Pergamon

Tetrahedron Letters 43 (2002) 3199–3201

TETRAHEDRON
LETTERS

A one-pot synthesis of thiophene and pyrrole derivatives from readily accessible 3,5-dihydro-1,2-dioxines

Cassie E. Hewton, Marc C. Kimber and Dennis K. Taylor*

Department of Chemistry, Adelaide University, South Australia 5005, Australia

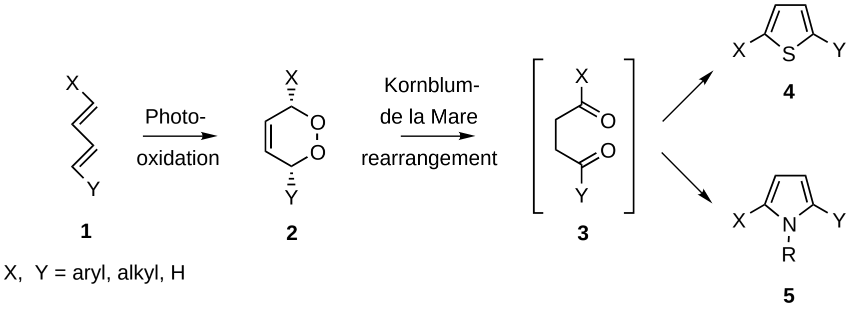
Received 16 January 2002; revised 18 February 2002; accepted 7 March 2002

Abstract—A one-pot synthesis of 2,5-disubstituted thiophene, 1,2,5-tri- and 2,5-disubstituted pyrrole derivatives from readily available 3,5-dihydro-1,2-dioxines is described. The reaction proceeds by an initial Kornblum–de la Mare rearrangement of the 3,5-dihydro-1,2-dioxine to its isomeric 1,4-diketone followed by condensation of the in situ 1,4-diketone with sulfur, ammonia or a primary amine. © 2002 Elsevier Science Ltd. All rights reserved.

The thiophene and pyrrole moieties play important roles in natural products,[1a,b] non-linear optics, and supramolecular chemistry[1c] and therefore, there is significant importance in developing new methods of synthesising these systems. A common approach to the synthesis of both the thiophene and pyrrole group involves the participation of 1,4-dicarbonyl compounds. In the thiophene case,[2a] the 1,4-dicarbonyl compound is reacted with a source of sulfur, usually from phosphorus sulfides such as Lawesson's reagent[2b] or bis(trimethylsilyl)sulfide.[2c] Similarly, pyrroles have traditionally been prepared via the condensation of 1,4-dicarbonyl compounds with ammonia or primary amines, a reaction known as the Paal–Knorr pyrrole synthesis.[3] However, one drawback of these syntheses has been the accessibility of suitable 1,4-dicarbonyl compounds.[4]

3,5-Dihydro-1,2-dioxines **2** can be readily converted into 1,4-dicarbonyl compounds **3** by treatment with an amine base via a Kornblum–de la Mare rearrangement.[5] In turn, 3,5-dihydro-1,2-dioxines **2** can be synthesised from readily available dienes **1** via oxidation in the presence of a photosensitiser and O_2.[6] In this communication we wish to report the first synthesis of thiophene **4** and pyrrole **5** derivatives from 3,5-dihydro-1,2-dioxines **2**. We propose that the reaction involves an initial Kornblum–de la Mare rearrangement of the 3,5-dihydro-1,2-dioxine **2** followed by condensation of the 1,4-dicarbonyl compound **3** in situ with sulfur, ammonia or a primary amine (Scheme 1).

The 3,5-dihydro-1,2-dioxines chosen for this study were **2a**–**d** (Scheme 2). They were efficiently synthesised from their parent dienes **1a**–**d** via photo-oxidation.[6] The

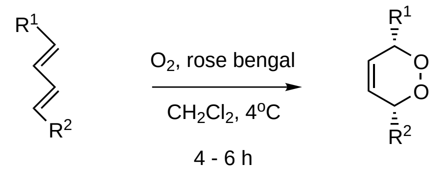


Scheme 1.

Keywords: substituted thiophenes; substituted pyrroles; 1,2-dioxines; Paal–Knorr reaction.

