Green Chemistry

Cite this: *Green Chem.*, 2012, **14**, 1597

www.rsc.org/greenchem

COMMUNICATION

Mechanosynthesis of nitrosobenzenes: a proof-of-principle study in combining solvent-free synthesis with solvent-free separations†

Igor Huskić,[a] Ivan Halasz,*[a] Tomislav Friščić[b] and Hrvoj Vančik[a]

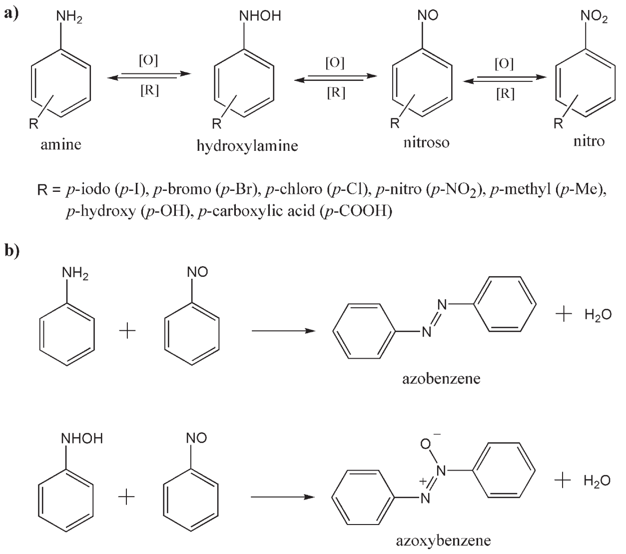
Received 20th March 2012, Accepted 17th April 2012
DOI: 10.1039/c2gc35410a

Mechanochemical *Oxone* oxidation of selected *para*-substituted anilines was used as a rapid and solvent-free route to nitrosobenzenes; besides avoiding bulk solvents and short reaction times, this method exploits high vapour pressures of nitrosobenzenes for the solvent-free separation of the product by sublimation, demonstrating an entirely solvent-free route to chemical synthesis and product isolation.

Interest in mechanosynthesis has rapidly increased in the past decade, through the realisation that mechanosynthesis is a solvent-free‡ and low-energy pathway[1] to organic molecules,[2] pharmaceutical materials and materials based on coordination bonds (*e.g.* metallodrugs, metallopharmaceuticals and porous metal–organic frameworks, MOFs).[3] Mechanochemistry has been used with great success for organic coupling reactions and condensations, including imine condensations,[4] [2 + 3] click coupling;[5a] Diels–Alder cycloadditions,[5b] Michael additions,[5c,d] Wittig reactions,[5e] Morita–Baylis–Hillman reactions[5f] as well as palladium-catalyzed Suzuki[6a] and Sonogashira reactions.[6b,c] Remarkable results have been obtained by applying mechanochemistry to organocatalytic reactions, especially in asymmetric catalysis[7a,b] and [2 + 2] photocycloadditions.[7c] Despite numerous successes, there are two principal obstacles to establish mechanochemistry as a viable alternative to solution-based synthesis. Firstly, the development of methods for functional group interconversion,[8] which is the basis for systematic organic chemistry, has so far not been adequately addressed. Secondly, whereas a number of mechanochemical reactions proceed in quantitative yields and their products can be structurally analysed *via* completely solvent-free routines (*e.g.* using powder X-ray diffraction),[9] organic reactions often require post-synthetic solvent-based purification steps, thus diminishing the value of solvent-free synthesis.

We now present a proof-of-principle study which addresses these two major problems of milling mechanochemistry. In particular, we demonstrate a mechanochemical methodology for the oxidation of anilines into nitrosobenzenes, accompanied by solvent-free product isolation. Formation of the nitroso group has been the missing step in methodologies for solvent-free interconversions of nitrogen-based organic functionalities. The high vapour pressures of nitrosobenzenes allow us to demonstrate how solvent-free synthesis can be coupled with solvent-free separation *via* sublimation.

