Multicomponent Synthesis of Pentyl-Sulfonyl Amidines via Diazoalkane

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Abstract: A series of pentyl-sulfonyl amidines was obtained using a multicomponent synthesis process. The rearrangement of unstable tosylazide–cyclopentanonenamine cycloadducts yielded a diazoalkane intermediate. This primary, unstable reaction product showed good reactivity with certain acid compounds in order to form the corresponding derivatives.

Key words: sulfonyl amidines, multicomponent reaction, diazoalkane, amino acids, antiresorptive agent

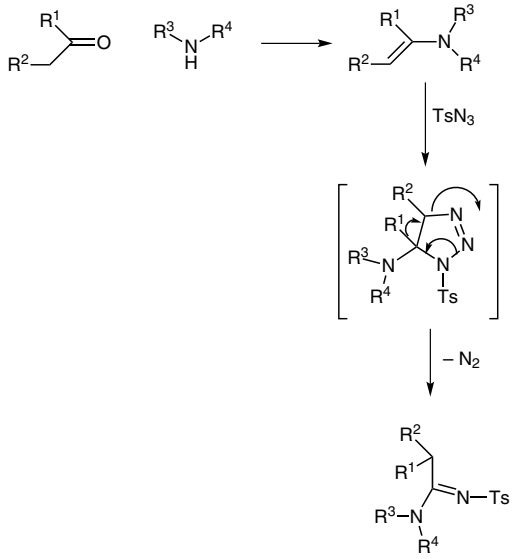
Amidines are versatile starting materials used in several synthetic contexts, mainly in the preparation of heterocyclic compounds.[1] In addition, amidines are prominent structural motifs found in numerous bioactive natural products,[2] which serve as important pharmacophores, synthetic intermediates, and efficient coordinating ligands.[3] In this study we proposed a simple, rapid, and inexpensive process for the synthesis of tosylamidines linked to a reactive moiety through a four-methylene alkyl chain. Similar structures have shown potent antiresorptive activities in vitro, and structure–activity relationship studies were also recently performed.[4]

Several years ago, our group reported a simple and versatile multicomponent reaction which offered a straightforward method for the creation of amidines via heterocyclic transformation.[5] The multicomponent reaction protocol used in the current study follows this general procedure.

At room temperature, a primary or secondary amine was added to a solution containing a carbonyl compound (aldehyde or ketone) in an inert solvent in the presence of a moderate amount of molecular sieves. After 15–30 minutes, an equivalent amount of azide was added, and the reaction was followed using TLC analysis. The use of tosylazide resulted in the isolation of products corresponding to tosylamidines (Scheme 1).

The proposed mechanism involves the azide cycloaddition of enamine, resulting in the formation of 4,5-dihydrotriazole, which, by nitrogen loss and transposition of the substituent from the 5- to 4-position, provides the desired amidines. Different behaviours were observed in some cases, and it is thought that the nature of the starting carbonyl reactant governs the outcome of the reaction.[5,6]

The use of cyclopentanone under these reaction conditions was previously considered, but a complex mixture of



Scheme 1

products was obtained, which was shown to be of no synthetic use. Surprisingly, when we performed the multicomponent reaction starting from cyclopentanone, tosylazide, and proline methyl ester hydrochloride in the presence of triethylamine we separated a single main product in good yields. Analytical data of the obtained compound indicated that tosyl and proline residues were intact. Moreover, ^{13}C NMR showed the presence of an amidine carbon (δ_C = 165.6 ppm) close to a quaternary carbon ester (δ_C = 171.0 ppm). A TOCSY experiment showed the presence of a four-methylene carbon open chain, which was connected to the amidine moiety (δ_H = 2.89 and 3.03 ppm; δ_C = 30.7 ppm) on one side, while the terminal methylene on the other side was connected to a heteroatom (δ_H = 3.62 ppm; δ_C = 43.6 ppm). The exact mass of 400.1220 correlated with the chemical formula $C_{18}H_{25}ClN_2O_4S$, which allowed us to assign product **1** to the formula depicted in Figure 1.

