Elaboration of Peptidomimetics Derived from a PADAM Approach: Synthesis of Polyfunctionalised 2(1*H*)-Pyrazinones via an Unexpected Aromatisation

Andrea Basso,* Luca Banfi, Giuseppe Guanti, Renata Riva, Paolo Tosatti[1]

Dipartimento di Chimica e Chimica Industriale, Università di Genova, via Dodecaneso 31, 16146 Genova, Italy
Fax +39(010)3536118; E-mail: andrea.basso@unige.it

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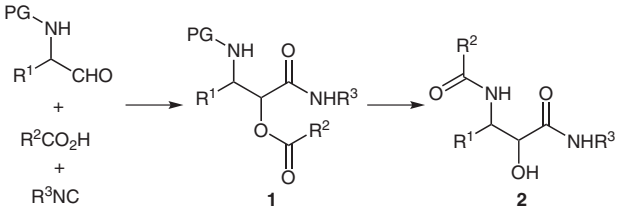
Abstract: When the PADAM (Passerini reaction–amine deprotection–acyl migration) strategy is applied to *N*-Boc amino acids, the resulting β-acylamino-α-hydroxyamides can be elaborated by secondary-alcohol oxidation, Boc deprotection, and intramolecular cyclisation. When TFA is employed to cleave the Boc group a spontaneous aromatisation to 2(1*H*)-pyrazinones is observed.

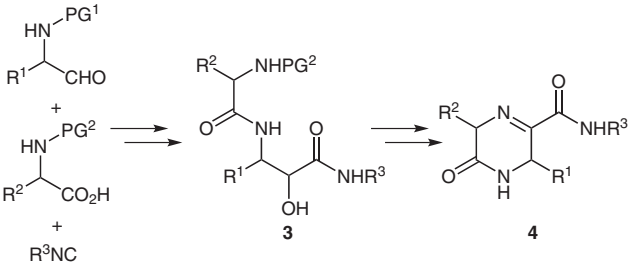
Key words: Passerini multicomponent reaction, isocyanides, heterocycles, ring closure, protecting groups, aromatisation

Multicomponent reactions (MCR) are a valuable tool for the expeditious synthesis of complex molecules with multiple points of diversity.[2] Among the plethora of methodologies developed over the years, the MCR based on the use of isocyanides[3] has played an important role in either target- and diversity-oriented synthesis. Of particular interest is the use of polyfunctionalised components that allow elaboration of postcondensation intermediates and rapid generation of skeletally and stereochemically diverse heterocyclic scaffolds.[4] One intriguing example of such general strategy has been developed in our group exploiting the following series of transformations: 1) Passerini reaction using an N-protected α-amino aldehyde, a carboxylic acid, and an isocyanide, 2) amine deprotection of intermediate **1**, and 3) intramolecular acyl migration to final α-acylamino amide **2** (Scheme 1).[5] This reaction sequence, often referred to as PADAM strategy, has been used by us[6] and others[7] for the preparation of peptidomimetics and has also been recently slightly modified to assemble a combinatorial library of oxazolines.[8]



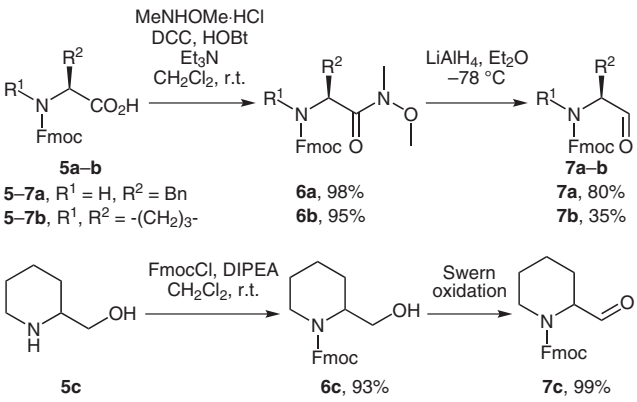
Scheme 1 The PADAM strategy featuring a Passerini reaction with an N-protected amino aldehyde followed by amine deprotection and in situ acyl migration

