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A novel three-component tandem protocol for the regioselective synthesis of 1-(2-arylmethyl-5-aryl-3-thienyl)pyrrolidines and piperidines

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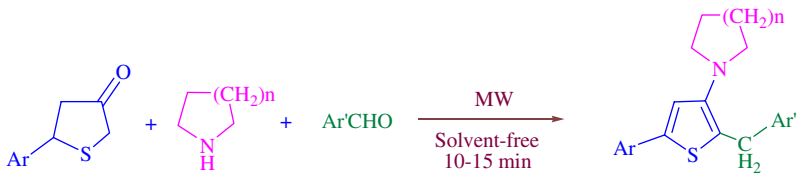
Abstract—A series of new substituted 1-(2-arylmethyl-5-aryl-3-thienyl)pyrrolidines and piperidines were synthesised by one-pot, three-component tandem reactions of 5-aryldihydro-3(2*H*)-thiophenone, aromatic aldehydes and pyrrolidine/piperidine under solvent-free microwave irradiation. This facile transformation occurs presumably via a tandem enamine formation–carbonyl addition–dehydration–isomerisation sequence.

Functionalised thiophenes form an integral part of numerous natural products[1] and pharmaceuticals.[2] The synthesis of highly substituted thiophenes has attracted a great deal of interest over the years due to their presence in natural products,[3] as novel conducting polymers[4] and as isosteric replacements for phenyl groups in medicinal chemistry.[5] Compounds possessing a pyrrolidine sub-structure exhibit antitumour,[6] anti-asthma and anti-Parkinson[7] activities. Compounds with the piperidine sub-structure exhibit anti-hypertensive,[8] antibacterial,[9] anticonvulsant,[10] anti-inflammatory and anti-proliferative[11] activities. The importance of thiophenes, pyrrolidines and piperidines in conjunction with our interest in employing novel tandem processes in organic synthesis[12] has prompted us to report a three-component tandem protocol for the regioselective synthesis of 1-(2-arylmethyl-5-aryl-3-thienyl)pyrrolidines **3a–g** and 1-(2-arylmethyl-5-aryl-3-thienyl)piperidines **3h–m**.

Tandem reactions are multi-step, one-pot processes that provide rapid access to complex molecules without isolation and purification of the intermediates, thus rendering the synthetic protocols convergent, elegant, economic and green.[13]

In the present investigation, an equimolar mixture of 5-aryldihydro-3(2*H*)-thiophenone[12g] **1**, an aromatic aldehyde and pyrrolidine or piperidine **2** (Scheme 1) was taken in a 10 mL sealed tube and subjected to



1 **2** **3**

Scheme 1.

Keywords: Thienylpyrrolidine; Thienylpiperidine; Tandem sequence; 3-Thiophenone; Microwave; Aldehyde.
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Table 1. Synthesis of 1-(2-arylmethyl-5-aryl-3-thienyl)pyrrolidines/piperidines **3**

Entry	Product	*n*	Ar	Ar′	Irradiation time (min)	Yield[a] (%)
1	**3a**	1	*p*-ClC_6H_4	*p*-MeC_6H_4	10	60
2	**3b**	1	*p*-MeC_6H_4	*o*,*p*-$Cl_2C_6H_3$	10	53
3	**3c**	1	*p*-MeC_6H_4	*m*-FC_6H_4	10	46
4	**3d**	1	*p*-ClC_6H_4	*p*-FC_6H_4	10	45
5	**3e**	1	*m*-$O_2NC_6H_4$	*p*-ClC_6H_4	10	60
6	**3f**	1	*o*,*p*-$Cl_2C_6H_3$	*p*-ClC_6H_4	10	57
7	**3g**	1	*m*-$O_2NC_6H_4$	1-$C_{10}H_7$	10	53
8	**3h**	2	*p*-ClC_6H_4	*p*-MeC_6H_4	15	30
9	**3i**	2	*p*-ClC_6H_4	*p*-ClC_6H_4	15	31
10	**3j**	2	*p*-MeC_6H_4	*p*-ClC_6H_4	15	35
11	**3k**	2	*m*-$O_2NC_6H_4$	*p*-MeC_6H_4	15	30
12	**3l**	2	C_6H_5	*m*-$O_2NC_6H_4$	15	33
13	**3m**	2	*m*-$O_2NC_6H_4$	1-$C_{10}H_7$	15	32

[a] Yield after column chromatographic purification.

microwave irradiation[14] at 100 °C for 10–15 min. The reaction progress was monitored by TLC. Moderate to good yields of thienylpyrrolidines (45–60%) were obtained by a one-pot tandem process. However, in the case of the reactions with piperidine, the yields were lower (30–35%) (Table 1).