* Corresponding author. Tel.: (+61) 8 8303 5494; fax: (+61) 8 8303 4358; e-mail: dennis.taylor@adelaide.edu.au

PII: S0040-4039(02)00503-8



1a, $R^1 = R^2 = Ph$

1b, $R^1 = Ph$, $R^2 = 4\text{-Br-Ph}$

1c, $R^1 = Ph$, $R^2 = Me$

1d, $R^1 = Ph$, $R^2 = H$

2a-d

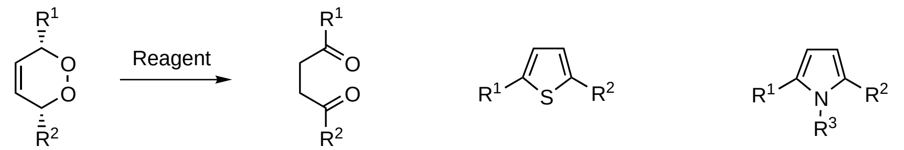
Scheme 2.

photo-oxidation reaction consisted of irradiation (three tungsten halogen lamps, 500 W, 6 h) of a solution of the diene in dichloromethane in the presence of the photosensitiser rose bengal (bis(triethylammonium) salt), at 4°C with a stream of O_2 passing through the solution. Although **2a**, **2c** and **2d** have been previously reported, we synthesised **2b**[7] since it contains the 4-bromophenyl grouping, a potential 'synthetic handle' which could be utilised in future studies, e.g. palladium-mediated couplings.

The reaction of 1,2-dioxines **2a–d** with Lawesson's reagent, *n*-butylamine or ammonium carbonate was then investigated. The results are shown below in Scheme 3 and Table 1.

For the synthesis of thiophenes **4a–d**, we chose dimethylformamide (DMF) as the solvent since we hoped that the Kornblum–de la Mare rearrangement of the 1,2-dioxines **2** to the isomeric 1,4-diketones **3** would be facilitated in this solvent. Hence, the reaction of 1,2-dioxines **2a–c** with Lawesson's reagent in DMF at 100°C resulted in good yields of the thiophenes **4a–c**, respectively (entries 1, 2 and 3). However, the reaction of **2d** with Lawesson's reagent gave a lower yield of **4d** as compared to those for **4a–c**, under similar conditions (entry 4). This may be due to the instability of the thiophene **4d** at elevated temperatures.

1,2,5-Trisubstituted pyrroles **5a** and **5b** were synthesised under different conditions to those used for thiophenes **4a–d**. DMF was not required for the rearrangement of the 1,2-dioxine to its 1,4-diketone since the basicity of the reagent, *n*-butylamine, could be utilised. Hence, refluxing methanol was used in place of DMF. Under these conditions 3,5-dihydro-1,2-dioxines **2a** and **2b** were each treated with excess *n*-butylamine in refluxing methanol for 16 h to furnish the 1,2,5-trisubstituted pyrroles **5a** and **5b**, respectively, in good yields (entries 5 and 6).[8] However, when 1,2-dioxines **2a** and **2b** were treated with ammonium carbonate in refluxing methanol only the isomeric 1,4-diketones **3a** and **3b** were obtained, both in near quantitative yields (entries 7 and 9). This was rectified when the lower boiling methanol was replaced by DMF as the solvent, furnishing the desired 2,5-disubstituted pyrroles **5c** and **5d** in



2a-d

3a, $R^1 = R^2 = Ph$

3b, $R^1 = Ph$, $R^2 = 4\text{-Br-Ph}$

4a, $R^1 = R^2 = Ph$

4b, $R^1 = Ph$, $R^2 = 4\text{-Br-Ph}$

4c, $R^1 = Ph$, $R^2 = Me$

4d, $R^1 = Ph$, $R^2 = H$

5a, $R^1 = R^2 = Ph$, $R^3 = {}^{n}Bu$

5b, $R^1 = Ph$, $R^2 = 4\text{-Br-Ph}$, $R^3 = {}^{n}Bu$

5c, $R^1 = Ph$, $R^2 = Me$, $R^3 = H$

5d, $R^1 = Ph$, $R^2 = R^3 = H$

Scheme 3.

Table 1. Reaction of 1,2-dioxines **2a–d** with Lawesson's reagent, *n*-butylamine or ammonium carbonate to generate thiophenes **4a–d** and pyrroles **5a–d**

Entry	1,2-Dioxine	Solvent	Reagent	Product	Yield (%)[a,b]
1	**2a**	DMF	Lawesson's	**4a**	62
2	**2b**	DMF	Lawesson's	**4b**	85
3	**2c**	DMF	Lawesson's	**4c**	72
4	**2d**	DMF	Lawesson's	**4d**	57
5	**2a**	MeOH	$n\text{-BuNH}_2$	**5a**	85
6	**2b**	MeOH	$n\text{-BuNH}_2$	**5b**	65
7	**2a**	MeOH	NH_4CO_3	**3a**	95
8	**2a**	DMF	NH_4CO_3	**5c**	65
9	**2b**	MeOH	NH_4CO_3	**3b**	96
10	**2b**	DMF	NH_4CO_3	**5d**	70

[a] Yields of isolated and purified products.

[b] All known compounds displayed physical and chemical data consistent with those already published apart from **5b**, which was fully characterised.

moderate yields of 65 and 70%, respectively (entries 8 and 10).

n conclusion, this communication demonstrates the first reported one-pot synthesis of substituted thiophenes and pyrroles from 3,5-dihydro-1,2-dioxines. This methodology involves the participation of a 1,4-diketone, derived from the Kornblum–de la Mare rearrangement of the 3,5-dihydro-1,2-dioxine precursor. If suitable dienes were available for the synthesis of the 3,5-dihydro-1,2-dioxines, then the synthesis of a large range of substituted thiophenes and pyrroles would be possible.

