Intrinsic sensing fluorescent probe for the solid phase synthesis of 1,4-benzodiazepine-2,5-dione

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Abstract

The synthesis of 4-*N*-naphthylethyl-1,4-benzodiazepine-2,5-dione (**1**) supported on solid phase is described. The fluorescent naphthyl group is used as internal sensor for monitoring various stages on the synthetic reaction by spectral differences in fluorescence. Our results show the efficacy of fluorescence as a direct method for the evaluation of reaction progress. This method is fast, sensitive and non-destructive. A target molecule was synthesized which could be used in the synthesis of a variety of benzodiazepines.

Keywords: Benzodiazepine, fluorescence, solid phase

Introduction

The synthesis of chemical libraries through combinatorial chemistry has been of great importance during the last decade due to the large number of compounds that can be prepared in a fast and efficient manner. Solid phase organic synthesis (SPOS) has become to be one of the most useful synthetic technique in combinatorial chemistry.

SPOS is an important tool in the discovery of new substances biologically activite with a suitable pharmacological profile to be used as drugs. This is demonstrated by the wide range of existing reports on diverse lines of research in organic synthesis. Some of these reports describe the synthesis of quinazolinediones[1], pyridine analogues[2] and benzodiazepines.[3] SPOS was originally developed by R. B. Merrifield[4] and is based on the use of a polystyrene resin in the form of spheres which are insoluble in most common solvents.

In the development of combinatorial chemistry to produce a great diversity of substances, the analytical evaluation and structure determination is a critical step. The finding of efficient and fast techniques that allow monitoring reaction progress and chemical changes on the solid phase supported compounds has become of great importance these days.[5] Proper structural analysis of

these libraries is fundamental for the complete characterization of compounds and determination of reaction yields and purity of final products. Evaluation techniques for SPOS are one of the drawbacks for this process, since various analytical methods require the cleavage of the bond linking the organic compounds to the polymer before analysis. In this regard, most common analytical methods such as IR, MS, etc. are destructive. On the other hand, Gel-phase[6] in ^{13}C NMR has been used in some commercial resins as Wang and Merrifield. However, since this technique is slow and limited it could not be applied to combinatorial chemistry. Therefore, it is fundamental to establish new methods with high sensitivity, which allows measuring the different stages of the reaction as well as the degree of conversion during the process.