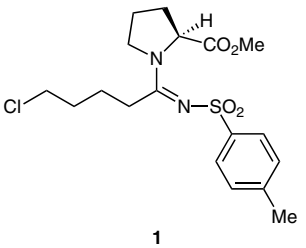


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Figure 1

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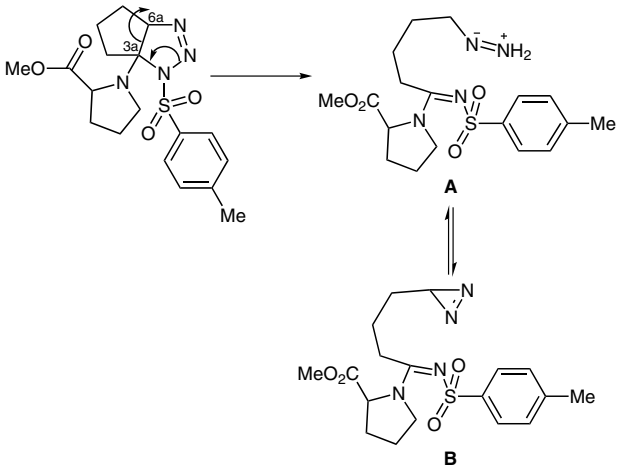
The assigned structure was compared with similar products that have been recently reported,[7] and the analytical data were found to be in agreement with the suggested hypothesis. It can therefore be assumed that the formation of product **1** derives from the initial breaking of the N_2–N_3 bond in the unstable dihydrotriazole, followed by amidine bond formation and the contemporary breaking of the C_{3a}–C_{6a} bond (Scheme 2).



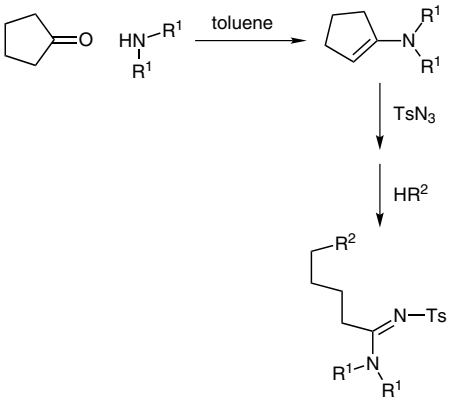
Scheme 2

The resultant diazoalkane **A**, which is stabilised by the diazirine form **B**,[8] reacts with HCl derived from triethylamine hydrochloride. This is, in turn, formed in the reaction between proline methyl ester hydrochloride and triethylamine. With the aim to remove the HCl source, we first performed the reaction by using equal volumes of proline methyl ester hydrochloride and sodium methoxide in a toluene solution. The solution of proline methyl ester was used in the routine synthetic protocol. When the TLC control showed a loss of tosylazide, we added a reactive acid, which was able to react with the diazoalkane, into the same reaction mixture. In the reaction scheme, the addition of benzoic acid resulted in the formation of ester **2a** (Table 1, entry 2)in good yields.

The one-pot method here described was then applied to other acid reagents, such as acetic acid, 4-toluensolfonic acid, *N*-Boc-alanine, and 4-nitrofenol, and the corresponding products **2b**–**e** (Table 1, entries 3–6) were obtained in good yields.[9] With the aim to further generalise this synthetic protocol, proline was replaced with morpholine, which is a plain secondary amine, and when the tosylazide cycloaddition reaction was complete, benzoic acid was added. As expected the obtained derivative **2f** (Table 1, entry 7) contained morpholine in the amidine portion.

This preliminary results show that this method can be applied to a large number of reagents. Furthermore, the products obtained in this preliminary survey are liable to further transformations, for example: the tosylate **2c** can undergo substitution reactions with nucleophiles. A particularly interesting result is described in entry 5 (Table 1). This prove that amino acids, opportunely protected, are able to react with the diazolcane intermediate **A**. As a consequence the pentylamidine moiety could be inserted into depsipeptide chains.[10]

Table 1 Synthesis of Compounds **2**



Entry		R^1NR^1	R^2	Yield (%)[a]
1	**1a**	proline	Cl	70
2	**2a**	proline	$PhCO_2$	65
3	**2b**	proline	$MeCO_2$	72
4	**2c**	proline	$MeC_6H_4SO_3$	62
5	**2d**	proline	$BocNHCHMeCO_2$	65
6	**2e**	proline	$O_2NC_6H_4O$	35
7	**2f**	morpholine	$PhCO_2$	68

[a] Related to chromatographically pure products, structures determined by ^1H and ^{13}C NMR spectroscopy.