Acknowledgements

This work was supported by the Australian Research Council (ARC).

References

1. (a) For pyrroles, see: Boger, D. L.; Boyee, C. W.; Labrili, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54 and references cited therein; (b) For thiophenes, see: Bohlmann, F.; Zdero, C. In *The Chemistry of Heterocyclic Compounds*, *Thiophene and its Derivatives*; Gronowitz, S., Ed.; Wiley: New York, 1985; Vol. 44, Part 1, p. 261; (c) Lehn, J.-M. *Supramolecular Chemistry*; *Concepts and Perspectives*; VCH: Weinheim, New York, 1995.
2. (a) For general methods, see: Gronowitz, S. In *The Chemistry of Heterocyclic Compounds*, *Thiophene and its Derivatives*; Gronowitz, S. Ed.; Wiley: New York, 1985; Vol. 44, Part 1, p. 1; (b) Jones, R. A.; Civcir, P. U. *Tetrahedron* **1997**, *53*, 11529; (c) Freeman, F.; Lee, M. Y.; Lu, H.; Wang, X.; Rodriguez, E. *J. Org. Chem.* **1994**, *59*, 3695.
3. (a) Knorr, L. *Chem. Ber.* **1884**, *17*, 1635; (b) Patterson, J. M. *Synthesis* **1976**, 281 and references cited therein; (c) Bean, G. P. In *The Chemistry of Heterocyclic Compounds*, *Pyrroles*; Jones, R. A., Ed.; Wiley: New York, 1990; Vol. 48, Part 1, p. 105.
4. For recent examples of pyrrole syntheses from 1,4-diketone precursors, see: (a) Surya Prakash Rao, H.; Jothilingham, S. *Tetrahedron Lett.* **2001**, *42*, 6595; (b) Braun, R. U.; Zeitler, K.; Muller, T. J. J. *Org. Lett.* **2001**, *3*, 3297.
5. (a) Kornblum, N.; de la Mare, H. *J. Am. Chem. Soc.* **1951**, *73*, 881; (b) Sengul, M. E.; Ceylan, Z.; Balci, M. *Tetrahedron* **1997**, *53*, 10401.
6. (a) Clennan, E. L. *Tetrahedron* **1991**, *47*, 1343 and references cited therein; (b) Avery, T. A.; Taylor, D. K.; Tiekink, E. R. T. *J. Org. Chem.* **2000**, *65*, 5531.
7. Spectral data for 3-(4-bromophenyl)-6-phenyl-3,6-dihydro-1,2-dioxine **2b**. Yield 35%; mp 83–84°C; IR (Nujol) 1774, 1681, 1590 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 5.57–5.58 (m, 1H), 5.67–5.70 (m, 1H), 6.26–6.37 (m, 2H), 7.32–7.45 (m, 7H), 7.50–7.54 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 79.2, 80.2, 122.7, 126.6, 127.9, 128.3, 128.5, 128.8, 129.9, 131.6, 136.9, 137.1; MS m/z (%) 318 (M$^+$, 10), 316 (12), 286 (78), 284 (76), 205 (65), 105 (85), 77 (100); HRMS calcd for $C_{16}H_{13}BrO_2$, 318.0079, found 318.0067.
8. A typical method. A solution of 1,2-dioxine **2b** (0.32 g, 1 mmol) and *n*-butylamine (0.17 g, 2.2 mmol) in dry methanol (5 ml) was heated to reflux for 16 h under N_2. The reaction was then allowed to cool and the solvent removed under reduced pressure to yield an orange oil. The crude mixture was then purified by chromatography (CH_2Cl_2) to yield 2-(4-bromophenyl)-1-butyl-5-phenyl-1*H*-pyrrole **5b** (0.23 g, 65%); mp 108–110°C; IR (Nujol) 1598, 1376, 1202 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 0.58 (t, J=7.2 Hz, 3H), 0.82–0.91 (m, 2H), 1.15–1.24 (m, 2H), 4.07 (t, J=7.5 Hz, 2H), 6.28 (s, 2H), 7.33–7.38 (m, 3H), 7.43–7.49 (m, 4H), 7.56–7.58 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 13.3, 19.3, 32.7, 45.0, 109.5, 109.8, 127.0, 120.8, 128.4, 128.9, 130.3, 131.6, 133.1, 133.9, 135.1, 137.1; MS m/z (%) 355 (M$^+$, 98), 353 (100), 312 (99), 310 (97), 299 (38), 297 (40), 231 (33), 217 (45), 115 (25); HRMS calcd for $C_{20}H_{20}BrN$, 353.0780, found 353.0786.