The structure of **3** is in accord with the one- and two-dimensional NMR spectroscopic data as illustrated for **3e**. The pyrrolidine ring protons, H-2 and H-5 appeared as a 4H triplet at 3.30 ppm ($J = 6.3$ Hz), which showed an HMBC correlation (Fig. 1) with C-8, while H-3 and H-4 appeared as a 4H multiplet at 1.91–1.95 ppm. From C,H-COSY correlations, the carbon signals at 51.8 and 25.1 ppm were assigned to C-2 and C-3, respectively. Protons H-11 of **3e** appeared as a 2H singlet at 4.17 ppm and showed HMBC correlations with the *ipso* carbons C-7, C-8 and C-1″, respectively, at 119.6, 147.2 and 139.3 ppm. Further, H-11 also showed an HMBC correlation with the *ortho*-carbon of the aryl ring (C-6″ at 129.7 ppm) attached to C-11. The 1H singlet at 7.11 ppm, which showed HMBC correlations with C-7 and C-8, was assigned to the proton of the thiophene ring (H-9). Similarly, from the HMBC, H,H-COSY and C,H-COSY correlations, the chemical shifts of all the protons and carbons of **3e** were assigned.

An examination of the structures of the regioisomers, **3** and **3′** (Figs. 1 and 2) suggest that they can be distinguished from either NOESY correlation between H-9

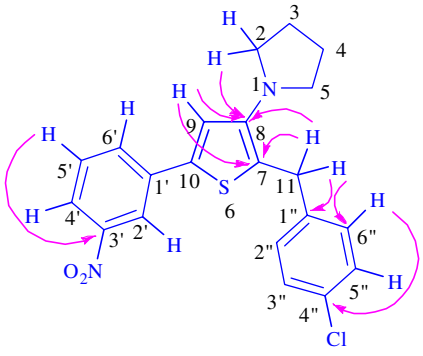


Figure 1. Selected HMBC correlations of **3e**.

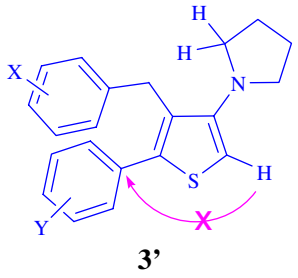
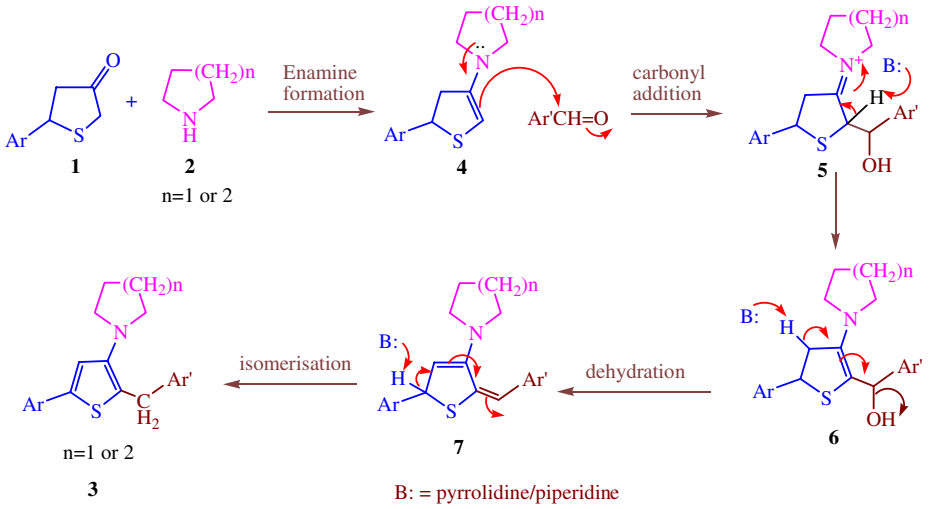


Figure 2. Unlikely $^4J_{C,H}$ correlation in **3′**.

and H-2′,6′ or HMBC correlation between H-9 and C-1′ in **3**, while both these correlations would not be expected in **3′**, as (i) H-9 and H-2′,6′ would be spatially distant and, (ii) the thiophene ring hydrogen would be four bonds away from the *ipso* carbon of the aryl ring of **3′** (Fig. 2). In the case of **3e**, both C-1′ and C-10 had very close chemical shifts (136.2 and 136.4 ppm) rendering it difficult to see clearly from the HMBC spectrum whether H-9 correlated with C-1′ or C-10 or both. Fortunately, for **3a**, the chemical shifts of C-1′ (132.4 ppm) and C-10 (137.7 ppm), which were unambiguously assigned by one- and two-dimensional NMR spectroscopic data and substituent induced chemical shifts (SCS) considerations, differed significantly and both showed HMBC correlations with H-9 as expected for regioisomer **3**.