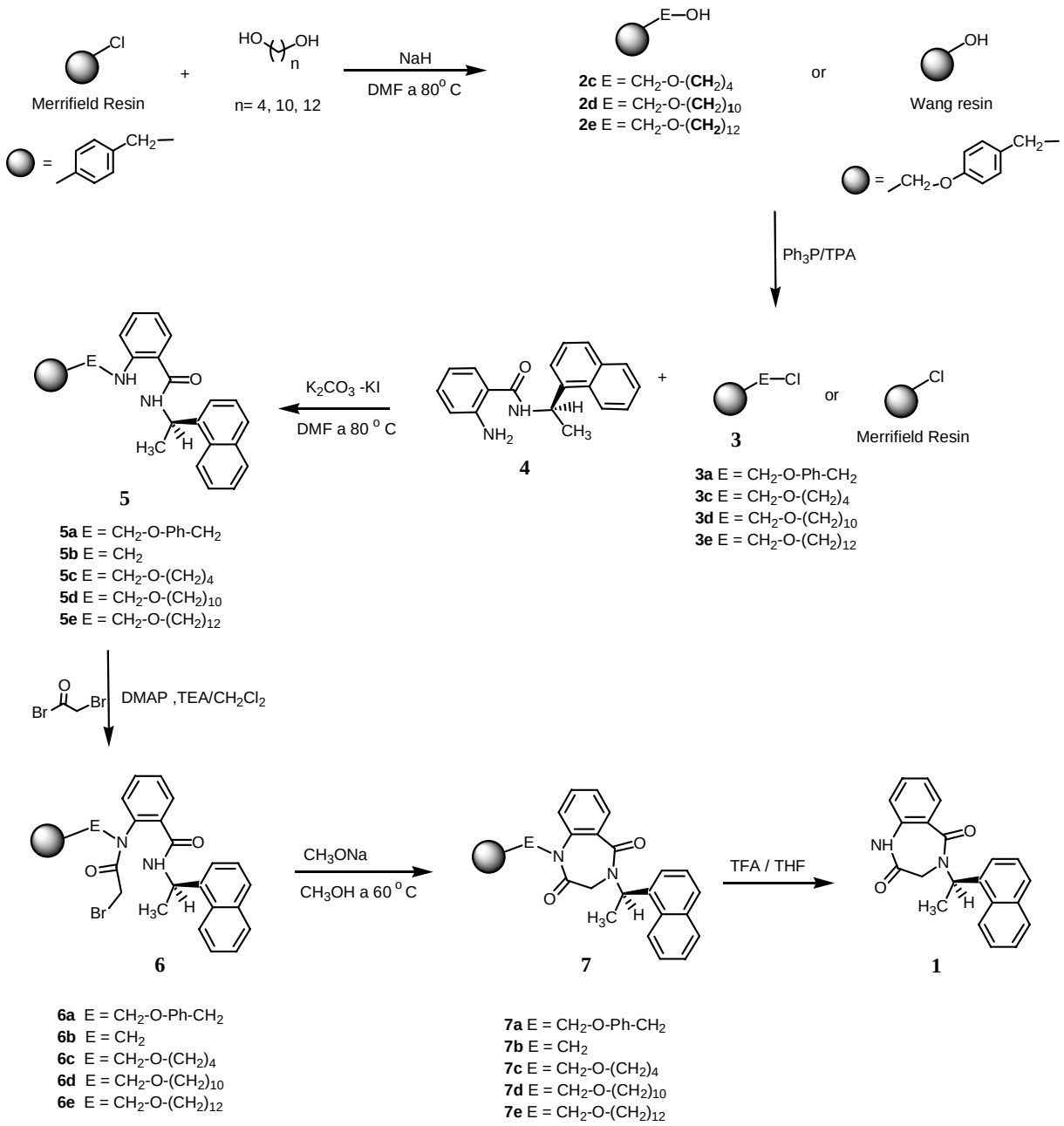
In this report, we show the use of the naphthyl group as an internal probe. This group allows direct monitoring by fluorescence spectroscopy of the several stages on a global reaction.

Results and Discussion

Polymer bound 4-*N*-naphthylethyl-1,4-benzodiazepine-2,5-dione (**1**) with the naphthyl group as the probe was synthesized according with Scheme 1. In order to evaluate the effect of the spacer length on the fluorescence, a comparison among 4-*N*-naphthylethyl-1,4-benzodiazepine-2,5-dione supported on Merrifield resin, Wang resin, and Merrifield resin with a condensed spacer of different aliphatic chains length (4, 10, and 12 methylenes), was performed.

The alkoxides from different diols (1,4-butanediol, 1,10-decanediol, and 1,12-dodecanediol were condensed with the Merrifield resin to yield the resins: Merrifield-1-oxi-4-butanol (**2c**), Merrifield-oxi-10-decanol (**2d**), and Merrifield-1-oxi-12-dodecanol (**2e**). The modified resins and Wang resin were chlorinated using triphenylphosphine and triphosgene to obtain the resins: Merrifield-1-oxi-4-chlorobutane (**3c**), Merrifield-1-oxi-10-chlorodecane (**3d**), Merrifield-1-oxi-12-chlorododecane (**3e**), and Wang-chlorinated (**3a**).

N-(*R*)-(+)-1-(1-Naphthyl)ethane-2-aminobenzamide (**4**) was prepared from *R*-(+)-1,1-ethylnaphthylamine and isatoic anhydride and then supported on Merrifield resin and the modified resins **3a**, **3c-d**. Chemistry in parallel using four different methods was applied for the coupling of *o*-aminobenzamide **4** with the solid support. The Best yields were achieved with method B, which is a modification of method A in which KI is added. The highest yield was achieved for Merrifield resin (100%, Method B, see Experimental), while the lowest was obtained with the resin Merrifield-1-oxy-12-chlorodecane (**3e**), (23%, Method A). Methods C and D showed a lower degree of coupling (92-34%). In these methods tetramethyl guanidine is used as a base with 3 and 6 equivalents, respectively. No significant effect on the yields was found. Of four methods examined, method B showed the highest degree of coupling for *o*-aminobenzamide **4** (100-32%). Additionally, it was established that increasing the length of the spacer chain up to 12 carbons leads to a decrease in the degree of coupling (32%).



