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COMMUNICATION

One-pot highly diastereoselective annulation to *N*-unprotected tetrasubstituted 2-pyrrolines

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A one-pot DABCO-catalysed Michael addition of glycine imine-derived esters to *trans*-2-aroyl-3-arylacrylonitriles followed by a deprotection/cyclization/tautomerization sequence afforded tetrasubstituted *N*-unprotected *trans*-2-pyrrolines in up to 96% yield.

Among the nitrogen containing heterocycles, pyrrolines (dihydropyrroles) are important structural moieties present in several biologically active compounds and pharmaceuticals.[1] Illustrative examples are spirotryprostatin B **1**, isolated from fermentation of *Aspergillus fumigatus* BM939,[2] showing growth inhibition toward leukemia K562 and HL-60 cells, antramicin **2**, isolated from actinomycetes with significant sequence-selective DNA-alkylation activity[3] and synthetic tetrasubstitued 2-pyrrolidine **3-(±)** showing antiproliferative activity towards HeLa and MCF7/AZ cell lines (Figure 1).[4]

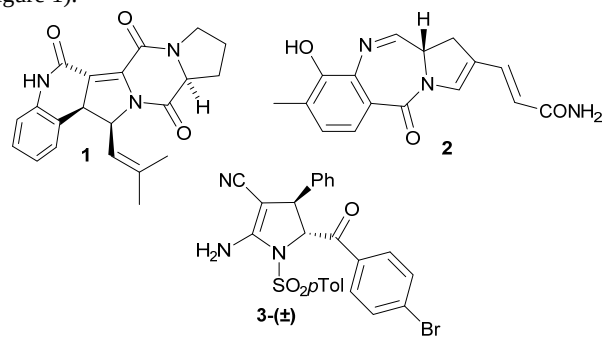
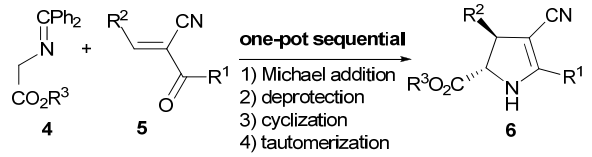


Fig. 1 Examples of naturally occurring and biologically active 2-pyrrolines.

Pyrrolines have also been used as key-intermediates in total synthesis of natural products and to access other classes of important heterocycles such as pyrrolidines and pyrroles.[5] A variety of studies focused on approaches to obtain 3-pyrrolines,[6] whereas comparatively less attention has been devoted to the synthesis of 2-pyrrolines. The most successful routes are centered on cycloaddition reactions,[7] metal-catalysed reactions,[8] Michael addition/cyclization sequence[9] mainly giving access to di- and trisubstituted *N*-protected 2-pyrrolines.

The development of novel one-pot processes to obtain 2-pyrrolines is highly desirable and attractive in terms of sustainability and advantageous in terms of time, costs saving issues and minimal manual operations. Being interested in the stereoselective synthesis of a variety of heterocyclic compounds[10] and inspired by reports on stereoselective Michael addition reactions of glycine-derived imine esters to α,β-unsaturated ketones,[11] we focused our efforts on the development of a convenient route to obtain challenging tetrasubstituted *N*-unprotected 2-pyrrolines of type **6** (Scheme 1). Herein we illustrate the feasibility of a sequential one-pot DABCO-catalyzed Michael addition/deprotection/cyclization/tautomerization approach starting from readily accessible glycine imine esters **4** and *trans*-2-aroyl-3-arylacrylonitriles **5**. *trans*-2-Pyrrolines **6** have been isolated in good yield and high diastereoselectivity (Scheme 1).



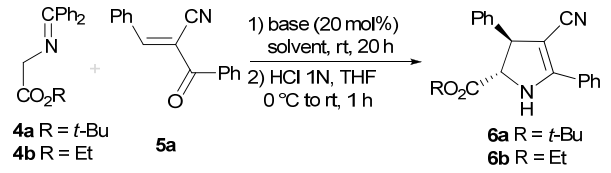
Scheme 1 One-pot sequential approach to *trans*-2-pyrrolines **6**.

