Tetrahedron Letters 51 (2010) 6000–6002

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Solvent free oxidative radical substitution process. Synthesis of pyrrole fused systems

Edwin Flórez-López, Liliana B. Gomez-Pérez, Luis D. Miranda *

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacan, México D.F. 04510, Mexico

ARTICLE INFO

Article history:
Received 13 August 2010
Revised 7 September 2010
Accepted 8 September 2010
Available online 21 September 2010

ABSTRACT

A xanthate-based, solvent free, homolytic substitution on selected substituted pyrrole systems is described. Additionally, a practical entry for the rapid construction of pyrrole fused systems using this solventless radical addition followed by a double nucleophilic alkylation sequence, is also reported.

Pyrrole fused cyclic systems are broadly distributed in nature.[1] These motifs are part of the framework of a number of natural and synthetic molecules, some of which display antitumor and anti-HIV activity, as well as antibacterial, analgesic, and antiinflammatory properties.[2] Ketorolac, **1** a five-membered pyrrole fused system for example, is a prescription synthetic medicine approved for the short-term treatment of moderate to severe pain (Fig. 1).[3] Poligotin B (**2**) and pilogotin A (**3**) are examples of a six-membered pyrrole fused systems which were isolated from the extracts of *Poliganotum sibircum*.[4] A seven-membered pyrrole fused systems is found in the natural product dehydrotuberoestemonine **4** that was isolated from *Esteromona tuberose*.[5] Thus, the development of practical protocols that provide rapid access to pyrrole fused systems is of great synthetic significance.

Intermolecular oxidative homolytic substitution of aromatic heterocyclic systems is a synthetically important C–C bond formation process, which often gives access to molecular scaffolds which can be difficult to construct by other methods.[6]

We have previously shown that certain substituted pyrrole derivatives could be alkylated in synthetically useful yields via a xanthate-based homolytic oxidative substitution process.[7] Conditions typical of this process involve the slow addition of dilauroyl peroxide (used as both the initiator and oxidant) to a boiling, 1,2-dichloroethane solution of the xanthate and the substituted pyrrole derivatives.[6a] We wondered if the product yields in these oxidative radical substitution processes could be improved by conducting the reactions under solvent free conditions. In the mechanism of xanthate-based radical chemistry depicted in Scheme 1, the radical **6** derived from the thermal fragmentation of a suitable initiator reacts with the thiocarbonyl group to afford the key intermediate radical **7a** that evolves to the desired radical **8** by a reversible β-fragmentation.[8] Solvent free radical polymerization reactions are now well documented,[9] but except for some scattered examples, the use of such methodology in free radical based organic synthesis is less known.[10] Indeed, the concept of solvent free radical reactions[3] might appear to be counterintuitive since a high radical concentration could well favor undesired fast radical dimerization and/or combination reactions. Nevertheless, given the mechanism of xanthate-based radical reactions, (Scheme 1),

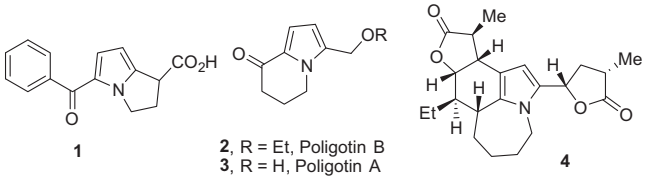
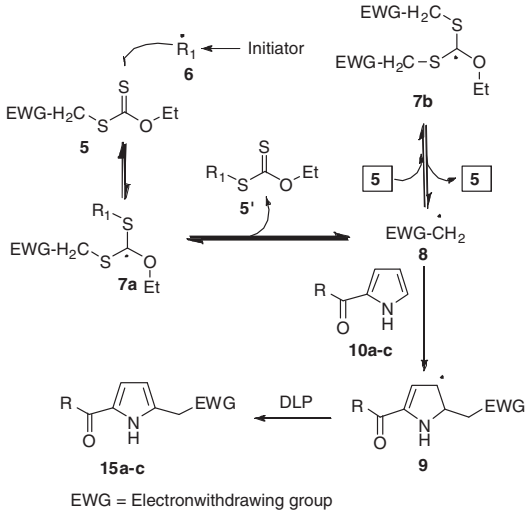


Figure 1.