Scheme 1

The amidation step of the *o*-aminobenzamide supported on solid phase (**5a-5e**) was performed with bromoacetyl bromide in the presence of TEA and DMAP to give the resins *o*-amidonaphthylbenzamide (**6a-e**). The resin-*o*-aminobenzamide with the highest degree of amidation was Wang-*o*-aminonaphthylbenzamide (**5a**) (100 %), while with Merrifield resin the yields decrease upon increasing the length of the aliphatic chain (14 % for the spacer with 12 carbons).

Also, chemistry in parallel for the ring formation was performed using four different methods. The best results were obtained with cesium carbonate in DMF (Method B) and the resin *o*-amidonaphthylbenzamide (**6b**), without the aliphatic spacer group (90%). The use of sodium methoxide in refluxing methanol yielded 30% for the hydrolysis of naphthylamide (Method D). It was also observed that increasing the length of the spacer chain to 12 carbons, the degree of ring formation increased, in contrast with the previous stage. Increasing the length of the aliphatic chain results in an increment of lipophylicity of the support, which in turn makes it more easily solvated by organic solvents. The yields of this stage depend on the type of base. Using either bases of low solubility in organic solvents like K_2CO_3 (Method A) or tetramethyl guanidine (Method C), lowers the yield of benzodiazepines **7**. Sodium methoxide, which is soluble in methanol, considerably increases the yields of ring formation as well as of hydrolysis. The last reaction involved ia the detachment of benzodiazepine from the polymeric support by treatment with THF/TFA (1:1) for 30 min to obtain *N*-naphthylethylamine-1,4-benzodiazepine-2,5-dione (**1**). The yields in this stage were quantitative for the Wang resin.

The resins synthesized in each stage were analyzed in a 0.2 mL fluorescence cell. The emission and excitation spectra of all the intermediates supported in Merrifield resin without spacer are shown in Figure 1. Fluorescence spectroscopy analysis for Merrifield resin (Bands A) shows, after supporting *o*-aminonaphthylbenzamide (**4**) an increment on the intensities of the excitation and emission bands (Bands C). These intensities are greater than those of the *o*-aminonaphthylbenzamide (**4**) (Bands B), and they appear at longer wavelength leading to considerably accurate measurements. Amidation of the *o*-aminobenzamide supported on solid phase (**5a**) with bromoacetyl bromide showed a quenching on the excitation and emission bands. This decrement of intensities is attributable to the incorporation of bromine, a heavy atom that deactivates fluorescence in the resin.[7]

Upon ring closing, the resin benzodiazepine (**7a**) is obtained. This product shows a wavelength shift on the emission band from λ_{max} 430 nm to λ_{max} 637 nm, and the excitation band from λ_{max} 382 nm to λ_{max} 560 nm. These notable shifts are due to the formation of a new ring, and therefore, increasing rigidity in the molecule. [7]

Fluorescence spectroscopy analysis of the other resins shows the same tendency as in Merrifield resins. The only difference observed was the decreasing of the intensities when increasing the number of carbons on the spacer group. This could be explained since molecules acquire greater mobility, and part of the energy is lost by intermolecular collisions. This tendency is lineal and allows identification of the maximum number of carbons in a spacer necessary to maintain accurate measurements in fluorescence, allowing the evaluation of reaction progress (Figure 2).