Hoping to further expand the scope of the strategy outlined in Scheme 1, we envisaged that the use of readily available N-protected α-amino acids as the carboxylic component of the Passerini reaction could give access to interesting intermediates **3** to be used for the preparation of heterocyclic scaffolds **4** as depicted in Scheme 2.[9]



Scheme 2 Proposed use of N-protected amino acids for the PADAM strategy

We started our investigations preparing *N*-Fmoc-protected amino aldehydes **7a–c** from commercially available amino acids or amino alcohols as reported in Scheme 3.[10] Aldehydes **7** were then reacted with a variety of isocyanides and N-protected α-amino acids and subsequently treated with diethylamine to cleave the Fmoc group and allow the intramolecular acyl migration. We wanted the protecting group on the amine coming from the carboxylic component (PG^2 in Scheme 2) to be orthogonal to the Fmoc, thus we chose to exploit readily available *N*-Boc- and *N*-Cbz-protected L-amino acids (Table 1).



Scheme 3 Synthesis of *N*-Fmoc-protected amino aldehydes

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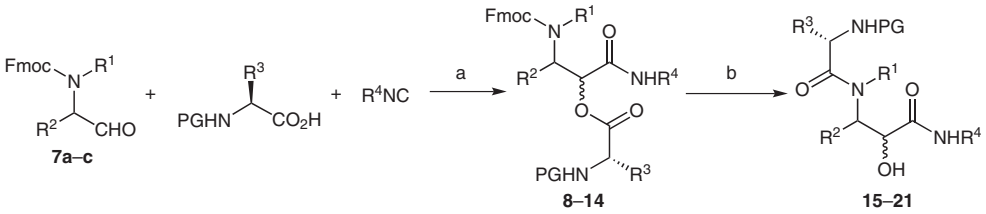
Table 1 Use of *N*-Fmoc-Protected Amino Aldehydes and N-Protected Amino Acids for the Proposed PADAM Strategy[a]



Entry	**7**	PG	R^3	R^4	Yield of **8–14** (%)	Yield of **15–21** (%)
1	(*S*)-**7a**	Cbz	*i*-Pr	*n*-Bu	**8** 95	**15** 65
2	(*S*)-**7a**	Cbz	Bn	*n*-Bu	**9** 93	**16** 68
3	(*S*)-**7a**	Boc	*i*-Pr	*n*-Bu	**10** 92	**17** 81
4	(*S*)-**7a**	Boc	Me	*n*-Bu	**11** 79	**18** 92
5	(*S*)-**7a**	Boc	Me	*t*-Bu	**12** 75	**19** 80
6	(*S*)-**7b**	Boc	Me	*n*-Bu	**13** 99	**20** 92
7	(±)-**7c**	Boc	*i*-Pr	*t*-Bu	**14** 96	**21** 88

[a] Reaction conditions: a) *N*-Fmoc-amino aldehyde (1.0 equiv), acid (1.1 equiv), and isocyanide (1.1 equiv) in CH_2Cl_2 for 18 h at r.t.; b) **8–14** in a CH_2Cl_2–Et_2NH (4:1) mixture for 18 h at r.t.

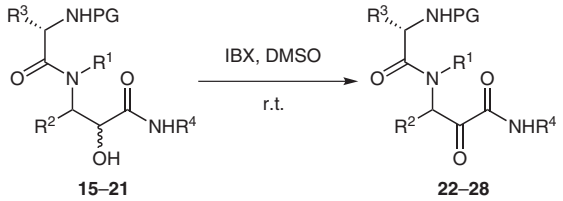
The multicomponent reaction proceeded smoothly giving the desired products in good to excellent yield. No substantial difference in reactivity was displayed between *N*-Boc- and *N*-Cbz-protected amino acids in the Passerini reaction (entries 1 and 3, Table 1) but lower yields were observed using Cbz as protecting group in the second step of the PADAM sequence for the generation of products **15** and **16**. Gratifyingly, *N*-Boc-protected amino acids gave good results affording the desired products **17–21** in high yield. As expected, the intrinsically low stereoselectivity of the Passerini reaction[11] resulted in products **15–21**, to be isolated as mixtures of diastereoisomers in a ratio ranging from 7:3 to 1:1.