It was previously demonstrated that anilines can be selectively oxidised, in a mechanochemical process using a planetary mill, to symmetrically substituted azoxybenzenes, azobenzenes or nitro compounds using a wide range of oxidising agents.[8a] These functional group interconversions generally involve the formation of a nitrosobenzene intermediate (Scheme 1a) which rapidly reacts with a hydroxylamine intermediate or an amine to give an azoxybenzene or an azobenzene, respectively (Scheme 1b). Alternatively, further oxidation of the nitroso compound yields the nitro compound. Conversions of other nitrogen functionalities (*e.g.* nitriles,[10] nitrones,[11] imines,[2a,b] oximes[12] and nitro[13] compounds) were also conducted either mechanochemically or using microwave-assisted solid-state routes,



R = *p*-iodo (*p*-I), *p*-bromo (*p*-Br), *p*-chloro (*p*-Cl), *p*-nitro (*p*-NO_2), *p*-methyl (*p*-Me), *p*-hydroxy (*p*-OH), *p*-carboxylic acid (*p*-COOH)

Scheme 1 (a) Oxidation and reduction reactions from anilines to nitrobenzenes and back. Oxidation reactions are denoted with [O], reduction with [R]. (b) Coupling of nitrosobenzene with amine to yield azobenzene and with hydroxylamine to yield azoxybenzene.

---

[a] *Department of Chemistry, Faculty of Science, University of Zagreb, Horvatovac 102a, HR-10002 Zagreb, Croatia. E-mail: ihalasz@chem.pmf.hr; Fax: +385 1 460 6401; Tel: +385 1 460 6416*
[b] *Department of Chemistry, McGill University, 801 Sherbrooke St. W., H3A 0B8 Montreal, Canada*

† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of products of mechanochemical synthesis before and after sublimation. Example thermogravimetric isothermal curve for *p*-bromonitrosobenzene demonstrating the ease of sublimation and detailed experimental results. See DOI: 10.1039/c2gc35410a

leaving the operations that generate the nitroso group or use it as a starting point as a missing link in the system of solvent-free conversions of nitrogen-based functionalities. At the same time, high reactivity and ease of oxidation make nitrosobenzenes difficult targets in traditional solution-based synthetic chemistry, with typical yields around 70%. In condensed phases (solution, solid) nitrosobenzenes rapidly undergo reversible dimerisation to form azodioxides.[14] However, the high reactivity of nitrosobenzenes has made them useful reagents in materials chemistry, most notably as precursors in the synthesis of photoactive non-symmetrical azobenzenes[15] and, very recently, as active sites in MOFs capable of covalently trapping small molecules.[16]

Considering the formation of nitrosobenzenes as intermediates during mechanochemical oxidation of anilines,[8a] and knowing that nitrosobenzenes can be readily purified by sublimation,[14] we decided to investigate if the synthesis and isolation of nitrosobenzenes could be accomplished in a selective and solvent-free procedure. We were inspired by the report of Priewisch and Rück-Braun[17] describing an efficient synthesis of nitrosobenzenes in a biphasic system that used Oxone[18] as the oxidant in dichloromethane.

Our exploration of the solvent-free mechanosynthesis of nitrosobenzenes is based on a limited set of differently substituted model molecules. While the yields resulting from our methodology are comparable to those in biphasic reaction systems, our methodology avoids bulk solvents, provides crude products in one short step and enables their solvent-free purification by sublimation. As model reactants, we have used *p*-iodoaniline, *p*-bromoaniline, *p*-chloroaniline, *p*-nitroaniline and *p*-methylaniline that were previously obtained in our laboratory through solution routes[19] (Scheme 1a). As the oxidising agent, potassium hydrogenperoxosulphate[8a,10] (commercially available as Oxone) was employed. Formation of the nitrosobenzene in a mechanochemical reaction was confirmed by extracting the mixture after grinding with chloroform ($CDCl_3$), collecting ^1H and ^{13}C NMR spectra (Fig. 1a, also see ESI†) and comparing them to those of standard samples prepared by solution methods.[19] With all anilines tested, the corresponding nitrobenzene also formed, and all reactions, except that with *p*-iodoaniline, also produced the azoxybenzene as a by-product (Fig. 1a). Since nitrosobenzenes exhibit high vapour pressures, the crude mixtures were sublimed under reduced pressure to isolate the product (Fig. 2).