Herein, we also show that 2-pyrrolines **6** can be transformed by oxidation or reduction into the corresponding fully substituted pyrroles or pyrrolidines, respectively.

Alkene **5a** and *t*-butyl ester glycinate benzophenone Schiff base **4a** were selected as model substrates to study the process, using different amines as the catalyst (Table 1). First, the Michael addition reaction was carried out for 20 h using 20 mol % loading of a base in toluene as solvent (entries 1-6). Then the solvent was removed under vacuum and the crude mixture was dissolved in THF at 0°C followed by HCl 1N addition and stirring up to room temperature for 1 h. Secondary bases led to the formation of the expected product **6a**

in moderate yield and complete control of the diastereoselectivity for the *trans*-isomer (entries 1 and 2).

Table 1. Optimization of the reaction conditions[a]



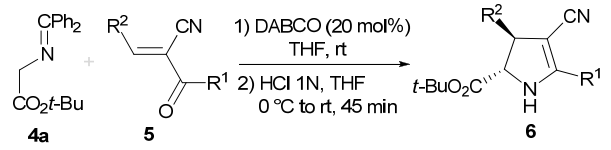
4a R = *t*-Bu
4b R = Et
5a
6a R = *t*-Bu
6b R = Et

Entry	4	Base	Solvent	Yield **6** (%)[b]	*trans*/*cis* (%)[b]
1	**4a**	pyrrolidine	toluene	64	>20/<1
2	**4a**	2-piperidinemethanol	toluene	55	>20/<1
3	**4a**	triethylamine	toluene	29	>20/<1
4	**4a**	DABCO	toluene	90(83)	>20/<1
5	**4a**	DBU	toluene	54	>20/<1
6	**4a**	*t*-BuOK	toluene	25	>20/1
7[c]	**4a**	DABCO	$CHCl_3$	46	>20/1
8[c]	**4a**	**DABCO**	**THF**	**88(80)**	**>20/1**
9[c]	**4a**	DABCO	CH_3CN	88	>20/1
10[c]	**4a**	DABCO	CH_3OH	35	>20/1
11[c]	**4b**	DABCO	THF	(74)	>20/1

[a] All reactions were carried out using **5a** (0.1 mmol), **4** (0.1 mmol), base (20 mol %), solvent (200 μL) for 20 h; then additional 200 μL of THF and 400 μL of HCl (1N) were added at 0 °C. [b] Determined by ^{1}H-NMR analysis of the crude reaction mixture with an internal standard. Value in parenthesis corresponds to isolated yield. [c] Reaction time for the first step was 16 h.

Among the tertiary bases tested (entries 3-5) DABCO afforded 2-pyrroline **6a** in good yield and high diastereoselectivity (entry 4). *t*-BuOK proved to be a poor base for the process (entry 6). A solvent screening for the first Michael addition step using DABCO as the most effective base, showed THF to be as good as toluene (entry 8). Being the most effective medium for all the steps, THF was chosen as the reaction solvent to simplify the entire process. The reaction performed with ethyl ester glycinate benzophenone Schiff base **4b** gave the *trans*-2-pyrroline **6b** in slightly inferior yield (compare entry 8 with entry 11).

Table 2. One-pot diastereoselective annulation to *trans*-2-pyrrolines **6**[a]



4a **5** **6**

Entry	R^1	R^2	time (h)	Yield **6** (%)[b]		dr (%)[c]
1	Ph	Ph	21	96	**6a**	>20/1
2	Ph	4-*t*-BuC_6H_4	23	68	**6c**	>20/1
3	Ph	3-MeC_6H_4	28	78	**6d**	>20/1
4	Ph	2-MeC_6H_4	40	77	**6e**	>20/1
5	Ph	4-BrC_6H_4	23	75	**6f**	>20/1
6	Ph	3-BrC_6H_4	24	68	**6g**	>20/1
7	Ph	4-$NO_2C_6H_4$	18	80	**6h**	>20/1
8	Ph	2-naphthyl	24	50	**6i**	>20/1
9	3-ClC_6H_4	Ph	21	58	**6j**	>20/1
10	4-MeOC_6H_4	4-BrC_6H_4	28	75	**6k**	>20/1
11	Ph$(CH_2)_2$	Ph	23	87	**6l**	>20/1
12	Ph	cyclohexyl	24	-	**6m**	-