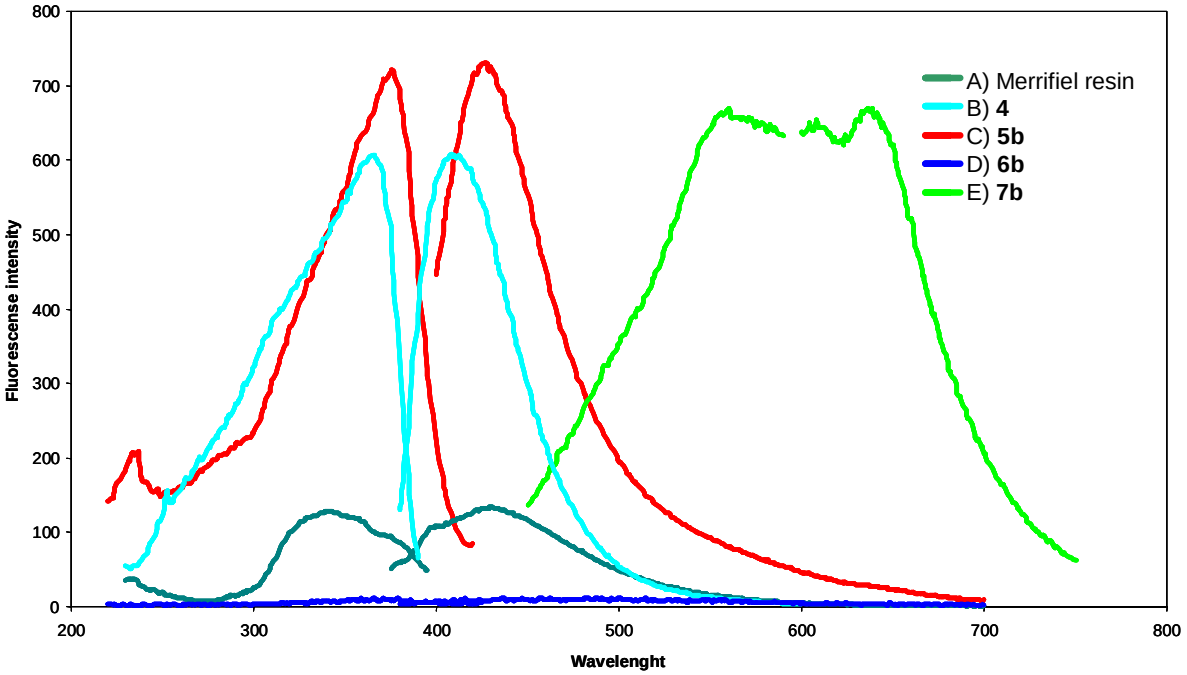


Figure 1. Fluorescence spectra of the resins: A) Merrifield Resin, FI = 131, Em_{max}: 430 nm (Exc.: 340 nm). B) *o*-Aminonaphthylbenzamide (**4**), FI = 568, Em_{max}: 405 nm (Exc.: 36 0nm). C) *o*-Aminonaphthylbenzamide bound to Merrifield Resin (**5b**), FI = 722, Em_{max}: 427 nm (Exc.: 375 nm). D) *o*-Amidonaphthylbenzamide bound to Merrifield Resin (**6b**), FI = 12, Em_{max}: 439 nm (Exc.: 365 nm). E) *N*-naphthylethylamine-1,4-benzodiazepine-2,5-dione bound to Merrifield Resin (**7b**), FI = 662, Em_{max}: 637 nm (Exc.: 560 nm).

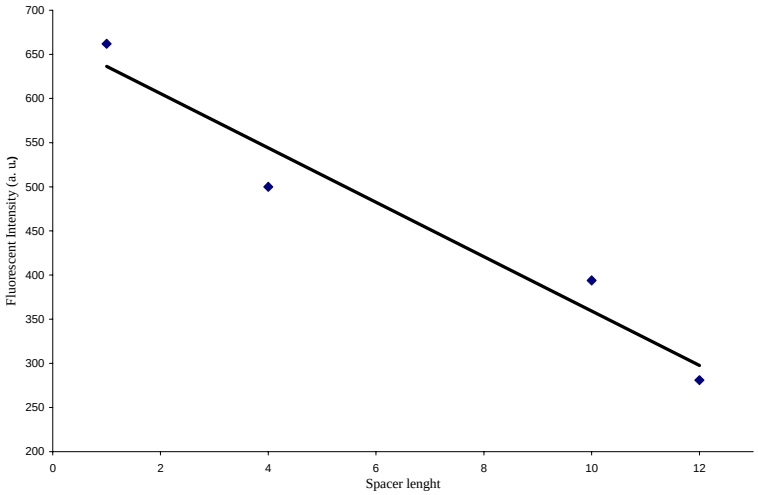


Figure 2. Fluorescence intensities related to the number of carbons on the spacer group spectra of *N*-naphthylethylamine-1,4-benzodiazepine-2,5-dione (**7**) bound to Merrifield Resins.