In conclusion, readily available starting materials have been used in one-pot reactions to obtain a series of new 5-substituted pentylamidines, using a rapid and inexpensive method. This synthetic protocol is really versatile, as it was demonstrated that it could be extended to several reagents, and the derivatives obtained can undergo many other transformations.

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(9) **General Procedure for the Preparation of Amidine 2a–e**
The proline methyl ester hydrochloride (1 g, 0.006 mol) was suspended in toluene (20 mL), and an equivalent amount of NaOMe (6 mL of 1 M solution) was added. After 30 min the solvent was concentrated to 10 mL under vacuum, and 5 g of molecular sieves were added. To the stirred mixture were added at first cyclopentanone (0.5 g, 0.006 mol) and after 15 min tosylazide (0.92 g, 0.006 mol). The reaction was monitored with TLC (EtOAc–hexane = 1:1), and after 15 min the tosylazide was completely disappeared. The suitable reactant was added (0.012 mol), and the stirring was continued for 1 h. Then the mixture was filtered, and toluene was removed under vacuum. The crude was dissolved in CH_2Cl_2, washed with H_2O (10 mL), dried with Na_2SO_4, filtered, and the filtrate concentrated in vacuo. The crude was purified by silica gel chromatography (EtOAc–hexane = 1:1) affording the pure amidines **1a**,**b** and **2a**–**e**

Methyl 1-[5-Chloro-1(tosylimino)pentyl]pyrrolidine-2-carboxylate (1)
Colorless oil (1.68 g, 70%); $[\alpha]_D$ –79.8 (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.92–2.08 (m, 6 H, 3 CH_2), 2.09–2.19 and 2.20–2.28 (2 m, 2 H, CH_2), 2.40 (s, 3 H, CH_3Ph), 2.85–2.92 and 2.99–3.08 (2 m, 2 H, CH_2), 3.49 (s, 3 H, OCH_3), 3.58–3.64 (m, 2 H, CH_2Cl), 3.61–3.68 and 3.73–3.80 (2 m, 2 H, CH_2N), 4.49–4.54 (m, 1 H, CH), 7.25(d, *J* = 8.20 Hz, 2 H, ArH), 7.77 (d, *J* = 8.20 Hz, 2 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH_3), 23.6 (CH_2), 24.8 (CH_2), 29.3 (CH_2), 31.6 (CH_2), 32.3 (CH_2), 44.5 (CH_2), 48.1 (CH_2), 52.2 (CH_3), 61.1 (CH), 126.3 (CH), 129.3 (CH), 141.3 (C), 142.1 (C), 166.6 (C), 172.0 (C). ESI-HRMS: *m/z* calcd for $C_{18}H_{25}ClN_2O_4S$: 400.1223; found: 400.1220.

Methyl 1-[5-(Benzoyloxy)-1-(tosylimino)pentyl]-pyrrolidine-2-carboxylate (2a)
Colorless oil (1.8g, 65%); $[\alpha]_D$ –67.8 (*c* 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.82–2.25 (m, 6 H, 3 CH_2), 2.37 (s, 3 H, CH_3Ph), 2.87–3.13 (m, 2 H, CH_2), 3.45 (s, 3 H, OCH_3), 3.50–3.75 (m, 3 H, CH_2), 4.34–4.401 (m, 2 H, OCH_2), 4.42–4.51 (m, 1 H, CH), 7.20 (d, *J* = 8.20 Hz, 2 H, ArH), 7.30–7.60 (m, 3 H, ArH), 7.73–7.85 (m, 2 H, ArH), 8.00 (d, *J* =8.20 Hz, 2 H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.6 (CH_3), 23.2 (CH_2), 24.8 (CH_2), 28.9 (CH_2), 29.3 (CH_2), 32.1 (CH_2), 48.1 (CH_2), 52.2 (CH_3), 61.1 (CH), 64.4 (CH_2), 126.4 (CH), 128.6 (CH), 129.1 (CH), 129.8 (CH), 130.5 (C), 133.1 (CH), 141.4 (C), 142.0 (C), 166.7 (C), 172.0 (C). ESI-HRMS: *m/z* calcd for $C_{25}H_{30}N_2O_6S$: 486.1824; found: 486.1822.