[a] All reactions were carried out using **5** (0.1 mmol), **4a** (0.1 mmol), DABCO (20 mol %), solvent (200 μL) for the indicated time; then additional 200 μL of THF and 400 μL of HCl (1N) were added at 0 °C. [b] Isolated yield after chromatography. [c] Determined by ^{1}H-NMR analysis.

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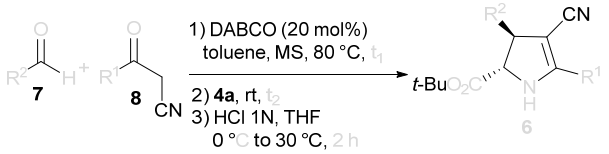
Under the optimized conditions we studied the substrate scope of the process by reacting a variety of alkenes **5** with compound **4a** in the presence of 20 mol% of DABCO in THF at room temperature (Table 2).

β-Phenyl substituted alkenes with either electron-rich or electron-poor groups at different positions were smoothly converted into the corresponding *trans*-2-pyrrolines in good yields (entries 1-8). Substitution is well-tolerated either at the aroyl portion and at the β-phenyl ring (entries 9-10).

Replacing the phenyl ketone with an aliphatic ketone as in alkene **4l** did not cause any detriment to the reaction sequence (entry 11), whereas alkyl substitution at the β-position of the alkene was found to be detrimental for the reactivity (entry 12).

The feasibility of a one-pot telescoped synthesis of *trans*-2-pyrrolines, starting directly from commercially available benzaldehydes **7**, aroylacetonitriles **8** and DABCO, via Knoevenagel condensation/Michael addition/deprotection/cyclization/tautomerization sequence has been also demonstrated (Table 3).

Table 3. One-pot sequential synthesis of *trans*-2-pyrrolines **6** from commercially available aldehydes and aroylacetonitriles[a]



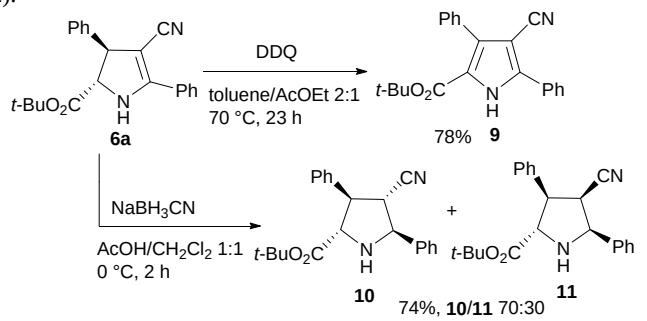
Entry	R^1	R^2	t_1,t_2 (h)	Yield **6** (%)[b]		dr (%)[c]
1	Ph	Ph	(4.5)(23)	77	**6a**	>20/1
2	Ph	4-*t*-BuC_6H_4	(7)(24)	70	**6c**	>20/1
3	Ph	3-MeC_6H_4	(6)(22)	60	**6d**	>20/1
4	Ph	4-BrC_6H_4	(7)(22)	82	**6f**	>20/1
5	Ph	3-BrC_6H_4	(7)(19)	73	**6g**	>20/1
6	Ph	4-$NO_2C_6H_4$	(4)(21)	62	**6h**	>20/1
7	Ph	2-naphthyl	(6)(25)	55	**6i**	>20/1
8	3-ClC_6H_4	Ph	(4)(24)	70	**6j**	>20/1
9	4-MeOC_6H_4	4-BrC_6H_4	(5)(26)	66	**6k**	>20/1

[a] All reactions were carried out stirring **7** (0.25 mmol), **8** (0.25 mmol), DABCO (20 mol %), solvent (500 μL) and MS (20 mg) at 80 °C for the indicated time (t_1). The reaction mixture was cooled down at rt and **4a** (0.25 mmol) was added, stirring maintained for the required time (t_2). Toluene was removed, the crude diluted with THF (1 mL) and then HCl (1N) (1 mL) was added at 0 °C leaving the mixture to warm up to 30 °C. [b] Isolated yield after chromatography. [c] Determined by ^{1}H-NMR analysis.