Scheme 1. Mechanism for the xanthate-based radical chemistry.[8]

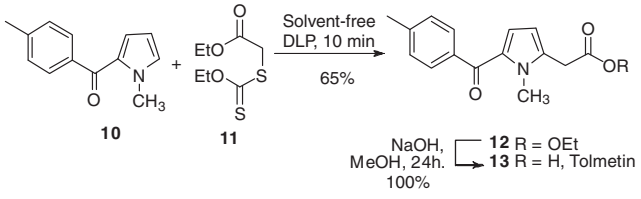
* Corresponding author. Tel.: +52 55 56 22 44 40; fax: +52 55 56 16 22 17.
E-mail address: lmiranda@unam.mx (L.D. Miranda).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.09.025

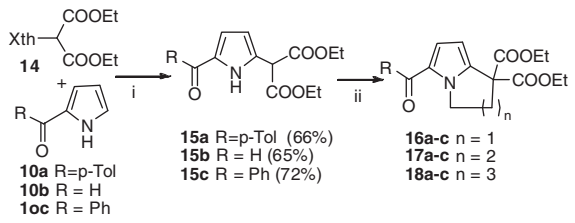
an excess of the xanthate radical precursor **5** should favor the reversible degenerate formation of the stabilized radical species **7b**.[8] This addition/elimination process between the species **8** and **7a** could well serve as a relatively long lived reservoir of the radical **8**, until the latter has encountered a suitable radical trap, for example, a substituted pyrrole such as **10a–c** (Scheme 1).[8] Indeed, Zard and co-workers have reported that high substrate concentrations (ca. 0.25 mol) are associated with improved product yields in xanthate-based radical reactions.[8] Building up on this effect we hypothesized that the xanthate-based technology might be used in oxidative homolytic substitutions under solvent free conditions for selected substrates, specifically if an excess of a liquid starting xanthate is used (Scheme 1).

To test our hypothesis we chose the reaction between the 2-*p*-toluoylpyrrole derivative **10** and the liquid xanthate **11** to afford the ethyl ester of the non-steroidal antiinflammatory agent tolmetin (**12**, Scheme 2). After considerable experimentation, it was found that the optimal conditions involved the use of 2.0 equiv of the xanthate and 2.0 equiv of DLP. Interestingly the excess of the liquid xanthate served as the solvent for the solid pyrrole substrate resulting in the formation of a homogeneous medium. Thus, the solid DLP (mp 55 °C) was added portionwise at the end of each minute, during a 10-min period, to the reaction mixture that was maintained at 100 °C (CAUTION if the DLP is added in one portion a violent reaction is observed). After each addition of DLP, gas evolution (CO_2), accompanied by a slight rise in the temperature, was observed. Indeed, in some cases, if the size and timing of the DLP additions were carefully adjusted, the reaction temperature (100 °C) could be maintained without external heating. Under the optimized conditions the expected product **12** was obtained in a yield similar to that observed under typical solution conditions (65% in refluxing dichloroethane, addition of DLP for 8 h). Hydrolysis of **12** under standard conditions afforded the non-steroidal antiinflammatory agent tolmetin[11] **13** in quantitative yield (65% overall yield from **10**).

We then turned our attention to the use of this process to construct pyrrole fused systems using the disubstituted pyrrole derivatives obtained from the solvent free direct alkylation of selected substituted pyrroles with malonyl xanthate derivative **14**. Thus the solvent free radical alkylation reactions proceeded in generally good yields when 2-*p*-toluoyl, 2-formyl, and 2-benzoyl pyrroles were used as the radical acceptor (**15a–c** Scheme 3). Then, the corresponding five-, six-, and seven-membered pyrrole fused systems

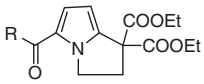
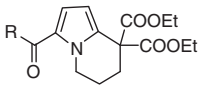
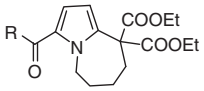


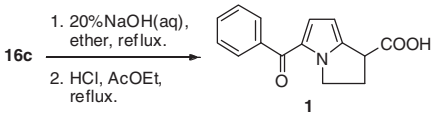
Scheme 2. Synthesis of tolmetin (**13**).



Scheme 3. Reagents and conditions: (i) DLP, solvent free conditions, 10 min; (ii) K_2CO_3, NBu_4Br, 2 h, **19a–c**, see Table 1.

Table 1
Annulation process of adducts **15a–c**

Entry	Reagent	Product	Yield (%)
1	 **19a**		**16a** R = *p*-tol (85) **16b** R = H (78) **16c** R = Ph (77)
2	 **19b**		**17a** R = *p*-tol (81) **17b** R = H (78) **17c** R = Ph (85)
3	 **19c**		**18a** R = *p*-tol (75) **18b** R = H (77) **18c** R = Ph (70)



Scheme 4. Synthesis of ketorolac (**1**).

16–18 were then efficiently constructed when adducts of the free radical process **15a–c** simply were submitted to a double alkylation process with a suitable α,ω-dibromoalkyl compound **19a–c** under basic phase-transfer conditions (Table 1).[12] It is noteworthy that all of these strategically substituted pyrrole fused systems represent valuable synthetic intermediates in the construction of pharmacologically important natural or synthetic targets. Along this line, the potent analgesic ketorolac **1** was obtained by the hydrolysis/decarboxylation process of **16c** in good yields as described previously (Scheme 4).[12a] Thus the synthesis of this latter product was accomplished in three steps from readily available 2-benzoylpyrrole in 44% overall yield.

