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An amino acid *N*-derivatising group that can be coloured on demand

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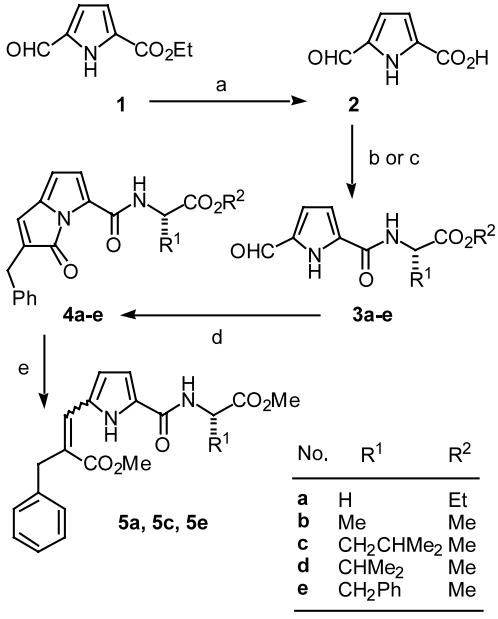
Abstract—A method is presented whereby an amino acid is reacted with 5-formyl-1*H*-pyrrole-2-carboxylic acid to give an *N*-derivatised tag that has a latent ability to be coloured. A characteristic red pyrrolizin-3-one (coloured tag) is then revealed on treatment with hydrocinnamoyl chloride. This sequence has been carried out on amino acids in solution, and on solid phase, and also on dipeptides.

We have recently embarked on a program to develop methods for the solution and solid phase labelling of compounds with a molecular tag that can be unmasked on specific and controlled chemical reaction. The idea is to produce a 'built-in' chemical label that has an ability to be revealed and hence identified on demand, a property that is unique amongst existing tagging systems.[1] This idea offers a number of potential applications and advantages over existing methods. It allows specific identification and/or isolation of tagged derivatives, or key intermediates, from synthetic mixtures or libraries of compounds on demand and subsequent to the initial step of chemical attachment of the tag precursor. A potential advantage of latency is that it removes the possibility of the process of identification, e.g. fluorescence, interfering with the particular study, or synthetic sequence, being undertaken. A set of such tags would also provide a method to encode the progress of a combinatorial synthetic sequence and the potential to sequence a peptide or the like.[2]

In this paper we demonstrate this principle with a method that releases a characteristic and highly coloured tag from a precursor that is conveniently attached to the free amino group of an amino acid, either in solution or on a solid support. The result is a new *N*-derivatising group that possesses a latent ability to be coloured. The method presented here is based on the *N*-derivatisation of an amino acid with 5-formyl-1*H*-pyrrole-2-carboxylic acid **2** to give *N*-(5-formyl-1*H*-pyrrole-2-carbonyl)amino acids, e.g. **3** (Scheme 1). These compounds are convenient precursors to highly coloured molecular tags, i.e. they give rise to the corresponding red pyrrolizin-3-ones **4**, on reaction with hydrocinnamoyl chloride under mild conditions.

The latent tags, **3**, were synthesised as detailed in Scheme 1. The pyrrole acid **2**, readily prepared by



Scheme 1. (a) KOH, H_2O, 40–50°C (82%); (b) EDCI, HOBt, DIPEA and amino acid·HCl (**3a**, 79%; **3b**, 43%; **3c**, 90%; **3d**, 53%; **3e**, 91%); (c) L-LeuOMe·HCl, DCC, HOBt, DIPEA (**3c**); (d) DMAP, DIPEA, CH_2Cl_2 then $Ph(CH_2)_2COCl$ (**4a**, 58%; **4b**, 21%; **4c**, 55%; **4d**, 35%; **4e**, 58%); (e) MeONa, MeOH (**5a**, 85%), (**5c**, 80%), (**5e**, 82%).

