ChemComm

This article is part of the

Mechanochemistry: fundamentals and applications in synthesis

web themed issue

Guest editors: Stuart James and Tomislav Friščić

All articles in this issue will be gathered together online at <u>www.rsc.org/mechanochemistry</u>



ChemComm

COMMUNICATION

Cite this: Chem. Commun., 2013, 49, 591

Received 8th November 2012, Accepted 26th November 2012

DOI: 10.1039/c2cc38099d

www.rsc.org/chemcomm

Published on 27 November 2012 on http://pubs.rsc.org | doi:10.1039/C2CC38099D

Downloaded by Universiteit Utrecht on 21 March 2013

Three-component access to pyrroles promoted by the CAN–silver nitrate system under high-speed vibration milling conditions: a generalization of the Hantzsch pyrrole synthesis^{†‡}

Verónica Estévez, Mercedes Villacampa and J. Carlos Menéndez*

A sequential multicomponent process involving the high-speed vibration milling of ketones with *N*-iodosuccinimide and *p*-toluenesulfonic acid, followed by addition of a mixture of primary amines, β -dicarbonyl compounds, cerium(w) ammonium nitrate and silver nitrate afforded polysubstituted, functionalized pyrroles. This one-pot, solid-state process can be considered as the coupling of an α -iodoketone preparation with a general version of the classical Hantzsch pyrrole synthesis.

Multibond forming reactions are one of the primary strategies to be considered in the search for synthetic efficiency. Furthermore, they are also particularly important in the current effort for the development of environmentally sustainable synthetic processes, since they avoid the generation of waste from solvents and chromatographic stationary phases in the purification of synthetic intermediates.¹ Multicomponent reactions (MCRs)^{2,3} are one of the best studied types of multibond forming processes, but the combination of MCRs and other methodologies aimed at reducing reaction waste is not so common. More specifically, we are aware of a single reference that describes a multicomponent reaction under solvent-free, mechanochemical conditions,⁴ and it has the limitation of requiring special equipment with fittings for circulating boiling water. The term "mechanochemistry" refers to reactions induced by mechanical energy, including grinding and ball milling, and it constitutes an emerging field of synthetic methodology that is particularly relevant because the reactions are normally performed in the solid state, avoiding or minimizing the use of solvents and offering many opportunities for the development of cleaner synthetic methods.⁵

Pyrrole is one of the most important simple heterocycles; it can be found as a structural fragment of many natural products⁶ and drugs such as the top-selling cholesterol-lowering drug atorvastatin,⁷ and it is also very important in materials science.⁸

In spite of the existence of a variety of approaches to substituted pyrroles, including the classical Knorr, Paal–Knorr and Hantzsch reactions, their synthesis remains challenging because it often poses difficult problems of regioselectivity and is often complicated by the low chemical stability of many pyrrole derivatives, which leads to their degradation unless the reaction conditions are very mild. Therefore, the efficient synthesis of highly substituted pyrroles remains far from trivial.

RSC Publishing

In view of its named reaction status, it is surprising that the Hantzsch pyrrole synthesis has received little attention in the literature. In a study published in 1970, Roomi and MacDonald mentioned that, in spite of the 80 year period elapsed since Hantzsch's original publication, which describes a single experiment,⁹ they had located only eight additional examples in the literature, proceeding in yields below 45% and allowing very little structural variation, which was limited to alkyl substituents at C-4 and C-5. These authors extended slightly the scope of the reaction and prepared compounds with substituents different from methyl at C-2 and esters different from ethyl at C-3, and they also obtained pyrroles with $R_5 = H$. Nevertheless, yields remained below 50% and the preparation of N-substituted pyrroles was not possible.10 More recent examples of the Hantzsch pyrrole synthesis under traditional conditions still suffer from these limitations. Recently, three-component variations of the Hantzsch pyrrole synthesis have been reported under non-conventional conditions, but they lack generality. In 1998, Jung et al. reported a solid phase version of the reaction,¹¹ which allowed the preparation of N-substituted pyrroles (but not of their unsubstituted counterparts) and was restricted to a methyl group at C-2 and a carbamoyl at C-3. On the other hand, it allowed the introduction of aryl substituents at C-4 and, in one case, at C-5. However, the authors failed to report any yields. The latest significant advancement in this area was due to Herath and Cosford and involved the use of flow conditions, which were focused on the preparation of carboxylic acids and their subsequent transformation into amides, although they also examined the synthesis of some esters during preparatory studies. Very high temperatures (200 °C) were required, although reaction times were short (8 min).¹²

Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense, 28040 Madrid, Spain. E-mail: josecm@farm.ucm.es; Fax: +34 913941822; Tel: +34 913941840