To exemplify the utility of compounds **15–21** as interesting intermediates for the synthesis of heterocyclic scaffolds as outlined in Scheme 2, we decided to oxidise the free secondary alcohol present on these compounds and use the resulting α-keto amide for the formation of dihydropyrazinones of general formula **4**. Oxidation with IBX in DMSO proceeded smoothly affording the desired products **22–28** in good yield (Table 2). Again, substrates containing a Boc-protected amine functionality proved to be superior to their Cbz-protected equivalents. Products deriving from optically pure amino aldehydes were obtained as single diastereoisomers at this stage, confirming that no racemisation/epimerisation occurred during the two steps of the PADAM sequence. Nevertheless, it was observed that products **22–28** tend to epimerise if stored for some days at room temperature, presumably due to the acidity of the proton in the α-position to the keto amide functionality.

To complete our synthetic plan we needed to cleave the protecting group still present on products **22–28** in order to promote the intramolecular formation of dihydropyrazinones of general formula **4**. To our surprise, Cbz removal under standard hydrogenation conditions only resulted in recovered starting materials **22** and **23**, whilst more drastic conditions [hydrogenation at 4.1 bar of H_2, in the presence of Pd/C or $Pd(OH)_2$] generated complex mixtures of degradation byproducts.

We then focused on the cleavage of the Boc protecting group on compound **24**. Surprisingly, treatment with TFA in CH_2Cl_2, not only resulted in Boc deprotection and spontaneous cyclisation, but also in a spontaneous aroma-

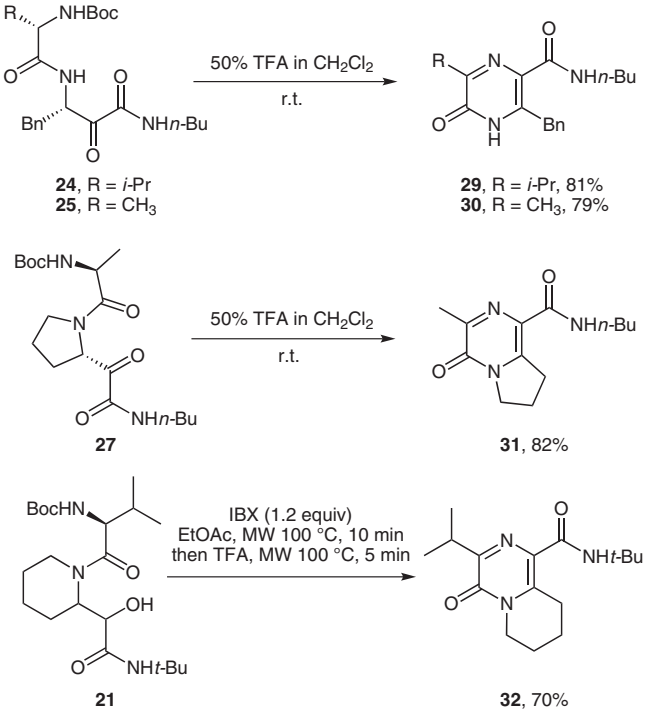
Table 2 Oxidation of α-Hydroxy Amides **17–25**[a]



Entry	**15–21**	Yield of **22–28** (%)
1	**15**	**22** 79
2	**16**	**23** 68
3	**17**	**24** 93
4	**18**	**25** 83
5	**19**	**26** 81
6	**20**	**27** 73
7	**21**	**28** 83

[a] Reaction conditions: α-hydroxy amide (1.0 equiv) and IBX (1.5 equiv) in DMSO for 3–16 h at r.t.

tisation to give the final compound **29**, which was obtained in good yield with no trace of the corresponding dihydropyrazinone (Scheme 4). In an attempt to survey the generality of this reaction, we reacted **25** and **27** under the same acidic conditions, and 2(1*H*)-pyrazinones **30** and **31** were again afforded in high yield. Intrigued by this unexpected aromatisation, we attempted to directly convert the PADAM adducts into the final 2(1*H*)-pyrazinones via a one-pot procedure. Therefore, compound **21** was subjected to a microwave-assisted oxidation employing IBX in EtOAc; the reaction proceeded smoothly in 10 minutes at 100 °C.