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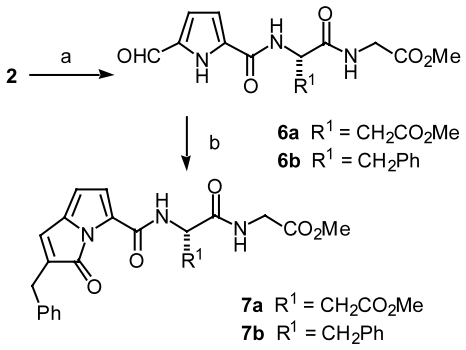
hydrolysis of **1**,[3] was coupled with a range of amino acid esters, using standard 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) peptide coupling methodology,[4] to give **3a–e** in good yields. Compound **3c** was also prepared in 89% yield using standard DCC–peptide coupling methodology. Next, separate dichloromethane solutions of each of **3a–e**, containing diisopropylethyl amine (DIPEA) and a catalytic amount of 4-dimethylaminopyridine (DMAP), were treated with hydrocinnamoyl chloride. The red pyrolizin-3-ones **4** were isolated after stirring at rt for 24 h (Scheme 1). The structures of these derivatives were fully characterised by one- and two-dimensional NMR spectroscopy, mass spectrometry, ultraviolet spectroscopy and in the case of **4a**, X-ray crystallography. Independent conformation of the structures of the red tags **4a**, **4c** and **4e** was provided by treating each with sodium methoxide in methanol to give the colourless pyrrole acrylic esters **5a**, **5c** and **5e** in yields of 85, 80 and 82%, respectively (Scheme 1).[†] This reaction also provides a means to remove the red coloration of the tag.

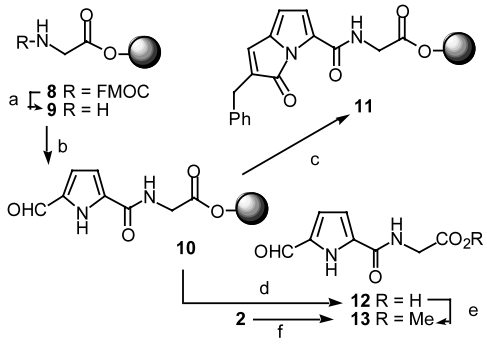
Next, we demonstrated that the method could be applied to dipeptides. L-Leucylglycine methyl ester and L-phenylalanylglycine methyl ester were separately reacted with **2** to give the corresponding *N*-pyrroloylpeptides **6a** and **6b**, respectively (Scheme 2). Reaction of each of these with hydrocinnamoyl chloride, as described for **3** above, gave the dipeptide-based pyrolizin-3-ones **7** which were fully characterised.

Finally, we investigated whether the method could be used to develop a red tagging system for resin bound amino acids (Scheme 3).[5] To this end, FMOC-glycine Wang resin **8** was deprotected by reaction with piperidine and the resulting free amine **9** was coupled with the pyrrole acid **2** to give the *N*-pyrroloyl protected resin bound amino acid **10**. Reaction of this sample with hydrocinnamoyl chloride, as per the formation of **3** in Scheme 1, gave the red resin beads, **11** (see Fig. 1 for a photograph). The resin bound intermediate **10** was characterised by cleaving it from the resin on treatment with TFA. Methylation of the resulting carboxylic acid **12**, with diazomethane, gave **13**, which was shown to be identical to a sample independently synthesised from **2** (see step f in Scheme 3).

The method reported here for the preparation of pyrrolizin-3-ones is much milder than existing literature methods.[6] The reaction is assumed to occur via *N*-acylation of **3** with subsequent intramolecular Knoevenagel-type condensation of the resulting *N*-acylated formylpyrrole intermediates. The nature of the acid chloride used in these reactions would appear to be important. An equivalent reaction of **3c**, using acetyl chloride in place of hydrocinnamoyl chloride, gave **14** rather than the corresponding pyrrolizin-3-one.



Scheme 2. (a) BOP, DIPEA, either L-LeuGlyOMe·HCl (45%) or L-PheGlyOMe·HCl (49%); (b) DMAP, DIPEA, CH_2Cl_2 then $Ph(CH_2)_2COCl$ (**7a**, 33%), (**7b**, 34%).



Scheme 3. (a) 20% piperidine in DCM; (b) **2**, EDCI, HOBt, DIPEA; (c) DMAP, DIPEA, CH_2Cl_2 then $Ph(CH_2)_2COCl$; (d) 20% TFA/DCM; (e) CH_2N_2; (f) glycine methyl ester hydrochloride, EDCI, BOP, DIPEA.