1-[5-Acetyloxy-1-(tosylimino)pentyl]pyrrolidine-2-carboxylate (2b)
Colorless oil (1.8g, 72%); $[\alpha]_D$ –80.9 (*c* 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.78–2.24 (m, 8 H, 4 CH_2), 2.05 (s, 3 H, CH_3CO), 2.38 (s, 3 H, CH_3), 2.89–3.18 (m, 2 H, CH_2), 3.46 (s, 3 H, CH_3O), 3.53–3.76 (m, 2 H, CH_2), 4.07–5.18 (m, 2 H, CH_3O), 4.46–4.52 (m, 1 H, CH), 7.22 (d, *J* =8.20 Hz, 2 H, ArH), 7.74 (d, *J* = 8.20 Hz, 2 H, ArH). ^{13}C NMR (50MHz, $CDCl_3$): δ = 21.2 (CH_3), 21.6 (CH_3), 23.2 (CH_2), 24.8 (CH_2), 28.8 (CH_2), 29.3 (CH_2), 32.1 (CH_2), 48.1 (CH_2), 52.3 (CH_3), 61.1 (CH), 63.9 (CH_2), 126.4 (CH), 129.1 (CH), 141.3 (C), 142.1 (C), 166.7 (C), 172.0 (C). ESI-HRMS: *m/z* calcd for $C_{20}H_{28}N_2O_6S$: 424.1668; found: 424.1666.

Methyl 1-[1-(Tosylimino)-5-(tosyloxy)pentyl]-pyrrolidine-2-carboxylate (2c)
This reaction was performed in cyclohexane. Colorless oil (1.9 g, 62%); [α] –78.2 (*c* 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.70–2.26 (m, 8 H, 4 CH_2), 2.37 and 2.44 (2 s, 6 H, 2 CH_3Ph), 2.91–2.99 (m, 2 H, CH_2), 3.45 (s, 3 H, CH_3O), 3.46–3.74 (m, 2 H, CH_2), 4.02–4.08 (m, 2 H, CH_2O), 4.43–4.49 (m, 1 H, CH), 7.21 (d, *J* = 8.16 Hz, 2 H, ArH), 7.35 (d, *J* = 8.10 Hz, 2 H, ArH), 7.71 (d, *J* = 8.16 Hz, 2 H, ArH), 7.78 (d, *J* = 8.10 Hz, 2 H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.6 (CH_3), 21.8 (CH_3), 22.5 (CH_2), 24.8 (CH_2), 28.9 (CH_2), 29.3 (CH_2), 31.7 (CH_2), 48.2 (CH_2), 52.2 (CH_3), 61.1 (CH), 70.0 (CH_2), 126.3 (CH), 128.1 (CH), 129.3 (CH), 130.2 (CH), 133.1 (C), 141.3 (C), 142.1 (C), 145.1 (C), 166.4 (C), 171.9 (C). ESI-HRMS: *m/z* calcd for $C_{25}H_{37}N_2O_7S_2$: 536.1650; found: 536.1651.

Methyl 1-{5-[(2-{[(*tert*-Butoxy)carbonyl]amino}-propanoyl)oxy]-1-(tosylimino)pentyl}pyrrolidine-2-carboxylate (2d)
Colorless oil (2.1, 65%); $[\alpha]_D$ –2.29 (*c* 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.39–144 (m, 12 H, 4 CH_3), 1.85–2.29 (m, 8 H, 4 CH_2), 2.37 (s, 3 H, CH_3Ph), 2.82–3.21 (m, 2 H, CH_2), 3.45 (s, 3 H, CH_3O), 3.46–3.75 (m, 2 H, CH_2), 4.05–4.25 (m, 3 H, CH and CH_2), 4.43–4.49 (m, 1 H, CH), 5.08–5.15 (m, 1 H, NH), 7.22 (d, *J* = 8.18 Hz, 2 H, ArH), 8.73 (d, *J* = 8.18 Hz, 2 H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.8 (CH_3), 21.6 (CH_3), 23.0 (CH_2), 24.8 (CH_2), 28.5 (CH_3), 29.3 (CH_2), 32.0 (CH_2), 48.1 (CH_2), 49.5 (CH_3), 52.2 (CH_3), 61.1 (CH), 64.6 (CH_2), 79.9 (C), 126.4 (CH), 129.1 (CH), 141.3 (C), 142.1 (C), 155.4 (C), 166.6 (C), 172.0 (C), 173.6 (C). ESI-HRMS: *m/z* calcd for $C_{26}H_{39}N_3O_8S$: 553.2457; found: 553.2458.