[†] This article is part of the *ChemComm* 'Mechanochemistry' web themed issue. ‡ Electronic supplementary information (ESI) available: Experimental

procedures and copies of spectra of all compounds. See DOI: 10.1039/c2cc38099d

In the context of our current research into MCRs based on the use of β -dicarbonyl building blocks for the synthesis of heterocycles, we became interested in realizing the full synthetic potential of the Hantzsch synthesis of pyrroles by development of a new multicomponent protocol¹³ that overcame its shortcomings and allowed it to be regarded as a truly general pyrrole synthesis. We also wished this method to proceed under solvent-free conditions and, to this end, we decided to use high-speed vibration milling (HSVM), a ball-milling technique that can be performed with very simple and affordable instruments but that has found little application in synthesis, especially in terms of the generation of carbon–heteroatom bonds.¹⁴

As shown in Scheme 1, the desired transformation was initiated by the milling-promoted reaction between ketones 1 and N-iodosuccinimide in the presence of p-toluenesulfonic acid. After 60 min of operation at a frequency of 20 Hz, a mixture of primary amines 2, β -dicarbonyl compounds 3, 5% of cerium(IV) ammonium nitrate (CAN)¹⁵ and silver nitrate (1 eq. with respect to 1) was added and milling was continued for an additional hour under the same conditions, leading to the formation of desired pyrroles 4. The mechanism of this process can be rationalized as a sequence of reactions starting from the initial α -iodination of the starting ketone **1**, which was verified by interrupting one of the reactions at this stage and identifying the corresponding intermediate I. The CAN-catalyzed reaction between the primary amine 2 and the β -dicarbonyl compound 3 affords the corresponding β -enaminone II,¹⁶ which then reacts with I to give III and a molecule of HI, which is trapped by silver nitrate. In the absence of silver nitrate, the liberated HI reacts with intermediate I, leading to its reductive dehalogenation to the starting compound 1 and lowering the yield of pyrrole.¹⁷ A final cyclocondensation, with loss of a molecule of water, affords the pyrrole products 4. The intermediacy of II was proved by the fact that an experiment starting from an isolated β-enaminone led to the same result as the multicomponent reaction.

The scope of the pyrrole synthesis was much broader than the one described in the literature for previous variations of the Hantzsch reaction. As shown in Fig. 1, our method could be adapted to the preparation of pyrroles bearing the following types of substituents at nitrogen: aryl (compound **4a**), primary



Scheme 1 Sequential three-component pyrrole synthesis.

alkyl (compounds 4b, 4d and 4f-p) secondary alkyl (4c) and dialkylamino (4e). Unsubstituted pyrroles (compounds 4q, r) were also accessible by employing commercially available ethyl 2-aminocrotonate as starting material. The possibility of having R₂ substituents different from methyl, including a side chain ending in an ester function, was also verified (compounds 4f-h). Regarding the carbonyl function at the pyrrole C-3 position, we normally prepared compounds having an ester (4a-h and 4k-r), but also demonstrated the possibility of introducing ketone (4i) and amide (4j) groups. Our method also accommodated the preparation of 4,5-disubstituted pyrroles (compounds 40 and 4p), which is not possible via previous Hantzsch-like strategies. Finally, a variety of aromatic substituents were introduced at the pyrrole C-5 position, including phenyl and its derivatives (compounds 4a-i and 4o-r), 2-naphthyl (4k), 3-indolyl (4l) and 2-thienyl (4m). It was also possible to have alkyl substituents at



Fig. 1 Scope of the pyrrole synthesis. ^aThe α -iodoketone derivatives were isolated from 1 and I₂ in the presence of CuO (4I and 4m)¹⁸ or by α -bromination of 1 with HBr/H₂O₂¹⁹ followed by exchange with NaI (4p).



Fig. 2 Compounds obtained in pseudo five-component double Hantzsch-like reactions.

C-5, as shown by the preparation of compound **4n**. In all cases, the reactions were complete after 2 h at room temperature and normally proceeded in good to excellent yields.

In order to further prove the flexibility of the method for the generation of molecular complexity, we examined two types of pseudo five-component reactions leading to the generation of two pyrrole rings. In the first example, use of 1,1'-(biphenyl-4,4'-diyl)diethanone (1 eq.), ethyl acetoacetate (3 eq.) and butyl-amine (3 eq.) as the starting materials afforded the quater-aryl derivative **4s** in an excellent 94% yield. Double Hantzsch-like reactions based on the use of diamines as starting materials were also possible. Thus, the reaction involving ethylenediamine and excess acetophenone and ethyl acetoacetate furnished compound **4t** in 60% yield (Fig. 2).