The entire procedure of nitrosobenzene preparation can thus be accomplished in a solvent-free manner. The only impurity found after sublimation was, as revealed by solution ^1H NMR spectroscopy, the corresponding nitrobenzene (Fig. 1b). This, however, is a very satisfactory outcome as the purification of nitrosobenzenes often presents difficulties due to their instability.[17] Indeed, if nitrosobenzene synthesis is directed, as is often the case, towards making a precursor for non-symmetrical azobenzene, the presence of a nitrobenzene would not be relevant.[17,19]

Compounds listed in Table 1 were, except for the p-NO_2 substituent, obtained in yields above 50% (and up to 85% for the *p*-I substituent). Comparing our solid-state route with the solution approach, *p*-Br was obtained in higher yield and comparable purity (Table 1). Formation of p-NO_2 was slowest and the yield could be increased by longer grinding, although at the expense of purity. We found that both purity and yield could be substantially improved upon addition of equimolar amount of $NaHCO_3$ in the reaction mixture as compared to neat grinding (Table 2). For instance, for *p*-Br the yield increased five-fold while it increased seven to eight times for *p*-I. This may be explained by $NaHCO_3$ acting as a base to neutralise acidic species formed during oxidation, so as to prevent the acid-catalysed reactivity between nitrosobenzene and hydroxylamine or amine.