In summary, the use of fluorescent probes anchored to the resin provided evidence for the progress of the ongoing structural changes. Fluorescence spectroscopy is a very sensitive technique that provides valuable information involving changes in quantum yields, which in turn induces changes in the degree of conversion in a given reaction. The shifts in the signals are indicative of structural changes related to rigidity and planarity in the molecule. The naphthyl group acts as a sensor allowing the use of fluorescence spectroscopy as an analytical technique for the analysis of each step and determination of the reaction kinetics on solid phase.

Experimental Section

General Procedures. Melting points were obtained on an Electrothermal 88629 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR 1600 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Varian Mercury 200 Spectrometer in $CDCl_3$ with TMS as internal standard (200 and 50.289 MHz, respectively). EIMS spectra were obtained on a Hewlett Packard 5989 MS Spectrometer at 70 eV by direct insertion. Combinatorial chemistry procedures were carried out in a Reactor Quest Argonaut model SLN-210. Fluorescence spectra were recorded on a Shimadzu RF-5301 PC.

General method for resin Merrifield-oxy-alkyl-alcohol 2c-e. Merrifield resin (1 g, 1.19 meq/g) was swollen in DMF (40 mL) with constant stirring for 30 min in three separate flasks. Alkoxides from different diols [1,4-butanediol (0.54 g, 5.95 mmol), 1,10-decanediol (1.04 g, 5.95 mmol) and 1,12-dodecanediol (1.20 g, 5.95 mmol)] were prepared by the addition of NaH (0.238 g, 5.95 mmol) and heating at 80 ^{o}C with constant stirring for 2 h. The alkoxides were transferred via cannula to the flasks containing the swollen resin, then added tetraethylammonium (0.1 g, 0.10 mmol) and refluxed with constant stirring for 72 h. The resin suspensions were filtered in three separate Buchner funnels and washed with the following solvents: (3 × 50 mL) H_2O; (3 × 50 mL) H_2O/MeOH (1:1); (3 × 40 mL) MeOH; (2 × 50 mL) DCM. The resins were then dried in high vacuum for 18 h. Resins Merrifield-1-oxi-4-butanol (**2c**), Merrifield-oxi-10-decanol (**2d**) and Merrifield-1-oxi-12-dodecanol (**2e**) showed 100% conversion determined by the Volhard titration of residual chlorine content in Merrifield resin,[8] and 95% resin recovering was obtained. IR (KBr): 3509-3446, 3025, 2912, 1600-1594, 1487, 1441, 1020 cm^{-1}.

General method of chlorination. Wang resin, and resins Merrifield-1-oxi-4-butanol (**2c**), Merrifield-oxi-10-decanol (**2d**), and Merrifield-1-oxi-12-dodecanol (**2e**) (0.238 mmol/g) were swollen in CH_2Cl_2 (20 mL) with stirring for 30 min. Chlorination reagent solutions for both kinds of resins were prepared in the following manner: a) for Wang resin, triphenylphosphine (0.19 g, 0.65 mmol) in CH_2Cl_2 (20 mL) was stirred at 0 ^{o}C for 5 min, then triphosgene (0.08 g, 0.65 mmol) was added with stirring in 5 min; b) for Merrifield-oxi-alkyl-alcohol resins, triphenylphosphine (0.34 g, 1.19 mmol) in CH_2Cl_2 (20 mL) was stirred at 0^{o}C for 5 min, then