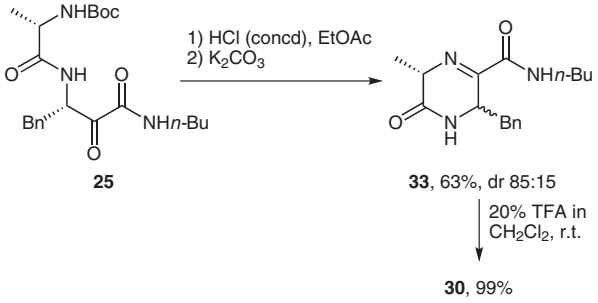


Scheme 4 Synthesis of 2(1*H*)-pyrazinones **29**–**32**

Upon oxidation, IBX side products, insoluble in EtOAc at room temperature, were filtered off; subsequent TFA addition and further heating (5 min at 100 °C) afforded pyrazinone **32** in an overall 70% yield after column chromatography (Scheme 4), paralleling the results obtained in two separate synthetic steps.

Attempts to avoid aromatisation performing the reaction in the presence of $NaBH(OAc)_3$ or under a hydrogen atmosphere in the presence of Pd catalysts were fruitless. Interestingly, the desired dihydropyrazinone was obtained by using different conditions for the cleavage of the Boc group according to a protocol reported by Najera et al.[12] In this case, when **25** was treated with concentrated HCl in place of TFA, product **33** was obtained in high yield, although as an 85:15 mixture of epimers, presumably due to the configurational instability of the position α to the keto amide functionality under the reaction conditions. To confirm that TFA caused the unexpected aromatisation, presumably via formation of transient species immediately oxidised to pyrazinone upon exposure to air, compound **33** was subjected to the same conditions described in Scheme 4, and it was readily converted into **30** (Scheme 5).

Even though we were initially more interested in the preparation of dihydropyrazinones, we were pleased to find a novel route to access highly functionalised 2(1*H*)-pyrazinones, as they are important heterocyclic constituents of natural products such as dragmacidin D, E, and F,[13] ma'edamine A and B[14] and flavacol. Moreover, they have been applied as building blocks in organic synthesis,[15] and they are important heterocyclic scaffolds that can be found in a wide variety of compounds exhibiting important biological activity.[16]



Scheme 5 Formation of dihydropyrazinone **33** using HCl

In summary we have expanded the scope of the PADAM methodology using orthogonally protected α-amino acids and demonstrated the utility of this strategy to the novel synthesis of interesting heterocycles with three points of diversity. Present studies are focussing on better understanding the effect of TFA on the aromatisation step. The combinatorial application of our novel one-pot procedure for the straightforward assembly of 2(1*H*)-pyrazinones is also being examined. It is worth noting that, being the final products achiral, also less common α-amino acids and α-amino aldehydes can be used as inputs without the need to preparing them in optically pure forms.

Representative Procedure for the Oxidation of Intermediates 15–21

Synthesis of (3*S*)-*N*-Butyl-3-{[(2*S*)-2-(*N*-Boc-amino)propionyl]amino}-4-phenyl-2-oxybutanamide (25)

