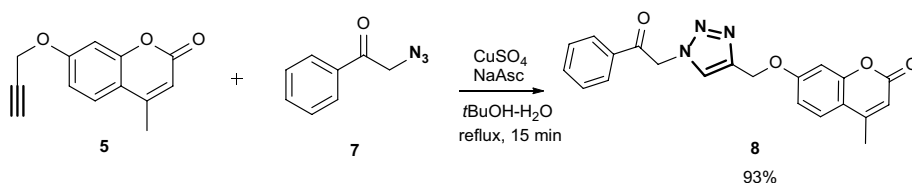
Fig. 2 A TLC of the different compounds eluted with a mixture of Hexane–EtOAc (1:2) and stained with potassium permanganate (left) and seen under the UV lamp (right). **B** Physical appearance of the different compounds

functional groups such as azide (seen at 2097 cm^{-1}), lactone (seen at 1719 and 1705 cm^{-1} for compound **5** and **8** respectively) and ketone (seen at 1693 and 1614 cm^{-1} for compound **7** and **8** respectively). Disappearance of the azide peak for example can be indicative of click reaction completion when monitoring the process by IR.

The propargyl coumarin (**5**) and triazole coumarin (**8**) absorbance and fluorescent emission was measured: absorption and emission characterization of compounds **5** and **8** revealed shared values of maximum absorbance at λ 320 nm and fluorescent emission at λ 390 nm (Fig. 4). These are very similar to the reported values for parent coumarin **3** (λ_{abs}318 nm/λ_{em} 380 nm) by Jamaludin et al. (2018).

The NMR spectra of azide, alkyne and click product increase in complexity gradually making them ideal for the students to learn ^{1}H NMR and ^{13}C NMR of organic compounds assigning the signals: from the simplest starting organic azide (Figs. S7–S9), the obtained alkyne-coumarin (Figs. S4–S6) and finally, the novel synthesised triazole **8**. In the ^{1}H-NMR spectrum of compound **8** (Fig. 5) the characteristic triazole peak above 8 ppm is seen (δ 8.27 ppm). From this distinct peak and making use of the integration value, the chemical shift and the coupling pattern and *J* values,
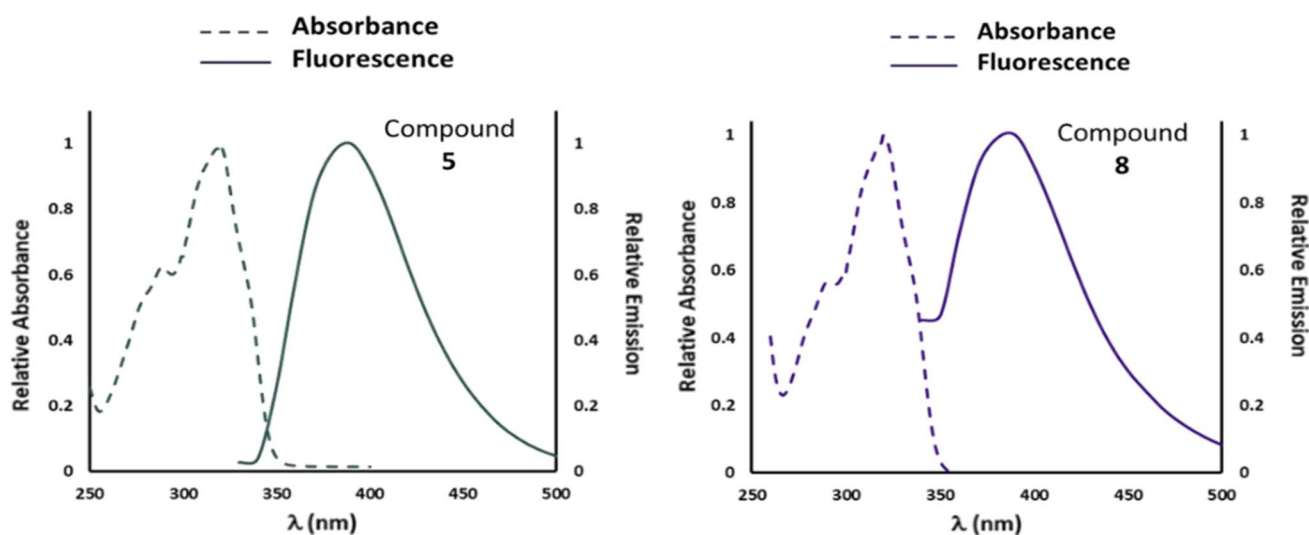
Characterization by IR of the obtained products (Fig. 3) can reinforce the knowledge of characteristic IR peaks for