triphosgene (0.15 g, 1.19 mmol) was added with stirring in 5 min. The solvent was removed in vacuum to obtain a white solid, which was then dissolved in CH_2Cl_2 (10 mL). The chlorination reagent solution was transferred to the various flasks containing the resins and stirred for 1 h at room temperature. The reaction mixtures were filtered through a fritted porcelain funnel and washed with CH_2Cl_2 (3 × 50 mL), then dried under high vacuum for 18 h. The following conversion degrees were obtained by the Volhard method: Wang-chlorinated (**3a**), 82.6 %; Merrifield-1-oxi-4-chlorobutane **(3c),** 39.7%; Merrifield-1-oxi-10-chlorodecane (**3d**), 46.8%; Merrifield-1-oxi-12-chlorododecane (**3e**)**,** 57.8%. IR (KBr): 3025, 2912-2913, 1593, 1490-1440, 1225, 750 cm^{-1}.

***N*-(*R*)-(+)-1-(1-Naphthyl)ethane-2-aminobenzamide (4).** To a stirring solution of (*R*)-(+)-1-(1-naphthyl)ethylamine (0.50 g, 2.92 mmol) in dry DMF (10 mL) at 55 ^oC, isatoic anhydride (0.57g, 3.49 mmol) was added portion-wise over a period of 20 min. During this addition, evolution of carbon dioxide was observed. After complete addition, the mixture was stirred for an additional two hours at 55-60 ^oC. The reaction was quenched with warm water. The solid was dried at room temperature to give a white residue (0.55 g, 86% yield), which was recrystallized from ethanol to give (**4**). Mp. 168-170 ^oC, IR (KBr): 3309(NH), 2982, 1626(NHCO), 1581, 1208, and 1021, cm^{-1}. ^1H RMN (200 MHz, $CDCl_3$); δ 8.08 (dd, 1H, *J* = 1.9, 7.3 Hz, Ar-Ha), 7.73 (m, 2H, Naphthyl-H), 7.42 (m, 4H, Naphthyl-H), 7.24 (dd, 1H, *J* =1.4, 7.9 Hz, Naphthyl-H), 7.06 (dd, 1H, *J* =1.3, 8.4 Hz, Ar-Hc), 6.85 (d, 1H, J = 8.5 Hz, NHCO), 6.57(dd, 1H, *J* =1.1, 8.2 Hz, Ar-Hd), 6.47 (dd, 1H, *J* = 1.1, 8.1 Hz, Ar-Hb), 5.95 (q, 1H, *J* = 7.4 Hz, Naphthyl-CH), 5.54 (bs, 2H, NH_2), 1.51 (d, 3H, *J* = 6.3 Hz, CH_3). IEMS (*m*/*z*): M^+ 290 (20), 170 (100), 275 (2), 155 (70), 120 (50). Fluorescence Intensity = 568, Em_{max}: 405 nm (Exc.: 360 nm).

Resin *o*-aminonaphthylbenzamide (5a-e). A 20, (5 mL) vessel reactor was used for the following methods.

Coupling method A. 0.20 g of each of the following resins: Wang-chlorinated (**3a**), Merrifield (**3b**), Merrifield-1-oxi-4-chlorobutano (**3c**), Merrifield-1-oxi-10-chlorodecane (**3d**) and Merrifield-1-oxy-12-chlorododecane (**3e**) were placed in vessels 1-5 in DMF (5 mL) and stirred for 30 min. Then, OAB **(4)** (0.07g, 0.24 mmol) and K_2CO_3 (0.50 g, 3.62 mmol), was added to each vessel and the mixtures were heated at 80º C for 12 h. The resins were filtered with the aid of argon pressure and washed with the following solvents: H_2O (3 × 5 mL); DMF (3 × 5 mL); CH_3OH (3 × 5 mL) y CH_2Cl_2 (3 × 5 mL), then dried under high vacuum for 18 h. Yields: **5a** (83 %), **5b** (93 %), **5c** (46 %), **5d** (52 %), **5e** (23 %).