Substrate **18** (51 mg, 0.12 mmol) was added to a solution of IBX (51 mg, 0.18 mmol) in DMSO (1.5 mL). The resulting mixture was vigorously stirred for 4 h and the mixture freeze-dried. The resulting white solid was purified by flash chromatography (SiO_2, PE–EtOAc = 8:2 to 1:1) to give **25** (43 mg, 83%) as a white solid (mp 144.1–145.7 °C). R_f = 0.49 (PE–EtOAc = 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.16 (3 H, m), 7.13–7.05 (2 H, m), 6.92 (1 H, t, *J* = 6 Hz), 6.73 (1 H, br d, *J* = 14 Hz), 5.54 (1 H, dt, *J* = 14, 7 Hz), 4.94 (1 H, br s), 4.13 (1 H, m), 3.40–3.29 (3 H, m), 3.14 (1 H, dd, *J* = 14, 7 Hz), 1.65–1.48 (2 H, m), 1.43 (9 H, s), 1.42–1.32 (2 H, m), 1.29 (3 H, t, *J* = 7 Hz), 0.95 (3 H, t, *J* = 7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.4, 172.2, 159.0, 154.3, 135.6, 129.4, 128.6, 127.1, 80.1, 55.6, 49.9, 39.1, 37.2, 31.2, 28.3, 20.0, 18.2, 13.6; HRMS (ES$^+$): *m/z* calcd for $C_{22}H_{33}N_3O_5Na$ [M + Na]$^+$: 442.2312; found: 442.2326.

Representative Procedure for the Synthesis of Products 29–31 Synthesis of 3-Benzyl-*N*-butyl-6-methyl-5-oxo-4,5-dihydropyrazine-2-carboxamide (30)

Substrate **25** (42 mg, 0.095 mmol) was dissolved in a TFA–CH_2Cl_2 mixture (2 mL, 1:1) and stirred at r.t. for 1 h. After this time the crude mixture was concentrated in vacuo and purified by flash chromatography (SiO_2, CH_2Cl_2–MeOH = 98:2) to give **30** (24 mg, 79%) as a white solid (mp 171.1–173.0 °C); R_f = 0.53 (CH_2Cl_2–MeOH = 9:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (1 H, t, *J* = 6 Hz), 7.40–7.20 (5 H, m), 4.66 (2 H, s), 3.50–3.38 (2 H, m), 2.41 (3 H, s), 1.66–1.52 (2 H, m), 1.49–1.35 (2 H, m), 0.96 (3 H, t, *J* = 7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.0, 157.7, 152.9, 141.5, 136.5, 129.5, 128.2, 127.2, 123.0, 39.0, 35.5, 31.8, 20.2, 19.8, 13.8. MS (EI): *m/z* (%) = 299 (63) [M$^+$], 226 (100), 198 (75), 129 (31), 91 (21), 72 (52), 42 (12). HRMS (ES$^+$): *m/z* calcd for $C_{17}H_{21}N_3O_2Na$ [M + Na]$^+$: 322.1526; found: 322.1516.

Microwave-Assisted One-Pot Synthesis of *N*-(*tert*-Butyl)-3-isopropyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrazine-1-carboxamide (32)

Substrate **21** (70 mg, 0.17 mmol) was dissolved in EtOAc (1 mL), IBX (56 mg, 0.20 mmol) was added, and the resulting suspension heated in a MW oven at 100 °C (150 W) for 10 min. After this time TLC analysis showed complete conversion, thus the crude mixture was filtered, washed with EtOAc (1 mL), and TFA (1 mL) was added to the filtrate. The resulting solution was then heated in a MW oven at 100 °C (50 W) for 5 min. Solvents were then evaporated and the crude purified by flash chromatography (SiO_2, EtOAc–PE = 6:4) to give **32** (35 mg, 70% over two steps) as a white foam; R_f = 0.37 (EtOAc–PE = 6:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97 (1 H, s), 3.99 (2 H, t, *J* = 7 Hz), 3.55 (2 H, t, *J* = 7 Hz), 3.41 (1 H, hept, *J* = 7 Hz), 1.94 (2 H, m), 1.80 (2 H, m), 1.44 (9 H, s), 1.23 (6 H, t, *J* = 7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 156.5, 156.0, 142.7, 122.3, 50.7, 42.9, 30.5, 29.0, 25.3, 21.5, 20.2, 18.1. MS (EI): *m/z* (%) = 291 (20) [M$^+$], 235 (15), 218 (100), 83 (18), 41 (6). HRMS (ES$^+$): *m/z* calcd for $C_{16}H_{25}N_3O_2Na$ [M + Na]$^+$: 314.1839; found: 314.1831.

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