Fig. 3 IR spectra of alkyne **5** (top), azide **7** (central) and click compound **8** (bottom)

Fig. 4 Normalized absorbance and fluorescence spectrum for compounds **5** and **8** in dichloromethane. λ_{ex}: 320 nm
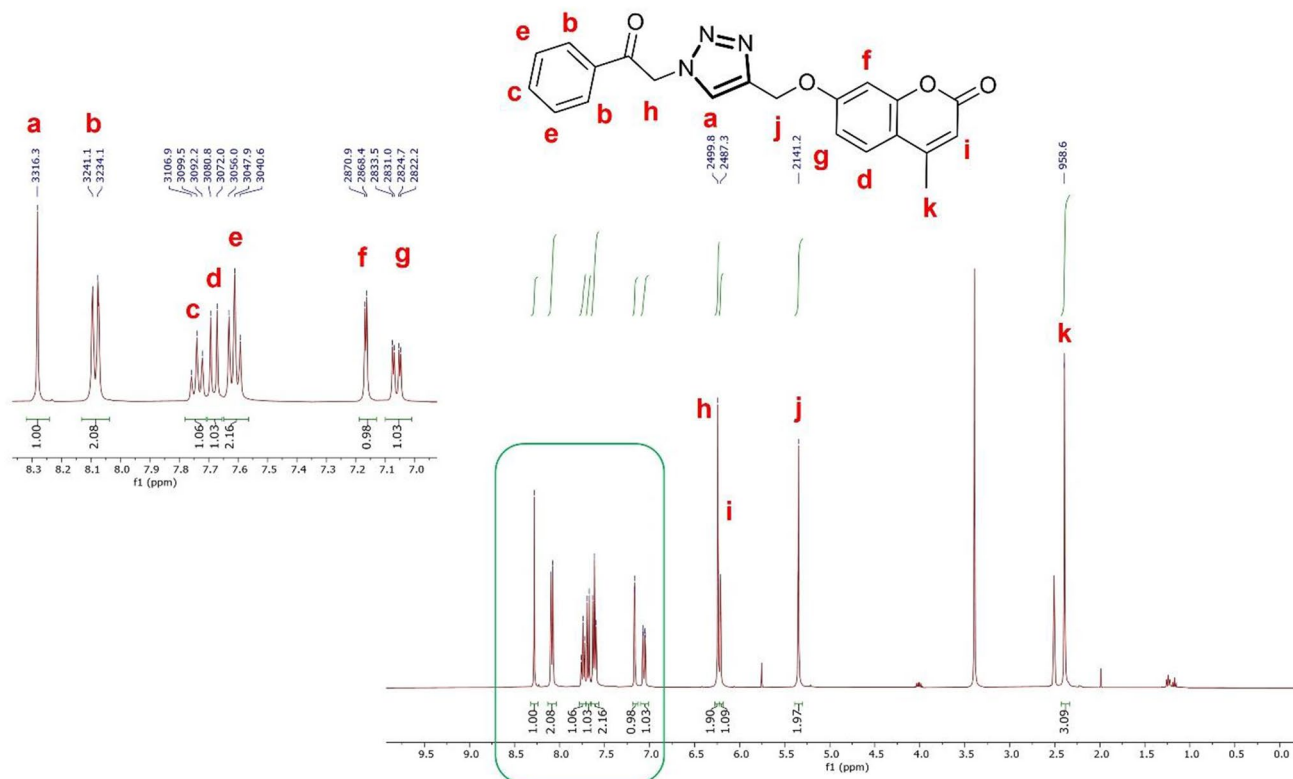

Fig. 5 ^{1}H-NMR spectrum of compound **8** in DMSO-d$_6$. Inset zoom of the aromatic region is shown on the left

all ^{1}H signals can be assigned for this novel molecule. The aromatic region in particular shows very good resolution and peaks not overlapping, allowing to discriminate between each of those H and even showing small couplings such as those between H$_f$ and H$_g$, making it very interesting from an academic perspective. Files containing the ^{1}H and ^{13}C