A possible mechanism for the formation of **3** is depicted in Scheme 2, which envisages a tandem sequence proceeding through the formation of enamine **4**. This enamine subsequently adds to the aldehyde to afford **6**, which undergoes dehydration and isomerisation to afford **3**. The aromatic stabilisation of the thiophene ring of **3** presumably provides the impetus for the isomerisation of **7** to **3**. The reaction proceeds regioselectively affording only one regioisomer, viz. **3**, wherein the arylmethyl group is present at the 2-position of the thiophene ring. Enamine **4** is probably more readily formed, as it is more stable than the alternative possible enamine **8** (Fig. 3). This is due to the conjugative interaction between nitrogen and sulfur via the C=C bond in the former leading to the observed regioselectivity.



Scheme 2. Proposed mechanism for the formation of **3**.

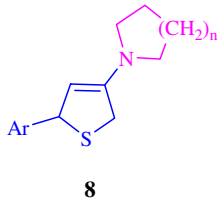


Figure 3. Enamine, regiosomer of **4**.

The present work describes a facile protocol for the regioselective synthesis of novel 1-(2-arylmethyl-5-aryl-3-thienyl)pyrrolidines and 1-(2-arylmethyl-5-aryl-3-thienyl)-piperidines via a tandem enamine formation–carbonyl addition–dehydration–isomerisation sequence. This one-pot transformation effects the creation of one C–C and one C–N bond in an experimentally convenient manner. A library of thienylpyrrolidines and thienylpiperidines bearing different substituents on the aryl rings can be rapidly accessed using this methodology.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.142.

References and notes

1. Koike, K.; Jia, Z.; Nikaido, T.; Liu, Y.; Zhao, Y.; Guo, D. *Org. Lett.* **1999**, *1*, 197.
2. (a) Beers, S. A.; Malloy, E. A.; Wu, W.; Wachter, M.; Ansell, J.; Singer, M.; Steber, M.; Barbone, A.; Kirchner, T.; Ritchie, D.; Argentieri, D. *Bioorg. Med. Chem.* **1997**, *5*, 779; (b) Fevig, T. L.; Phillips, W. G.; Lau, P. H. *J. Org. Chem.* **2001**, *66*, 2493.
3. (a) Bohlmann, F.; Zdero, C. In *Thiophene and its Derivatives*; Gronowitz, S., Ed.; Springer: New York, 1985.
4. Press, J. B.; Pelkey, E. T. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. W., Eds.; Pergamon Press: New York, 1997.
5. Jarvest, R. L.; Pinto, I. L.; Ashman, S. M.; Dabrowski, C. E.; Fernandez, A. V.; Jennings, L. J.; Lavery, P.; Tew, D. G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 443.
6. Hemming, K.; Patel, N. *Tetrahedron Lett.* **2004**, *45*, 7553.
7. Bundy, G. L.; Banitt, L. S.; Dobrowolski, P. J.; Palmer, J. R.; Schwartz, T. M.; Zimmermann, D. C.; Lipton, M. F.; Mauragis, M. A.; Veley, M. F.; Appell, R. B.; Clouse, R. C.; Daugs, E. D. *Org. Process Res. Dev.* **2001**, *5*, 144.
8. Petit, S.; Nallet, J. P.; Guillard, M.; Dreux, J.; Chermat, R.; Poncelet, M.; Bulach, C.; Simon, P.; Fontaine, C.; Barthelmebs, M.; Imbs, J. L. *Eur. J. Med. Chem.* **1991**, *26*, 19.
9. Zhou, Y.; Gregor, V. E.; Ayida, B. K.; Winters, G. C.; Sun, Z.; Murphy, D.; Haley, G.; Bailey, D.; Froelich, J. M.; Fish, S.; Webber, S. E.; Hermann, T.; Wall, D. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1206.
10. Ho, B.; Crider, A. M.; Stables, J. P. *Eur. J. Med. Chem.* **2001**, *36*, 265.
11. Ranise, A.; Schenone, S.; Bruno, O.; Bondavalli, F.; Filippelli, W.; Falcone, G.; Rivaldi, B. *Il Farmaco* **2001**, *56*, 647.
12. (a) Alex Raja, V. P.; Perumal, S. *Tetrahedron* **2006**, *62*, 4892; (b) Savitha Devi, N.; Perumal, S. *Tetrahedron* **2006**, *62*, 5931; (c) Srinivasan, M.; Perumal, S. *Tetrahedron* **2006**, *62*, 7726; (d) Indumathi, S.; Ranjith Kumar, R.; Perumal, S. *Tetrahedron* **2007**, *63*, 1411; (e) Srinivasan, M.; Perumal, S. *Tetrahedron* **2007**, *63*, 2865; (f) Kamal Nasar, M.; Ranjith Kumar, R.; Perumal, S. *Tetrahedron Lett.* **2007**, *48*, 2155; (g) Karthikeyan, S. V.; Perumal, S.