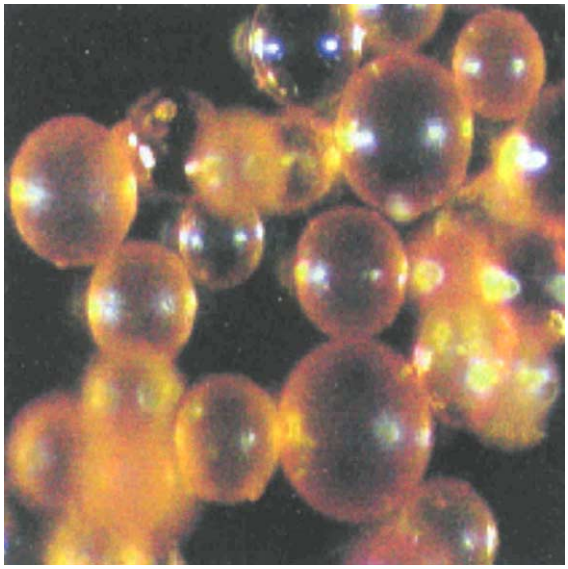
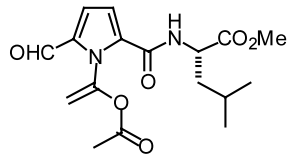


Figure 1. Resin bound **11**.

[†] It is interesting to note that in the case of the leucine and phenylalanine examples **5c** and **5e**, only the (*Z*)-isomer was observed by ^1H NMR. However, in the case of the glycine example **5a**, a mixture of the (*Z*)- and (*E*)-isomers was obtained in a ratio of 3:1 (by ^1H NMR). Subsequent recrystallization of this mixture gave a pure sample of the (*E*)-isomer which was fully characterized. The assignment of a (*Z*)-configuration for the alkene **5c** (and by analogy for **5a** and **5e**) was based on an observed strong positive NOE enhancement between the acrylic proton and the methylene protons of the benzyl group.



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In conclusion, we present a method whereby a latent coloured molecular tag can be conveniently attached to the free amino group of an amino acid in either solution or the solid phase. A characteristic red tag can then be revealed, on demand, upon treatment with hydrocinnamoyl chloride. Ongoing work is centred on identifying milder methods for introducing the *N*-derivatising group and also developing a set of tags. This chemical sequence presented here offers a convenient method to tag on demand, and hence identify compounds containing an amino group.

Acknowledgements

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References

1. For a discussion of latent chemical reactivity, see: Abell, A. D. In *Detailed Reaction Mechanisms*: *Mechanisms of Biological Importance*; Coxon, J., Ed.; JAI: London, 1992; Vol. 2, pp. 243–260.
2. Still, W. C. *Acc. Chem. Res.* **1996**, *29*, 155.
3. Wallace, D. M.; Leung, S. H.; Senge, M. O.; Smith, K. M. *J. Org. Chem.* **1994**, *59*, 5230.
4. Tian, Z.-Q.; Brown, B. B.; Mack, D. P.; Hutton, C. A.; Bartlett, P. A. *J. Org. Chem.* **1997**, *62*, 514.
5. For an existing method of detecting solid-phase bound amines, see: Madder, A.; Farcy, N.; Hosten, N. G. C.; De Muynck, H.; Clercq, P. J.; Barry, J.; Davis, A. P. *Eur. J. Org. Chem.* **1999**, 2787.
6. (a) Campbell, S. E.; Comer, M. C.; Derbyshire, P. A.; Despinoy, X. L. M.; McNab, H.; Morrison, R.; Sommerville, C. C.; Thornley, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2195; (b) McNab, H.; Thornley, C. *Heterocycles* **1994**, *37*, 1977; (c) Bestmann, H. J.; Bansal, R. K. *Tetrahedron Lett.* **1981**, *22*, 3839; (d) Flitsch, W.; Neumann, U. *Chem. Ber.* **1971**, *104*, 2170; (e) Ermili, A.; Castro, A. J.; Westfall, P. A. *J. Org. Chem.* **1965**, *30*, 339.