Coupling method B. In reactors 6-10 the same resins were treated in a similar manner with K_2CO_3 (0.25 g, 1.81 mmol) and KI (0.25 g, 1.51 mmol). Yields: **5a** (88 %), **5b** (100 %), **5c** (75 %), **5d** (72 %), **5e** (32 %),

Coupling method C. In reactors 11-15, the same resins were treated in a similar manner with N-methyl-2-pirrolidone (5 mL), tetramethyl guanidine (TMG, 3 equiv). Yields: **5a** (92 %), **5b** (53 %), **5c** (33 %), **5d** (75 %), **5e** (34 %),

Coupling method D. In reactors 16-20, the same resins were treated in a similar manner with N-methyl-2-pirrolidone (5 mL), (TMG, 6 equiv). Yields: **5a** (88 %), **5b** (50 %), **5c** (42 %), **5d** (45 %), **5e** (47 %),
IR (KBr): 3500-3300, 3025, 2923-2912, 1672-1651, 1600-1594, 1492, 1446, 1149-1146, 1215-1179 cm^{-1}. Fluorescence for resins *o*-aminonaphthylbenzamide: **5a**, FI = 750, Em_{max}: 425 nm (Exc.: 377 nm), **5b**, FI = 722, Em_{max}: 427 nm (Exc.: 375 nm). **5c**, FI = 580, Em_{max}: 424 nm (Exc.: 375 nm), **5d**, FI = 470, Em_{max}: 430 nm (Exc.: 377 nm), **5e**, FI = 363, Em_{max}: 429 nm (Exc.: 377 nm).

Resins *o*-amidonaphthylbenzamide (6a-e). 0.20 g of each of the following resins, Wang-*o*-aminonaphthylbenzamide (**5a**), Merrifield-*o*-aminonaphthylbenzamide (**5b**), Merrifield-1-oxi-butil-*o*-aminonaphthylbenzamide (**5c**), Merrifield-1-oxi-decil-*o*-aminonaphthylbenzamide (**5d**) and Merrifield-1-oxi-dodecil-*o*-aminonaphthylbenzamide (**5e**), were swollen in CH_2Cl_2 (1 mL), then added TEA (0.129 g, 1.27 mmol) and DAMP (0.005 g, 0.04 mmol). Bromoacetyl bromide (0.257 g, 1.27 mmol) was added drop wise and the solution was stirred for 12 h at room temperature. The resins were washed through an integrated filter with the aid of argon pressure, with the following solvents: CH_3OH/H_2O (1:1; 1 × 5 mL), $NaHCO_3$ saturated solution (1 × 5 mL), H_2O (2 × 5 mL), CH_3OH (3 × 3 mL), CH_2Cl_2 (3 x 3 mL). The resins were then dried under high vacuum for 18 h. Yields: **6a** (100 %), **6b** (53 %), **6c** (30 %), **6d** (51 %), **6e** (14 %). IR (KBr): 3025-3018, 2919-2903, 1748-1729, 1702-1651, 1600-1594, 1490-1440, 1160-1066, 1025 cm^{-1}. Fluorescence for resins *o*-amidonaphthylbenzamide: **6a**, FI = 13, Em_{max}: 380 nm (Exc.: 330 nm). **6b**, FI = 12, Em_{max}: 439 nm (Exc.: 365 nm). **6c**, FI = 10, Em_{max}: 427 nm (Exc.: 375 nm). **6d**, FI = 10, Em_{max}: 430 nm (Exc.: 377 nm). **6e**, FI = 10, Em_{max}: 429 nm (Exc.: 377 nm).

Resin-4-*N*-Naphthylethyl-1,4-benzodiazepine-2,5-dione (7a-e). Chemistry in parallel for the ring formation was performed using four different methods.

Ring formation method A. The reactions in this stage were performed in the same order of resins as in previous stages. In vessels 1-5, 0.20 g of each of the following resins, Wang-*o*-amidonaphthylbenzamide (**6a**), Merrifield-*o*-amidonaphthylbenzamide (**6b**), Merrifield-1-oxi-butyl-*o*-amidonaphthylbenzamide (**6c**), Merrifield-1-oxy-decyl-*o*-amidonaphthylbenzamide (**6d**) and Merrifield-1-oxy-dodecil-*o*-amidonaphthylbenzamide (**6e**), were swollen with DMF (5 mL) for 30 min with constant stirring. The resins were then treated with K_2CO_3 (0.090 g, 0.65 mmol) at 80º C for 12 h. The resins were washed through an integrated filter with the aid of argon pressure, with the following solvents: H_2O (3 × 5 mL); DMF (3 x 5 mL) and CH_2Cl_2 (3 × 5 mL), the dried under high vacuum for 18 h. Yields: **7a** (43 %), **7b** (39 %), **7c** (58 %), **7d** (48 %), **7e** (67 %).