Tetrahedron Lett. **2007**, *48*, 2261; (h) Savitha Devi, N.; Perumal, S. *Tetrahedron Lett.* **2007**, in press, doi:10.1016/j.tetlet.2007.06.024.

13. (a) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831; (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131; (c) Bunce, R. A. *Tetrahedron* **1995**, *48*, 13103; (d) Ho, T.-L. *Tandem Organic Reactions*; Wiley Interscience: New York, 1992; (e) Tietze, L. F.; Brasche, C.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH, 2006.
14. *General procedure for the synthesis of 1-(2-arylmethyl-5-aryl-3-thienyl)pyrrolidines* (**3a**–**g**) *and 1-(2-arylmethyl-5-aryl-3-thienyl)piperidines* (**3h**–**m**): A mixture of 5-aryldihydro-3(2*H*)-thiophenone **1**, aromatic aldehyde and pyrrolidine or piperidine **2** in a 1:1:1 molar ratio was taken in a sealed tube (10 mL) and subjected to MW irradiation (CEM Discover BenchMate, 100 °C, 300 W, 100 psi) for 10–15 min. The progress of the reaction was monitored by thin-layer chromatography and the product purified by flash chromatography on silica gel employing petroleum ether–ethyl acetate [100:1 (v/v)] as eluent to afford pure **3**. The spectroscopic data of representative thienylpyrrolidine **3e** and thienylpiperidine **3h** are provided.

1-[2-(4-Chlorobenzyl)-5-(3-nitrophenyl)-3-thienyl]pyrrolidine, **3e** (Table 1, entry 5): Pale yellow viscous liquid; IR (CH_2Cl_2): 692, 1267, 3052 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.91–1.95 (m, 4H), 3.30 (t, 4H, $J = 6.3$ Hz), 4.17 (s, 2H), 7.11, (s, 1H), 7.21 (d, 2H, $J = 8.1$ Hz), 7.29 (d, 2H, $J = 8.1$ Hz), 7.47 (t, 1H, $J = 8.1$ Hz), 7.78 (d, 1H, $J = 7.8$ Hz), 8.04 (dd, 1H, $J = 8.1$, 1.8 Hz), 8.35 (t, 1H, $J = 1.8$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 25.1, 33.5, 51.8, 118.0, 119.4, 119.6, 121.3, 128.6, 129.6, 129.7, 130.6, 132.1, 136.2, 136.4, 139.3, 147.2, 148.6. Anal. Calcd for $C_{21}H_{19}ClN_2O_2S$: C, 63.23; H, 4.80; N, 7.02. Found: C, 63.25; H, 4.86; N, 7.10.

1-[5-(4-Chlorophenyl)-2-(4-methylbenzyl)-3-thienyl]piperidine, **3h** (Table 1, entry 8): Pale yellow viscous liquid; IR (CH_2Cl_2): 688, 1270, 3050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.54–1.56 (m, 3H), 1.66–1.73 (m, 4H), 2.33 (s, 3H), 2.85 (t, 3H, $J = 5.3$ Hz), 4.08 (s, 2H), 7.11 (d, 2H, $J = 7.8$ Hz), 7.15, (s, 1H), 7.19 (d, 2H, $J = 8.1$ Hz), 7.27 (d, 2H, $J = 8.7$ Hz), 7.43 (d, 2H, $J = 8.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.0, 24.2, 26.5, 32.7, 54.7, 117.7, 126.1, 128.5, 128.8, 129.1, 132.0, 132.5, 133.4, 135.8, 137.6, 138.2, 150.5. Anal. Calcd for $C_{23}H_{24}ClNS$: C, 72.32; H, 6.33; N, 3.67. Found: C, 72.25; H, 6.40; N, 3.75.