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Conversion of isomeric 2:3 adducts (aminoacid–formaldehyde) to *N*-acyl-pseudoprolines derivatives

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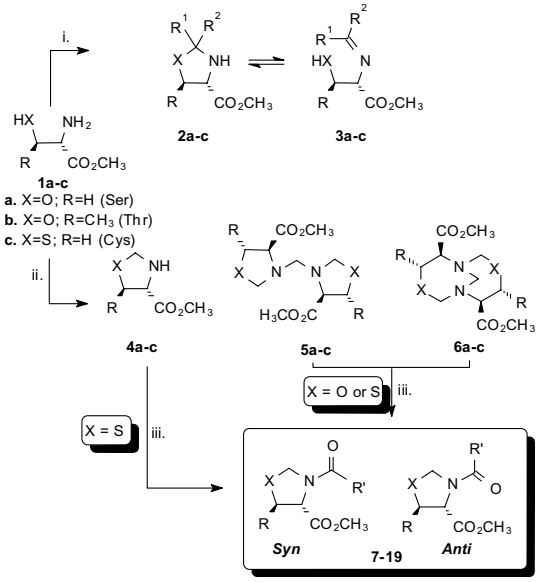
Abstract—Reaction of acyl chlorides or acid anhydrides with isomeric 2:3 adducts derived from condensation of L-serine (**1a**), L-threonine (**1b**) and L-cysteine (**1c**) methyl esters with formaldehyde afforded *N*-acyl-pseudoprolines **7**–**19** in various yields. These 2:3 adducts can be considered as synthetic equivalents of oxaproline and thiaproline moieties. The present work revealed the versatile behaviour of the two 2:3 adducts as a consequence of the ring-chain tautomerism occurring in the five- and/or seven-membered rings.

Condensation of carbonyl compounds ($R^1 \neq H$ and/or $R^2 \neq H$) with primary β-hydroxyamine moieties afforded *NH*-free oxazolidines type **2** (X = O: oxaproline) (Scheme 1), which are generally poorly stable and non-isolable. The latter proved to exist as a tautomeric mixture with the imine open-chain forms type **3**,[1] in contrast to sulfur derivatives (X = S: thiaproline).[2] Depending on the experimental conditions, condensation of formaldehyde ($R^1 = H$ and $R^2 = H$) has been reported to afford isomeric 2:3 adducts:[3] *N*,*N*-methylenebis(oxazolidine) derivatives type **5** (X = O) and/or isomeric 1,6-diaza-3,9-dioxabicyclo[4.4.1]undecane structures type **6** (X = O), instead of the expected oxazolidines type **4** (X = O).

Common strategic routes to *N*-substituted pseudoprolines are prone to ring-chain tautomerism and/or competing reactions.[4] In a recent paper, we reported that 2:3 adducts **5b** (X = O; R = CH_3) and/or **6b** (X = O; R = CH_3) derived from L-threonine methyl ester **1b** could be converted into *N*-acyloxaprolines **13** and **14**,[5] which are usually prepared by cyclocondensation of *N*-monoacylated aminoesters with carbonyl compounds. Such observation prompted us to examine the scope of this approach, since these *N*-acyl derivatives have potential in various fields[6,7] including development of peptides mimics.[8] The procedure has now been investigated on similar and easily accessible 2:3 adducts **6a**[9] (X = O; R = H) and **5c**[10] (X = S; R = H) derived from L-serine methyl ester **1a** and L-cysteine methyl ester **1c**, respectively.



Scheme 1. Reagents and conditions: (i) $R^1R^2C{=}O$, Et_3N, CH_2Cl_2, rt; (ii) $(HCHO)_3$, Et_3N, CH_2Cl_2, rt; (iii) R′COCl, Na_2CO_3, H_2O/CH_3CN.

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Table 1.