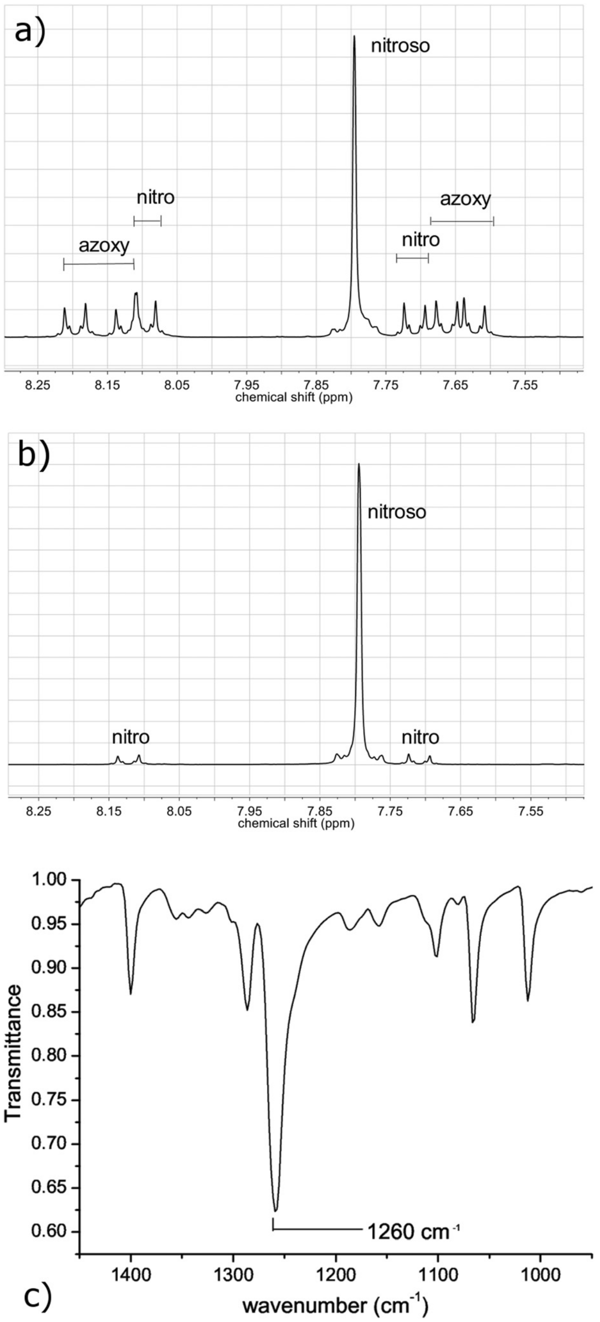


Fig. 1 Segments of example NMR spectra ($CDCl_3$) for the mechanochemical nitrosobenzene synthesis: (a) product of *p*-bromoaniline oxidation after milling and (b) after sublimation. (c) Fourier-transform infrared spectrum of dimeric *p*-bromonitrosobenzene product, highlighting the characteristic band of the azodioxy group.[14]

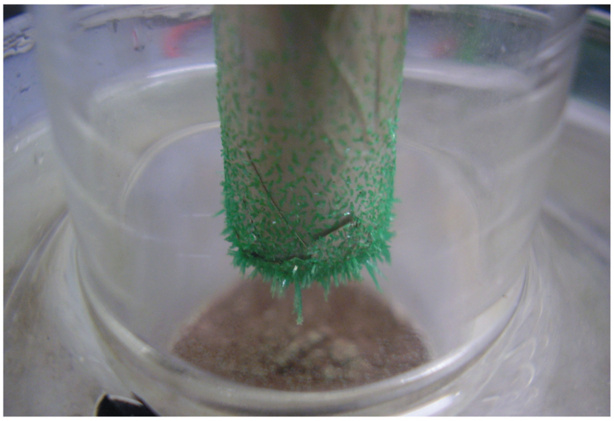


Fig. 2 Separation of the nitrosobenzene product by sublimation following mechanochemical synthesis, illustrated in case of *p*-iodonitrosobenzene: the green monomeric nitrosobenzene is collected on the cold finger.

Table 1 Results of nitrosobenzene syntheses by mechanochemical *Oxone* oxidation of anilines. The only impurity found following sublimation was the corresponding nitrobenzene

Substituent	*p*-I	*p*-Br[c]	*p*-Cl	*p*-NO_2	*p*-Me
Yield[a]/%	85	80 (70)	70	26	52
Purity[b]/%	92	90 (95)	80	90	69
Milling time/min	20	20	20	30	20
$NaHCO_3$ addition	Yes	Yes	Yes	No	Yes

[a] Yield is calculated only for the nitrosobenzene taking into account the mixture composition after sublimation. [b] Purity is reported as the molar fraction of nitrosobenzene in a mixture with the corresponding nitrobenzene obtained after sublimation, determined by ^{1}H NMR. [c] Numbers in brackets relate to solution synthesis.[15]

Table 2 Comparison of reaction yields (in %) and purities (in %, in brackets) of neat mechanochemical syntheses of nitrosobenzenes with and without added $NaHCO_3$

$NaHCO_3$	*p*-I	*p*-Br	*p*-Cl
Yes	85 (92)	80 (90)	70 (80)
No	~12 (~80)	~15 (~60)	~8 (~65)

The successful application of mechanochemical Oxone milling for the synthesis of the halo- or methyl-substituted nitrosobenzenes led us to explore the reactivity of *p*-aminophenol and *p*-aminobenzoic acid. Attempted oxidations of *p*-OH and *p*-COOH anilines did not yield the corresponding nitrosobenzenes, but resulted in the formation of non-characterised tars. This is most likely due to the more acidic environment which can catalyse the formation of azobenzenes and azoxybenzenes. Grinding with an excess of $NaHCO_3$, in an attempt to neutralise the mixture, also did not result in the formation of nitrosobenzenes.

We have also explored the synthesis using the liquid-assisted grinding (LAG) technique with protic polar solvents, as well as either protic or aprotic non-polar solvents. Although LAG has previously been reported to improve reactivity in other reaction systems,[3a,9] introducing a liquid phase in our case reduced both the purity and the yield of nitrosobenzenes (see ESI†). Mechanochemical nitrosobenzene synthesis under LAG conditions was more successful with aprotic and non-polar liquids, suggesting that protic liquid phases facilitate the formation of azobenzene or azoxybenzene.