The DABCO-catalysed Knoevenagel condensation was carried out in toluene at 80 °C in the presence of molecular sieves. When the conversion to alkenes **5** was almost complete, the mixture was cooled down to room temperature and compound **4a** was added. At the end of the reaction, toluene was removed under vacuum, the crude mixture diluted with THF before adding the HCl solution. Pleasingly, *trans*-**6** products were isolated in comparable yields than those reported in Table 2, although the process could not be applied to obtain product **6l**.[12] Notably, the one-pot process illustrated in Table 3, is highly convenient as it embodies five steps and only three

operations: solvent evaporation, extraction and one column purification.

The synthetic utility of compounds **6** is exemplified by oxidation and reduction to tetrasubstituted pyrroles and proline esters (Scheme 2).[13]



Scheme 2 Derivatization of *trans*-2-pyrrolines to pyrroles and pyrrolidines.

The oxidation of compound **6a** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), performed in toluene/AcOEt mixture at 70 °C, afforded pyrrole **9** in 78% yield. The reduction of 2-pyrroline **6a** was carried out using $NaBH_3CN$ in $AcOH/CH_2Cl_2$ medium at 0 °C.[14] A mixture of proline esters **10** and **11** was isolated in 74% yield with 70:30 dr ratio.[15] We have theoretically studied the reaction mechanism and in agreement with indole reduction,[13,16] the protonation of the 4-position of compound **6a** is the most plausible event. The observed dr ratio can be traced back to the different free energies of the two iminium ions **I** and **II**. According to DFT computations, iminium ion **I**, giving rise to compound **10**, is predicted to be more stable by 1.5 kcal/mol than **II**, leading to compound **11** (Fig. 2).

The selective reduction of iminium ions **I** and **II**, to diastereoisomers **10** and **11** respectively, might be explained via coordination of $NaBH_3CN$ by the ester group followed by hydride attack onto the *Re*-face.[17]

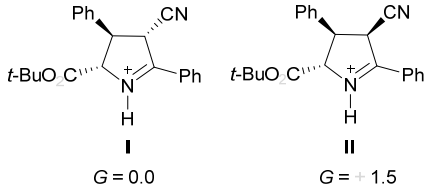


Fig. 2 Protonated adducts of **6a** and their predicted relative Gibbs free energies (*G*, kcal/mol).

Conclusions

In summary, we developed a simple one-pot approach to novel *N*-unprotected-tetrasubstituted *trans*-2-pyrrolines from *trans*-2-aroyl-3-arylacrylonitriles and glycine imine esters exploiting a Michael addition/deprotection/cyclization/tautomerization sequence. The functionalised *trans*-2-pyrrolines have been obtained in good yield and complete control of the diastereoselectivity. Notably, a one-pot sequence to *trans*-2-pyrrolines can be conveniently applied starting directly from commercially available aldehydes and α-cyanoketones. *trans*-2-Pyrrolines proved to be of synthetic utility to access pyrroles and proline ester derivatives. Further studies aimed to enlarge the scope of the reaction and develop an asymmetric version are currently underway.

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Notes and references

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Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data and copies of NMR spectra for all new compounds, computational details and predicted ^{1}H-NMR chemical shifts. See DOI: 10.1039/c000000x/

1 For reviews, see: (a) E. Fattorusso and O. Taglialatela-Scafati, *Modern Alkaloids: Structure, Isolation, Synthesis and Biology* Wiley-VCH: Weinheim, 2008; (b) F. Bellina and R. Rossi, *Tetrahedron* 2006, **62**, 7213. For selected examples, see: (c) C. Marti and E. M. Carreira, *J. Am. Chem. Soc.*, 2005, **127**, 11505.