FID for compounds **5**, **7** and **8** are also provided as supporting information to give the students the opportunity to process the spectra using the software to integrate, calculate *J* values, etc. In the ^{13}C-NMR spectra (Fig. 6) the molecule showed a total of 19 signals, as expected for **8** (C$_{21}$H$_{17}$N$_3$O$_4$) considering the equivalent carbons in the monosubstituted
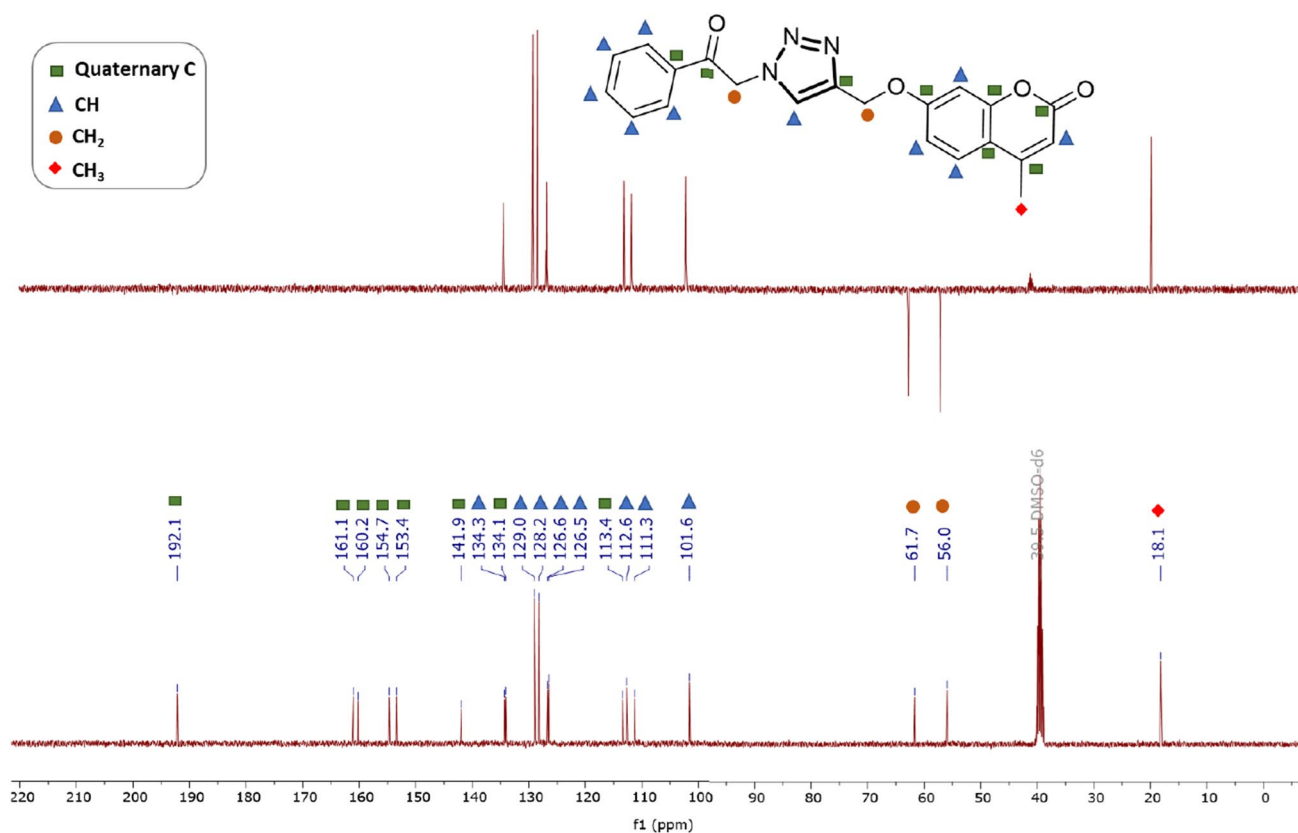
Fig. 6 ^{13}C-NMR spectrum (bottom) and DEPT 135 (top) of compound **8** in DMSO-d_6

phenyl ring. DEPT 135 spectra helped to identify all the signals of the different carbons based on their substitution as quaternary, tertiary, secondary (CH$_2$ at 61.7 and 56.0 ppm) and the only primary CH$_3$ at 18.1 ppm. The assignment of C and H signals was also confirmed with the 2D-NMR spectra HSQC and COSY (Fig. 7). With the homonuclear correlation 2D COSY experiment we observed as expected correlation peaks (out of the diagonal) for H$_d$ with H$_g$ and for H$_e$ with protons H$_b$ and H$_c$ as these are the only ones that arise from neighboring protons. The heteronuclear HSQC spectra revealed directly-bonded proton-carbon resonances. Once each signal in the ^{1}H-NMR spectra has been assigned, using the cross peaks in the HSQC the assignment of C signals directly bonded can be completed by the students.

In addition, HRMS afforded a peak at *m/z* 376.1282, matching the expected mass for compound **8** (376.1297 [M+H]$^+$, Fig. S15, ESI).