The unprecedented xanthate-based homolytic solvent free substitution of selected pyrrole derivatives described in the present Letter, demonstrates that the high selectivity of a free radical process even under putatively high radical concentration conditions. Additionally, the radical addition/double alkylation sequence featured in this Letter represents a practical entry for the rapid construction of pyrrole fused systems.

Acknowledgments

Financial support from the DGAPA, UNAM (project PAPIIT-IN213407) is gratefully acknowledged. We also thank R. Patiño, A. Peña, E. Huerta and E. García-Rios, L. Velasco, and J. Pérez for technical support. EFL is a CONACyT graduate scholarship holder.

Supplementary data

Supplementary data (experimental procedures and ^1H and ^{13}C NMR spectra for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.09.025.

References and notes

1. (a)For reviews on pyrrole, see: *Comprehensive Heterocyclic Chemistry*; Sundberg, R. J., Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2, pp 119–206; (b) Sobenina, L. N.; Demenev, A. P.; Mikhaleva, A. L. *Chem. Rev.* **2004**, *104*, 2481.
2. d'Ischia, M.; Napolitano, A.; Pezzella, A.. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J., Eds.; Elsevier, 2008; Vol. 3, pp 353–588.
3. Muchowski, J. M.. In *Advances in Medicinal Chemistry*; Jai Press Inc., 1992; Vol. 1. p 109.

4. (a) Sun, L.-R.; Wang, S.-X.; Li, X. *J. Asian Nat. Prod. Res.* **2005**, *7*, 127; (b) Dinsmore, A.; Mandy, K.; Michael, J. P. *Org. Biomol. Chem.* **2006**, *4*, 1032.
5. (a) Tanis, S. P.; Raggonlb, J. W. *J. Org. Chem.* **1987**, *52*, 819; (b) Jiang, R. W.; Hon, P. M.; Zhou, Y.; Chan, Y. M.; Xu, Y. T.; Xu, H. X.; Greger, H.; Shaw, P. C.; But, P. H. *J. Nat. Prod.* **2006**, *69*, 749; (c) Frankowski, K. J.; Golden, J. E.; Zeng, Y.; Lei, Y.; Aubé, J. *J. Am. Chem. Soc.* **2008**, *130*, 6018; (d) Zhou, X.; Leung, P. H. H.; Li, N.; Ye, Y.; Zhang, L.; Zuo, Z.; Lin, G. *Planta Med.* **2009**, *75*, 575; (e) Lin, W.-H.; Ye, Y.; Xu, R.-S. *J. Nat. Prod.* **1992**, *55*, 571.
6. For a review see: (a) Bowman, W. R.; Storey, J. M. D. *Chem. Soc. Rev.* **2007**, 1803; (b) Bowman, W. R.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747. and references therein.
7. (a) Osornio, Y. M.; Cruz-Almanza, R.; Jiménez-Montaño, V.; Miranda, L. D. *Chem. Commun.* **2003**, 2316; (b) Guerrero, M. A.; Miranda, L. D. *Tetrahedron Lett.* **2006**, *47*, 2517; (c) Guadarrama-Morales, O.; Méndez, F.; Miranda, L. D. *Tetrahedron Lett.* **2007**, *48*, 4515; (d) Reyes-Gutiérrez, P. E.; Torres-Ochoa, R. O.; Martínez, R.; Miranda, L. D. *Org. Biomol. Chem.* **2009**, *7*, 1388; See also: (e) Furst, L.; Matsuura, B. S.; Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. *J. Org. Lett.* **2010**, *12*, 3104.
8. (a) Quiclet-Sire, B.; Zard, S. Z. *Chem. Eur. J.* **2006**, *12*, 6002; (b) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201; (c) Zard, S. Z. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley VCH: Weinhem, 2001; p 90; (d) Zard, S. Z. *Angew. Chem., Int. Ed.* **1997**, *36*, 672; (e) Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **1997**, *69*, 645; (f) Zard, S. Z. *Actual. Chim.* **1993**, 10.
9. Odell, P. G.; Listigovers, N. A.; Quinlan, M. H.; Georges, M. K. *ACS Symp. Ser.* **1998**, *713*, 80.
10. (a) Jereb, M.; Zupan, M.; Stavber, S. *Helv. Chim. Acta* **2009**, *92*, 555; (b) Metzger, J. O.; Mahler, R.; Francke, G. *Liebigs Ann. Recl.* **1997**, *11*, 2303; (c) Metzger, J. O.; Mahler, R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 902–904.
11. Carson, J. R.; McKinstry, D. N.; Wong, S. *J. Med. Chem.* **1971**, *14*, 646.
12. (a) Artis, D. R.; Cho, I.-S.; Muchowski, J. M. *Can. J. Chem.* **1992**, *70*, 1838; (b) Schloemer, G. C.; Greenhouse, R.; Muchowski, J. M. *J. Org. Chem.* **1994**, *59*, 5230.