In summary, we have demonstrated a rapid and selective solvent-free synthesis of nitrosobenzenes under mechanochemical conditions. The reported strategy complements existing approaches for the solvent-free interconversions of nitrogen functionalities, such that mechanochemical treatment of anilines with a range of oxidising agents can now be selectively directed to a variety of products, including nitrosobenzenes, azoxybenzenes, azobenzenes or nitrobenzenes.

Our results complement the work on Oxone oxidation of anilines by Stolle's group,[8a] who used acidic inorganic auxiliaries to direct the formation of azobenzenes and azoxybenzenes. Specifically we demonstrate that weakly basic inorganic auxiliaries facilitate the formation of the nitrosobenzenes under similar conditions. We are currently trying to develop mechanochemical approaches to asymmetric azobenzenes and azoxybenzenes, as well as solvent-free routes to nitrosobenzenes bearing protic (phenol, carboxylic acid) functionalities.

Experimental section

Mechanochemical synthesis of the *para*-substituted nitrosobenzenes was conducted by placing stoichiometric amounts of the corresponding aniline (0.25 mmol) and Oxone® ($K_2SO_5 \times K_2SO_4 \times KHSO_4$, 0.50 mmol) in a custom made stainless steel jar with two 7 mm stainless steel balls which was then milled at a frequency of 25 Hz for variable amount of time (5 to 40 minutes) on a Retsch MM 200 ball mill. Neat and liquid assisted grinding were employed in the optimization of reaction conditions, as was grinding with $NaHCO_3$ (~1.0 mmol) to neutralise potassium hydrogensulphate and other acidic species. The nitrosobenzene was separated from the mixture by sublimation under reduced pressure (~0.1 mbar) during which some of the nitro side-product also sublimed. An aluminium foil cylinder was placed over the cold finger to ensure easier and complete collection of the sublimation product.

Acknowledgements

This work was supported by the Ministry of Science, Education and Sport of the Republic of Croatia (Grant No. 119-1191342-1334). We are grateful to Mr Boris Milić for the grinding jars and to Dr Ivica Đilović for critical discussions. T.F. acknowledges the support of McGill University and the FQRNT Centre for Green Chemistry and Catalysis.

Notes and references

‡ The term "solvent-free" is used here to denote the avoidance of bulk external solvent. In cases when the nitrobenzene as the principal byproduct of the nitrosobenzene synthesis is liquid, the reactions cannot be mechanistically considered to be truly "solvent-free". This is true in a number of mechanochemical syntheses, including those of certain

organic molecules,[2a,b] metal–organic materials and cocrystals, whose mechanism involves the loss of solvent of crystallisation from a reactant or the transient formation of a liquid eutectic phase.

1 (*a*) 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. Waddel, *Chem. Soc. Rev.*, 2012, **41**, 413; (*b*) T. Friščić, *J. Mater. Chem.*, 2010, **20**, 7599; (*c*) A. Stolle, T. Szuppa, S. E. S. Leonhardt and B. Ondruschka, *Chem. Soc. Rev.*, 2011, **40**, 2317; (*d*) G. Kaupp, *CrystEngComm*, 2009, **11**, 388; (*e*) M. K. Beyer and H. Clausen-Schaumann, *Chem. Rev.*, 2005, **105**, 2921; (*f*) K. Tanaka and F. Toda, *Chem. Rev.*, 2000, **100**, 1025; (*g*) A. Bruckmann, A. Krebs and C. Bolm, *Green Chem.*, 2008, **10**, 1131.