In addition to the process described previously, where azide and alkyne are prepared separately and made to react in the click reaction, an alternative methodology in one-pot (Fig. 8) was also tested and afforded very good results. It could be very useful when a shorter practical session is needed, and also in this way the concept of one-pot is experienced in the laboratory by the students. In addition, the

one-pot procedure explored during this study avoided the isolation of the organic azide, which is formed and reacted in situ minimizing any safety hazard related with the isolation of organic azides. Starting from bromoacetophenone **6**, a sequential process involved adding first the sodium azide (TLC monitoring is not easy at this point as starting material and product have very similar R$_f$) and after 1 h, the alkyne and the catalytic system of copper sulfate/sodium ascorbate, continuing the reaction for 90 min. Alternatively, all reagents (sodium azide, alkyne and the catalyst) can also be mixed together from the beginning achieving in this one-pot procedure a very decent yield (71%). The only disadvantage of this one-pot procedure versus the step-wise procedure described before, is that the one-pot reaction required purification by column chromatography in order to isolate the triazole with high purity.

Educational implications

The educational nature of this experimental session is evidenced by the number of chemistry topics the students are exposed to. In addition to the general concepts of click chemistry, atom economy and one-pot reactions, the students can practice an interesting set of reaction types from

Fig. 7 A 2D-HSQC NMR
spectrum of compound **8**. **B**
2D-COSY NMR spectrum of
compound **8**
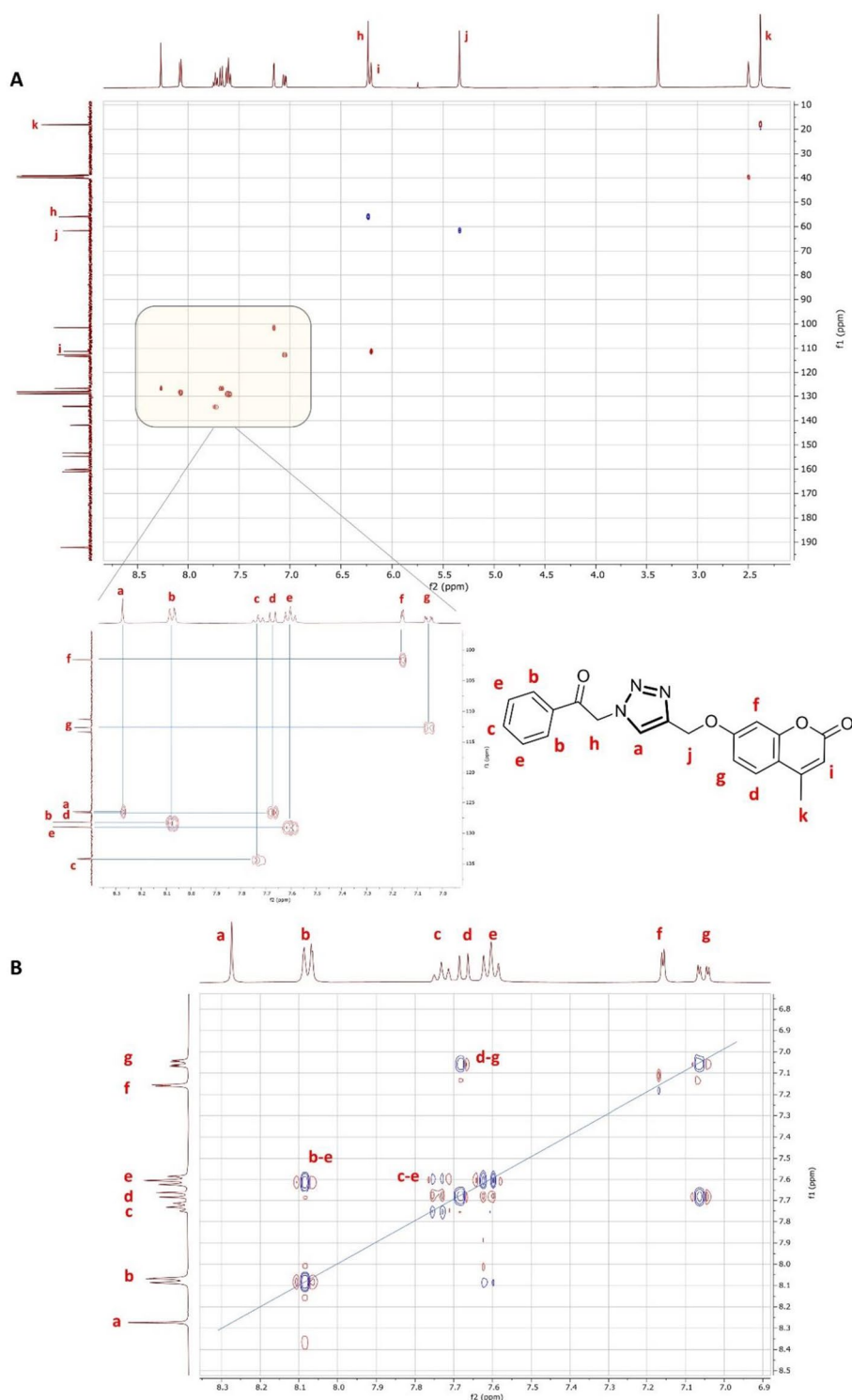
nucleophilic substitution, *O*-alkylation, Pechmann condensation and dipolar cycloaddition. Hands-on learning implies also important organic laboratory techniques such as liquid–liquid extraction, thin layer chromatography, filtration, different types of purification, waste disposal, etc. Finally, full characterization provides experience on melting point measurements, NMR, IR, UV–Vis, fluorescence spectroscopy and mass spectrometry and data analysis.