2 C. B. Cui, H. Kakeya and H. Osada, *J. Antibiot.* 1996, **49**, 832.

3 (a) H. M. Bates, W. Kuenzig and W. B. Watson, *Cancer Res.*, 1969, **29**, 2195; (b) L. H. Hurley, L. Petrusek, *Nature*, 1979, **282**, 529.

4 I. V. Magedov, G. Lucchetti, N. M. Evdokimov, M. Manpadi, W. F. A. Steelant, S. Van slambrouck, P. Tongwa, M. Y. Antipin and A. Kornienko *Bioorg. Med. Chem. Lett.* 2008, **18**, 1392.

5 (a) *Comprehensive Heterocyclic Chemistry*; Bird, C. W., Ed.; Pergamon Press: Oxford, 1996; Vol. 2; (b) T. J. Donohoe and R. E. Thomas, *Chem. Rec.* 2007, **7**, 180; (c) I. Coldham and R. Hufton, *Chem. Rev.*, 2005, **105**, 2765; (d) D. O'Hagan, *Nat. Prod. Rep.*, 2000, **17**, 435.

6 Fore selected examples, see: (a) T. J. Donohoe and D. House, *J. Org. Chem.*, 2002, **67**, 5015; (b) L.-G. Meng, P. Cai, Q. Guo and S. Xue, *J. Org. Chem.*, 2008, **73**, 8491; (c) J. U. Rhee and M. J. Krische, *Org. Lett.*, 2005, **7**, 2493; (d) D. X. Zeng and Y. Chen, *Synlett*, 2006, 490; (e) H. Ohno, Y. Kadoh, N. Fujii and T. Tanaka, *Org. Lett.*, 2006, **8**, 947; (f) R. Castarlenas, C. Vovard, C. Fischmeister and P. H. Dixneuf, *J. Am. Chem. Soc.*, 2006, **128**, 4079; (g) M. Sai and S. Matsubara, *Org. Lett.*, 2011, **13**, 4676; (h) A. Desmarchelier, V. Coeffard, X. Moreau and C. Greck, *Chem. Eur. J.*, 2012, **18**, 13222; (j) S. Senthil K. Boominathan, W.-P. Hu, G. C. Senadi and J.-J. Wang, *Adv. Synth. Catal.*, 2013, **355**, 3570.

7 For selected examples, see: (a) T. Junjun, R. Zhou, H. Sun, H. Song and Z. He, *J. Org. Chem.*, 2011, **76**, 2374; (b) M. Sampath, P.-Y. B. Lee and T.-P. Loh, *Chem. Sci.*, 2011, **2**, 1988; (c) X. Yu, G. Zhou and J. Zhang, *Chem. Commun.*, 2012, **48**, 4002; (d) C.-R. Liu, B.-H. Zhu, J.-C. Zheng, X.-L. Sun, Z. Xie and Y. Tang, *Chem. Commun.*, 2011, **47**, 1342; (e) E. Li, P. Jia, L. Liang and Y. Huang, *ACS Catal.*, 2014, **4**, 600; (f) L.-Q. Lu, J.-J. Zhang, F. Li, Y. Cheng, J. An, J.-R. Chen, and W.-J. Xiao, *Angew. Chem. Int. Ed.*, 2010, **49**, 4495.

8 For selected examples, see; (a) S. S. Kinderman, J. H. Van Maarseveen, H. E. Schoemaker, H.; Hiemstra and F. P. J. T. Rutjes, *Org. Lett.*, 2001, **3**, 2045; (b) J. Fan, L. Gao and Z. Wang, *Chem. Commun.* 2009, 5021; (c) D. Monge, K. L. Jensen, P .T. Franke, L. Lykke, and K. A. Jørgensen, *Chem. Eur. J.*, 2010, **16**, 9478; (d) L. A. Polindara-García and L. D. Miranda, *Org. Lett.*, 2012, **14**, 5408; (e)

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DOI: 10.1039/C4GC02191F

G. Guo, M.-X. Xue, M.-K. Zhu and L.-Z. Gong, *Angew. Chem. Int. Ed.*, 2008, **47**, 3414; (f) T. Miura, T. Tanaka, K. Hiraga, S. G. Stewart and M. Murakami, *J. Am. Chem. Soc.*, 2013, **135**, 13652.