2 (*a*) O. Dolotko, J. W. Wiench, K. W. Dennis, V. K. Pecharsky and V. P. Balema, *New J. Chem.*, 2010, **34**, 25; (*b*) G. Rothenerg, A. P. Downie, C. L. Raston and J. L. Scott, *J. Am. Chem. Soc.*, 2001, **123**, 8701; (*c*) C.-C. Hsu, N.-C. Chen, C.-C. Lai, Y.-H. Liu, S.-M. Peng and S.-H. Chiu, *Angew. Chem., Int. Ed.*, 2008, **47**, 7475; (*d*) V. Declerck, P. Nun, J. Martinez and F. Lamaty, *Angew. Chem., Int. Ed.*, 2009, **48**, 9318; (*e*) R. Thorwirth, A. Stolle, B. Ondruschka, A. Wildb and U. S. Schubert, *Chem. Commun.*, 2011, **47**, 4370; (*f*) G. W. Wang, T.-H. Zhang, Y.-J. Li, P. Lu, H. Zhan, Y.-C. Liu, Y. Murata and K. Komatsu, *Tetrahedron Lett.*, 2003, **44**, 4407; (*g*) G.-W. Wang, K. Komatsu, Y. Murata and M. Shiro, *Nature*, 1997, **387**, 583.

3 (*a*) V. André, A. Hardeman, I. Halasz, R. S. Stein, G. J. Jackson, D. G. Reid, M. J. Duer, C. Curfs, M. T. Duarte and T. Friščić, *Angew. Chem., Int. Ed.*, 2011, **50**, 7858; (*b*) T. Friščić, I. Halasz, F. C. Strobridge, R. E. Dinnebier, R. S. Stein, L. Fábián and C. Curfs, *CrystEngComm*, 2011, **13**, 3125; (*c*) E. H. H. Chow, F. C. Strobridge and T. Friščić, *Chem. Commun.*, 2010, **46**, 6368; (*d*) D. Braga, F. Grepioni, V. Andre and M. T. Duarte, *CrystEngComm*, 2009, **11**, 2618; (*e*) T. Friščić, D. G. Reid, I. Halasz, R. S. Stein, R. E. Dinnebier and M. J. Duer, *Angew. Chem., Int. Ed.*, 2010, **49**, 712; (*f*) W. B. Yuan, J. O'Connor and S. L. James, *CrystEngComm*, 2010, **12**, 3515; (*g*) K. Užarević, M. Rubčić, M. Radić, A. Puškarić and M. Cindrić, *CrystEngComm*, 2011, **13**, 4314; (*h*) D. Cinčić and B. Kaitner, *CrystEngComm*, 2011, **13**, 4351.

4 D. Cinčić, I. Brekalo and B. Kaitner, *Cryst. Growth Des.*, 2012, **12**, 44.

5 (*a*) R. Thorwirth, A. Stolle, B. Ondruschka, A. Wild and U. S. Schubert, *Chem. Commun.*, 2011, **47**, 4370; (*b*) P.-N. Chen, C.-C. Lai and S.-H. Chiu, *Org. Lett.*, 2011, **13**, 4660; (*c*) Y.-F. Wang, R.-X. Chen, K. Wang, B.-B. Zhang, Z.-B. Li and D.-Q. Xu, *Green Chem.*, 2012, **14**, 893; (*d*) Z. Zhang, Y.-W. Dong, G.-W. Wang and K. Komatsu, *Chem. Lett.*, 2004, **33**, 168; (*e*) V. P. Balema, J. W. Wiench, M. Pruski and V. K. Pecharsky, *J. Am. Chem. Soc.*, 2002, **124**, 6244; (*f*) B. Rodriguez, A. Bruckmann, T. Rantanen and C. Bolm, *Adv. Synth. Catal.*, 2007, **349**, 2213.

6 (*a*) F. Schneider and B. Ondruschka, *ChemSusChem*, 2008, **1**, 622; (*b*) D. A. Fulmer, W. C. Shearouse, S. T. Medonza and J. Mack, *Green Chem.*, 2009, **11**, 1821; (*c*) R. Thorwirth, A. Stolle and B. Ondruschka, *Green Chem.*, 2010, **12**, 985.