The educational aims for the student can be summarised as: (i) Synthesis of starting materials and CuAAC reaction (ii) Monitoring of reactions (iii) Isolation and purification techniques (iv) Obtaining and interpretation of
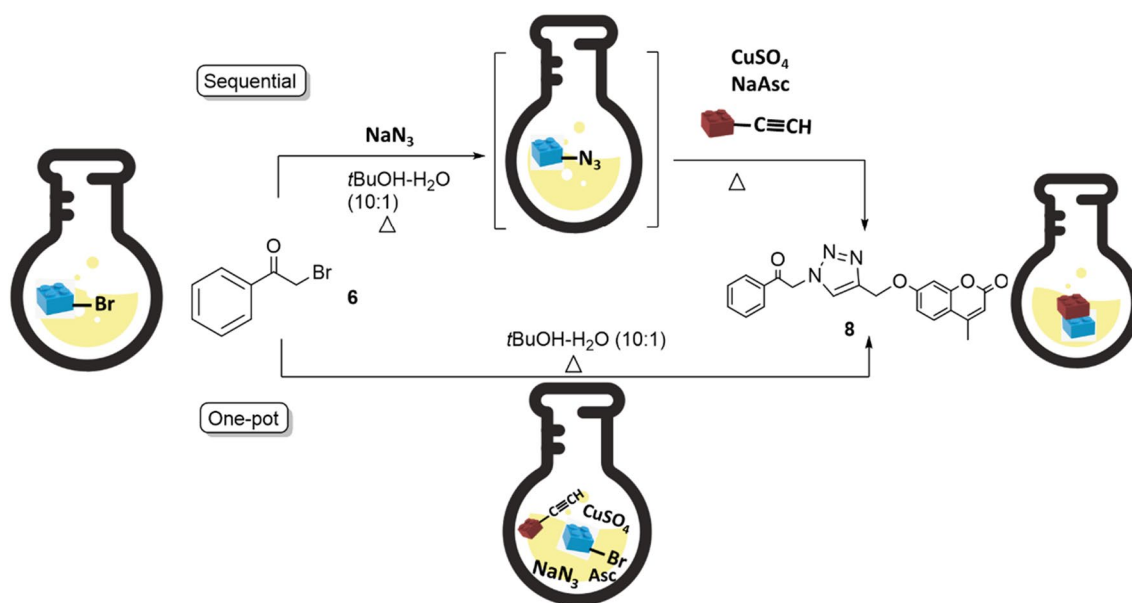
Fig. 8 One-pot methodology for the synthesis of triazole from bromo derivative, sodium azide and alkyne

characterization data (v) Understanding the click concept (vi) Practice of a one-pot procedure. The combination of all these should result in a complete and rewarding learning experience with many benefits for the students.

These experiments provided an excellent opportunity for the students to develop an appreciation for the principles of click chemistry using a conceptual and practical approach as an addition to the undergraduate curriculum in Organic Chemistry. A lab manual for the students is also provided (ESI) and the experimental program split into 2-4 h lab sessions could be achieved in three or four sessions depending on the use of the alternative one-pot protocol. Suggested program could be: Day 1: Synthesis of 2-azidoacetophenone, Day 2: Pechmann reaction, Day 3: Propargylation, Day 4: CuAAC reaction.

Conclusions

In the experiment optimized here for a laboratory training in Organic Chemistry, the students should be able to learn not only a contemporary reaction as the CuAAC, but also the principles of interesting and relevant concepts such as click chemistry and one-pot reactions, in addition to practicing a variety of techniques for the synthesis and full characterization of their obtained products with a very rich NMR analysis which could be extremely productive and beneficial as a hands-on learning experience.

Declarations

Conflict of interest There are no conflicts to declare.

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