Methyl 1-[5(4-Nitrophenyloxy)-1-(tosylimino)pentyl]-pyrrolidine-2-carboxylate (2e)
Colorless oil (1.0g, 35%); $[\alpha]_D$ –99.5 (*c* 1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.82–2.23 (m, 8 H, 4 CH_2), 2.37 (s, 3 H, CH_3Ph), 2.87–3.12 (m, 2 H, CH_2), 3.45 (s, 3 H, CH_3), 3.54–3.73 (m, 2 H, CH_2), 4.05–4.21 (m, 2 H, CH_2), 4.45–4.51 (m, 1 H, CH), 6.94 (d, *J* = 8.16 Hz, 2 H, ArH), 7.20 (d, *J* = 8.06 Hz, 2 H, ArH), 7.73 (d, *J* = 8.06 Hz, 2 H, ArH), 8.19 (d, *J* = 8.16 Hz, 2 H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.6 (CH_3), 23.2 (CH_2), 24.8 (CH_2), 29.0 (CH_2), 29.3 (CH_2), 32.1 (CH_2), 48.1 (CH_2), 52.2 (CH_3), 61.1 (CH), 68.3 (CH_2), 114.7 (CH_2), 126.1 (CH), 126.35 (CH), 129.2 (CH), 129.3 (CH), 141.3 (C), 141.7 (C), 142.1 (C), 164.2 (C), 166.5 (C), 172.0 (C). ESI-HRMS: *m/z* calcd for $C_{24}H_{29}N_3O_7S$: 503.1726; found: 503.1724.

5-Morpholino-5-(tosylimino)pentyl Benzoate (2f)
Morpholine (0.2 g, 0.0023 mol) and cyclopentanone (0.19 g, 0.0023 mol) were dissolved in CH_2Cl_2 (10 mL), and 2 g of molecular sieves were added. The mixture was stirred for 30 min, and tosylazide (0.35 g, 0.0023 mol) was added. After 15 min benzoic acid (0.56 g, 0.0046 mol) was added, and the stirring was continued for 1 h. Then the mixture was filtered, washed with H_2O (10 mL), dried with Na_2SO_4, filtered, and the filtrate was concentrated in vacuo. The crude was purified by silica gel chromatography (EtOAc–hexane = 1:1) affording the pure **2f**. Colorless oil (0.68g, 68%). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.64–2.01 (4 H, m, 2 CH_2), 2.38 (3 H, s, CH_3Ph), 2.97–3.10 (2 H, m, CH_2), 3.42–3.78 (8 H, m, 4 CH_2-morpholine), 4.25–4.39 (2 H, m, CH_2O), 7.23 (2 H, d, *J* = 8.20 Hz, ArH), 7.42–7.61 (3 H, m, ArH), 7.90 (2 H, d, *J* = 8.15 Hz, ArH), 8.02 (2 H, d, *J* = 8.20 Hz, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.6 (CH_3), 23.8 (CH_2), 28.9 (CH_2), 30.3 (CH_2), 45.0 (CH_2), 46.8 (CH_2), 64.1 (CH_2), 66.5 (CH_2), 66.7 (CH_2), 126.4 (CH), 128.7 (CH), 129.4 (CH), 129.7 (CH), 130.4 (C), 133.3 (CH), 141.4 (C), 142.3 (C), 166.7 (C), 167.4 (C). ESI-HRMS: *m/z* calcd for $C_{23}H_{28}N_2O_5S$: 444.1718; found: 444.1719.

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