7 (*a*) A. Bruckmann, B. Rodriguez and C. Bolm, *CrystEngComm*, 2009, **11**, 404; (*b*) J. G. Hernández, V. García-López and E. Juaristi, *Tetrahedron*, 2012, **68**, 92; (*c*) A. N. Sokolov, D.-K. Bučar, J. Baltrusaitis, S. X. Gu and L. R. MacGillivray, *Angew. Chem., Int. Ed.*, 2010, **49**, 4273.

8 (*a*) R. Thorwirth, F. Bernhardt, A. Stolle, B. Ondruschka and J. Asghari, *Chem.–Eur. J.*, 2010, **16**, 13236; (*b*) A. Shaabani and D. G. Lee, *Tetrahedron Lett.*, 2001, **42**, 5833; (*c*) J. Mack, D. Fulmer, S. Stofel and N. Santos, *Green Chem.*, 2007, **9**, 1041; (*d*) M. Nüchter, B. Ondruschka and R. Trotzki, *J. Prakt. Chem.*, 2000, **342**, 720.

9 (*a*) V. Štrukil, L. Fábián, D. G. Reid, M. J. Duer, G. J. Jackson, M. Eckert-Maksić and T. Friščić, *Chem. Commun.*, 2010, **46**, 9191; (*b*) C. J. Adams, M. F. Haddow, M. Lusi and A. G. Orpen, *CrystEngComm*, 2011, **13**, 4324; (*c*) S. Karki, L. Fábián, T. Friščić and W. Jones, *Org. Lett.*, 2007, **9**, 3133; (*d*) T. Friščić and W. Jones, *Cryst. Growth Des.*, 2009, **9**, 1621.

10 D. S. Bose and A. V. Narsaiah, *Tetrahedron Lett.*, 1998, **39**, 6533.

11 (*a*) E. Colacino, P. Nun, F. M. Colacino, J. Martinez and F. Lamaty, *Tetrahedron*, 2008, **64**, 5569; (*b*) H. Valizadeh and L. Dinparast, *Heteroat. Chem.*, 2009, **20**, 177.

12 (*a*) C. B. Aakeröy and P. D. Chopade, *Org. Lett.*, 2011, **13**, 1; (*b*) J. T. Li, Z. X. Chen, X. L. Li and H. J. Deng, *Asian J. Chem.*, 2007, **19**, 2236.

13 S. Wada, M. Urano and H. Suzuki, *J. Org. Chem.*, 2002, **64**, 8254.

14 (*a*) I. Halasz and H. Vančik, *CrystEngComm*, 2011, **13**, 4307; (*b*) H. Vančik, V. Šimunić-Mežnarić, E. Meštrović and I. Halasz, *J. Org. Chem.*, 2004, **69**, 4829; (*c*) I. Halasz, E. Meštrović, H. Čičak, Z. Mihalić and H. Vančik, *J. Org. Chem.*, 2005, **69**, 8461; (*d*) A. Knežević, T. Medančić, S. Milovac, I. Biljan, I. Halasz and H. Vančik, *Croat. Chem. Acta*, 2011, **84**, 21.

15 G. W. Lee, N.-K. Kim and K.-S. Jeong, *Org. Lett.*, 2010, **12**, 2634.

16 H. Sato, R. Matsuda, K. Sugimoto, M. Takata and S. Kitagawa, *Nat. Mater.*, 2010, **9**, 661.

17 B. Priewisch and K. Rück-Braun, *J. Org. Chem.*, 2005, **70**, 2350.

18 Milling with *Oxone* and NaBr was recently used for solvent-free bromination reactions, see: G.-W. Wang and J. Gao, *Green Chem.*, 2012, **14**, 1125.

19 (*a*) I. Halasz, I. Biljan, P. Novak, E. Meštrović, J. Plavec, G. Mali, V. Smrečki and H. Vančik, *J. Mol. Struct.*, 2009, **918**, 19; (*b*) I. Biljan, G. Cvjetojević, V. Smrečki, P. Novak, G. Mali, J. Plavec, D. Babić, Z. Mihalić and H. Vančik, *J. Mol. Struct.*, 2010, **979**, 22.