9 G. Zhang, Y. Zhang, X. Jiang, W. Yan and R. Wang, *Org. Lett.*, 2011, **13**, 3806.

10 (a) A. Lattanzi, *Adv. Synth. Catal.* 2006, **348**, 339; (b) C. De Fusco, T. Fuoco, G. Croce and A. Lattanzi, *Org. Lett.*, 2012, **14**, 4078; (c) S. Meninno, G. Croce and A. Lattanzi, *Org. Lett.*, 2013, **15**, 3436; (d) S. Meninno, T. Fuoco, C. Tedesco and A. Lattanzi, *Org. Lett.*, 2014, **16**, 4746.

11 (a) A. E. Sheshenev, E. V. Boltukhina, A. J. P. White, and K. K. Hii, *Angew. Chem. Int. Ed.*, 2013, **52**, 6988.

12 DABCO did not catalyse the Knoevenagel reaction to compound **5l**. Indeed, alkene **5l** has been synthesized using L-proline as the catalyst according to procedure: P. K. Amancha, Y.-C. Lai, I.-C. Chen, H.-J. Liu, J.-L. Zhu, *Tetrahedron*, 2010, **66**, 871.

13 For selected examples, see: (a) I. Bergner and T. Opatz, *J. Org. Chem.*, 2007, **72**, 7083; (b) P. Fontaine, G. Masson and J. Zhu, *Org. Lett.*, 2009, **11**, 1555; (c) M. Zhao, F. Wang and X. Li, *Org. Lett.*, 2012, **14**, 1412; (d) Y. Kuroda, K. Imaizumi, K. Yamada, Y. Yamaoka and K. Takasu, *Tetrahedron Lett.*, 2013, **54**, 4073; (e) J. Hernández-Toribio, R. Gómez Arrayás, B. Martín-Matute and J. C. Carretero, *Org. Lett.*, 2009, **11**, 393; (f) Ö Dogan, H. Koyuncu, P. Garner, A. Bulut, W J. Youngs| and M. Panzner, *Org. Lett.*, 2006, **8**, 4687; (g) L. Crovetto and R. Rios, *Synlett*, 2008, 1840.

14 (a) G. W. Gribble, P. D. Lord, J. Skotnicki, S. E. Dietz, J. T. Eaton and J. L. Johson, *J. Am. Chem. Soc.* 1974, **96**, 7812; (b) G. W. Gribble and J. H. Hoffman, *Synthesis* 1977, 859.

15 The relative configuration of the stereocentres for compounds **6a**, **10** and **11** were confirmed by NOESY experiments. Predicted ^{1}H-NMR chemical shifts of compounds **10** and **11** were also added (see the ESI).

16 For hydrogenation of *N*-unprotected indoles and pyrroles under acidic conditions, see: (a) D.-S. Wang, Q.-A. Chen, W. Li, C.-B. Yu, Y.-G. Zhou and X. Zhang, *J. Am. Chem. Soc.*, 2010, **132**, 8909; (b) D.-S. Wang, Z.-S. Ye, Q.-A. Chen, Y.-G. Zhou, C.-B. Yu, H.-J. Fan and Y. Duan, *J. Am. Chem. Soc.*, 2010, **133**, 8866. For other examples of reduction with $ZnCl_2$/$NaBH_3CN$ and TFA/$NaBH_3CN$ systems, see: (c) K. Gräbe, B. Zwafelink, and S. Doye, *Eur. J. Org. Chem.*, 2009, 5565; (d) T. Kercher and T. Livinghouse, *J. Org. Chem.*, 1997, **62**, 805.

17 We anticipate that the most accessible TS for the reduction of iminium ion **I** leading to product **10** is predicted to be 4 kcal/mol more stable than TS deriving from the attack of the reducing agent onto the *Si*-face, which would lead to a product not observed experimentally.

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An effective one-pot sequential Michael addition/deprotection/cyclization/tautomerization approach to *N*-unprotected fully substituted *trans*-2-pyrrolines has been developed.