In conclusion, we have developed a sequential multicomponent synthesis of polysubstituted, functionalized pyrroles under solvent-free mechanochemical conditions and using ketones, primary amines and β -dicarbonyl compounds as building blocks. This one-pot process proceeds entirely in the solid-state and can be viewed as the coupling of α -iodoketone preparation with a general version of the classical Hantzsch pyrrole synthesis. Furthermore, it is the first multicomponent reaction carried out under high-speed vibration milling conditions using a simple instrument without temperature control and with the sole input of mechanical energy. Our protocol proceeded in a 77% average yield for the 20 examples studied, generating one cycle, one C–C and two C–N bonds.

Financial support from MICINN (grants CTQ2009-12320-BQU and CTQ2012-33272), UCM (Grupos de Investigación, grant GR35/10-A-920234) and CAM (fellowship to VE) is gratefully acknowledged.

Notes and references

- 1 For a review of multibond forming reactions as a pathway towards eco-compatible chemistry, see: Y. Coquerel, T. Boddaert, M. Presset, D. Mailhol and J. Rodriguez, Ideas in Chemistry and Molecular Sciences, in *Advances in synthetic chemistry*, ed. B. Pignataro, Wiley-VCH, Weinheim, vol. 1, ch. 9, 2010.
- 2 For a recent monograph, see: E. Ruijter and R. V. A. Orru, Synthesis of heterocycles *via* multicomponent reactions, vol. 1 and 2, Springer Verlag, 2010 (Topics in Heterocyclic Chemistry series, volumes 23 and 25).
- 3 For selected recent reviews, see: (a) A. Dömling, Chem. Rev., 2006, 106, 17; (b) B. B. Touré and D. G. Hall, Chem. Rev., 2009, 109, 4439; (c) E. Ruijter, R. Scheffelaar and R. V. A. Orru, Angew. Chem., Int. Ed., 2011, 50, 6234; (d) H. Eckert, Molecules, 2012, 17, 1074; (e) C. de Graaff, E. Ruijter and R. V. A. Orru, Chem. Soc. Rev., 2012, 41, 3969.
- 4 S. Mashkouri and M. R. Naimi, *Molecules*, 2009, 14, 474.
- 5 For a review, see: S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed and D. C. Waddelli, *Chem. Soc. Rev.*, 2012, 41, 413.
- 6 A. Fürstner, Angew. Chem., Int. Ed., 2003, 42, 3582.
- 7 B. D. Roth, Prog. Med. Chem., 2002, 40, 1.
- For selected reviews, see: (a) A. Berlin, B. Vercelli and G. Zotti, *Polym. Rev.*, 2008, 48, 493; (b) S. J. Higgins, *Chem. Soc. Rev.*, 1997, 26, 247.
 A. Hantzsch, *Ber. Dtsch. Chem. Ges.*, 1890, 23, 1474.
- 10 M. W. Roomi and S. F. MacDonald, Can. J. Chem., 1970, 48, 1689.
- 11 A. W. Trautwein, R. D. Süssmuth and G. Jung, *Bioorg. Med. Chem. Lett.*, 1998, 8, 2381.
- 12 A. Herath and N. D. P. Cosford, Org. Lett., 2010, 12, 5182.
- 13 For a review of the synthesis of pyrroles by multicomponent strategies, see: V. Estévez, M. Villacampa and J. C. Menéndez, *Chem. Soc. Rev.*, 2010, **39**, 4402.
- 14 For the use of HSVM in the formation of C-C bonds, see:
 (*a*) B. Rodríguez, A. Bruckmann, T. Rantanen and C. Bolm, *Adv. Synth. Catal.*, 2007, 349, 2213; (*b*) for a general review of the use of ball mills as reactors in organic synthesis, see: A. Stolle, T. Szuppa, S. E. S. Leonhardt and B. Ondruschka, *Chem. Soc. Rev.*, 2011, 40, 2317.
- 15 For a review of the use of CAN as a catalyst in organic synthesis, see: V. Sridharan and J. C. Menéndez, *Chem. Rev.*, 2010, **110**, 3805.
- 16 CAN catalysis allows the very fast generation of β -enaminones from amines and β -dicarbonyl compounds: V. Sridharan, C. Avendaño and J. C. Menéndez, *Synlett*, 2007, 2133.
- 17 For precedent of a related reductive dehalogenation of a phenacyl iodide by HI, see: R. Seshadri, W. J. Pegg and M. Israel, *J. Org. Chem.*, 1981, **46**, 2596.
- 18 G. Yin, M. Gao, N. She, S. Hu, A. Wu and Y. Pan, Synthesis, 2007, 3113.
- 19 A. Podgoršek, S. Stavber, M. Zupan and J. Iskra, *Green Chem.*, 2007, 9, 1212.