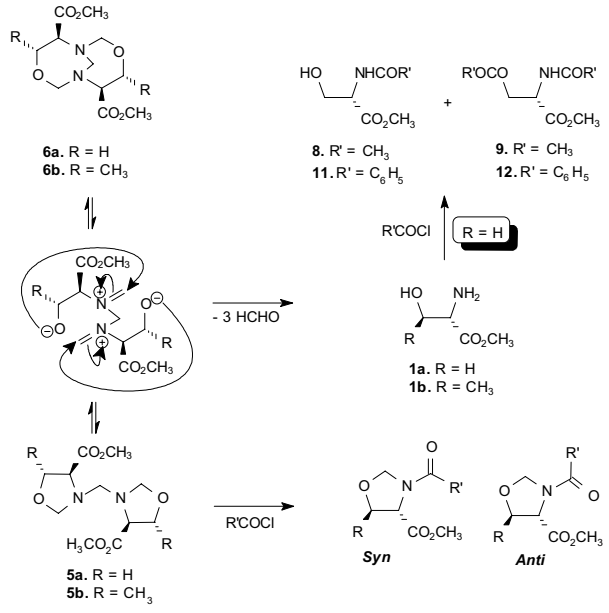
Starting 2:3 adducts	X	R	R′	Product	Yield (%)
6a	O	H	CH_3	**7**	31
	O	H	C_6H_5	**10**	6
5b and/or **6b**	O	CH_3	CH_3	**13**	70[5]
	O	CH_3	C_6H_5	**14**	60[5]
	O	CH_3	*p*-OMe-C_6H_4	**15**	54
	O	CH_3	*p*-NO_2-C_6H_4	**16**	58
5c	S	H	CH_3	**17**	71
	S	H	C_6H_5	**18**	83
	S	H	*p*-OMe-C_6H_4	**19**	56

The reaction was performed in water/acetonitrile at room temperature overnight with various acylating agents according to previous procedure[5] and the results listed in Table 1. All products were isolated on silica gel column chromatography and gave satisfactory spectroscopic data.[11] Mass spectrum in positive FAB ionization mode displayed the molecular ion $[M+H]^+$ and the fragments $[M+H-R'C{=}O]^+$ and $[R'C{=}O]^+$ resulting from the amide bond scission. As already reported for compounds **13** and **14**,[5] ^1H NMR spectra of the novel compounds **7**, **10** and **15**–**19** displayed the expected deshielding of intracyclic protons that are closed to the N–C=O grouping and the duplication of NMR signals reflecting the existence of two *syn*/*anti*-rotational isomers (Scheme 1). This was confirmed by NMR signals coalescence upon raising temperature.

As shown in Table 1, condensation with 2:3 adduct **5c** afforded compounds **17**–**19** in satisfactory yields (56–83%). The latter were very closed to those obtained when starting from the thiaproline **4c** (X = S; R = H). Therefore, the potential of this procedure seemed to be confirmed.

For L-threonine derivatives **5b/6b**, the conversion occurred with yields ranging from 54% to 70%. Similar yields (±5%) were obtained when starting from either pure isomers **5b** and **6b** or from the equilibrium mixture, thus allowing to bypass the separation step. In contrast, using the same conditions, isomer **6a** afforded a mixture of *N*-acylated and *N*,*O*-diacylated by-products **8/9** and **11/12**,[12] besides the expected compounds **7** or **10**, respectively. Formation of these by-products gave clear-cut evidence of the existence of a ring-chain tautomerism occurring in the N–C–O grouping of the seven-membered rings (Scheme 2).

The efficiency of the procedure in the case of pure bicyclic derivative **6b** should be ascribed to its rapid isomerization[10] into *N*,*N*-methylenebis(oxazolidine) isomer **5b** via transient open-chain forms. In contrast, the slow conversion[10] **6a** → **5a** should favour their decomposition into their parent aminoester **1a** as demonstrated for similar derivatives.[13] Subsequent acylation led to the by-products **8/9** or **11/12**. The overall experiments suggested that *N*,*N*-methylenebis(oxa- or thiazolidine) structures type **5** are the more reactive forms.



Scheme 2.

The present findings open an alternative way to prepare *N*-acyl-pseudoprolines derived from L-threonine and L-cysteine. Further investigations are in progress for the particular but not definitive case of L-serine. These results supported the expectations that *N*,*N*-methylenebis(oxazolidine) and 1,6-diaza-3,9-dioxabicyclo[4.4.1]-undecane structures could be considered as synthetic equivalents of the non-isolable oxaprolines **4a** and **4b**. This procedure will be extended to the synthesis of pseudopeptides containing pseudoproline residues.