Ring formation method B. In vessels 6-10 the same resins were treated in a similar manner, using Cs_2CO_3 (0.212 g, 0.65 mmol) as a base. Yields: **7a** (50 %), **7b** (90 %), **7c** (87 %), **7d** (77 %), **7e** (84 %),

Ring formation method C. In vessels 11-15 the same resins were treated in a similar manner, using tetramethyl guanidine (TMG, 3 equiv.) en N-methyl-2-pirrolidone (5 mL) as the base, at 60º C for 12 h. Yields: **7a** (66 %), **7b** (52 %), **7c** (75 %), **7d** (84 %), **7e** (80 %),

Ring formation method D. In vessels 16-20 the same resins were treated in a similar manner, using CH_3ONa (1 mL, 0.1 M) as the base, in CH_3OH (5 mL) at 60º C for 12 h. Yields: **7a** (77 %), **7b** (85 %), **7c** (100 %), **7d** (100 %), **7e** (90 %),

IR (KBr): 3025-3024, 2923-2912, 1675-1666, 1652-1635, 1601-1594, 1492-1489, 1450-1442, 1174-1117, 1020 cm^{-1}. Fluorescence for resins *o*-amidonaphthylbenzamide: **7a**, FI = 672, Em_{max}: 663 nm (Exc.: 560 nm). **7b**, FI = 662, Em_{max}: 662 nm (Exc.: 560 nm). **7c**, FI = 500, Em_{max}: 660 nm (Exc.: 578 nm). **7d**, FI = 394, Em_{max}: 657 nm (Exc.: 575 nm). **7e**, FI = 281, Em_{max}: 648 nm (Exc.: 573 nm).

***R*-(+)-4-*N*-Naphthylethyl-1,4-benzodiazepine-2,5-dione (1).** In order to release the resin, in separate 10 mL round bottom flasks, 0.20 g of each of the following resins, Wang-4N-naphthylethyl-1,4-benzodiazepine-2,5-dione (**7a**), Merrifield-4N-naphthylethyl-1,4-benzodiazepine-2,5-dione (**7b**), Merrifield-1-oxy-butyl-4N-naphthylethyl-1,4-benzodiazepine-2,5-dione (**7c**), Merrifield-1-oxy-decyl-4N-naphthylethyl-1,4-benzodiazepine-2,5-dione (**7d**) and Merrifield-1-oxy-dodecyl-4N-naphthylethyl-1,4-benzodiazepine-2,5-dione (**7e**) were stirred in TFA/THF (1:1) (5 mL) for 30 min. After this, each reaction mixture was filtered through a fritted Buchner funnel. The solvent was distilled out to obtain **1** as a white solid. Mp. 168-170 ºC, IR (KBr): 3330, 3320, 2918, 1642, 1628, 1585 cm^{-1}. ^1H RMN ($CDCl_3$): δ 8.22 (s, 1H, NHCO), 8.16-6.82 (m, 10H, Ar-H, Naph-H), 6.78 (q, 1H, *J* = 6.77 Hz, N-C<u>H</u>-CH_3), 3.57 (d, *J* = 15.1, Hz $COCH_aN$), 3.49 (d, *J* = 15.1 Hz, $COCH_bN$), 1.80 (d, *J* = 6.77 Hz, CH_3). ^{13}C RMN ($CDCl_3$): δ 171.1, 166.5, 135.8, 134.6, 133.8, 132.4, 131.8, 131.7, 129.3, 128.8, 126.9, 126.0, 125.5, 125.1, 125.0, 123.6, 120.5, 50.0, 45.2, 16.9. IEMS (*m*/*z*): M^+ 330 (3), 290 (100 %). Liberation yields from: **7a** (100 %), **7b** (95 %), **7c** (93 %), **7d** (90 %), **7e** (92 %).

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