Acknowledgements

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References and notes

1. Fülöp, F.; Pihlaja, K. *Tetrahedron* **1993**, *49*, 6701–6706.
2. Fülöp, F.; Mattinen, J.; Pihlaja, K. *Tetrahedron* **1990**, *46*, 6545–6552.
3. See for examples: (a) Aitken, D. J.; Guillaume, D.; Husson, H.-P.; Chiaroni, A.; Riche, C. *J. Heterocycl. Chem.* **1991**, *28*, 705–709; (b) Kostyanovsky, R. G.; El'natanov, Yu. I.; Krutius, O. N.; Chervin, I. I.; Zàddach, H.; Koehler, K. F. *Russ. Chem. Bull.* **1994**, *43*, 321–322; (c) Bolm, C.; Chuang, T.-H.; Raabe, G.; Fang, J.-M. *Synth. Commun.* **1999**, *29*, 43–51; (d) Aitken, D. J.; Besson, L.; Fournier, F.; Husson, H.-P.; Lemoine, P.; Lesage, D.; Libot, F.; Martin, P.-G.; Mellin-Morlière, C.; Monnier, V.; Tabet, J.-C.; Viossat, B. *Heterocycles* **2004**, *64*, published on line.
4. See for example: Luo, Y.; Evindar, G.; Fishlock, D.; Lajoie, G. A. *Tetrahedron Lett.* **2001**, *42*, 3807–3809.
5. Sélambarom, J.; Monge, S.; Carré, F.; Roque, J.-P.; Pavia, A. A. *Tetrahedron* **2002**, *58*, 9559–9566.
6. Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8645–8658.
7. Taylor, W. G.; Hall, T. S.; Schreck, C. E. *Can. J. Chem.* **1992**, *70*, 165–172.

8. (a) Kern, D.; Schutkowski, M.; Drakenberg, T. *J. Am. Chem. Soc.* **1997**, *119*, 8403–8408; (b) Nishi, T.; Fukazawa, T.; Kurata, H.; Ishibashi, K.; Nakajima, K.; Yamaguchi, T.; Itoh, K. EP-776893-A1, 1996, Sankyo Co., Ltd; (c) Nishi, T.; Fukazawa, T.; Ishibashi, K.; Nakajima, K.; Sugioka, Y.; Iio, Y.; Kurata, H.; Itoh, K.; Mukaiyama, O.; Satoh, Y.; Yamaguchi, T. *Bioorg. Med. Chem.* **1999**, *9*, 875–880.
9. Sélambarom, J.; Monge, S.; Carré, F.; Fruchier, A.; Roque, J.-P.; Pavia, A. A. *Carbohydr. Res.* **2001**, *330*, 43–51.
10. Sélambarom, J.; Carré, F.; Fruchier, A.; Roque, J.-P.; Pavia, A. A. *Tetrahedron* **2002**, *58*, 4439–4444.
11. *For instance*, compound **17**: FAB^+ MS (NBA) *m*/*z*: 190 $M+H^+$; 212 $[M+Na]^+$; 43 $[CH_3–C{=}O]^+$; 148 $[M+H-CH_3–C{=}O]^+$; 379 $[2M+H]^+$; ^1H NMR ($CDCl_3$; 200 MHz) δ: (*syn*- and *anti*-rotational isomers): 2.05 and 2.19 (each s, 3H, CH_3CO); 3.24 and 3.27 (each m, 2H, S–C*H*$_2$–CH); 3.77 and 3.82 (each s, 3H, OCH_3) ; 4.61 and 4.64 (each m, 2H, S–C*H*$_2$–N); 4.77 and 5.12 (each dd, J = 5.7 Hz, J = 3.81 Hz and J = 6.6 Hz, J = 4.02 Hz, 1H, S–CH$_2$–C*H*).
12. *For instance*, compound **11**: FAB^+ MS (NBA) *m*/*z*: 224 $M+H^+$; 105 $[Ph–C{=}O]^+$; ^1H NMR ($CDCl_3$; 200 MHz) δ: 3.21 (br s, 1H, OH); 3.81 (s, 3H, OCH_3); 4.06 (dd, J = 11.2 Hz, J = 7.5 Hz, 2H, O–C*H*$_2$–CH); 4.85 (dt, J = 7.5 Hz, J = 3.5 Hz, 1H, O–CH$_2$–C*H*); 7.26 (d, J=11.2 Hz, 1H, NH); 7.43–7.86 (m, 5H, H-ar). Compound **12**: FAB^+ MS (NBA) *m*/*z*: 328 $[M+H]^+$; 105 $[Ph–C{=}O]^+$; ^1H NMR ($CDCl_3$; 200 MHz) δ: 3.86 (s, 3H, OCH_3); 4.80 (dd, J=7.5 Hz, J = 3.5 Hz, 2H, O–C*H*$_2$–CH); 5.21 (dt, J=3.5 Hz, J=3.5 Hz, 1H, O–CH$_2$–C*H*); 7.14 (d, J=7.3 Hz, 1H, NH); 7.40–7.94 (m, 5H, H-ar).
13. Moloney, G. P.; Iskander, M. N.; Craik, D. J. *Magn. Reson. Chem.* **1997**, *35*, 337–341.