RSC Advances

RSC Publishing

COMMUNICATION

Cite this: DOI: 10.1039/c3ra43252a

Received 27th June 2013,
Accepted 23rd July 2013

DOI: 10.1039/c3ra43252a

www.rsc.org/advances

A simple and straightforward synthesis of phenyl isothiocyanates, symmetrical and unsymmetrical thioureas under ball milling†

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Promoted by KOH under ball milling, anilines were efficiently transformed into isothiocyanates (in presence of 5.0 equiv. CS_2) or symmetrical thioureas (in presence of 1.0 equiv. CS_2), without using any other harsh or toxic decomposition reagent. Some *in situ* generated isothiocyanates can directly "click" with other amines to afford unsymmetrical thioureas.

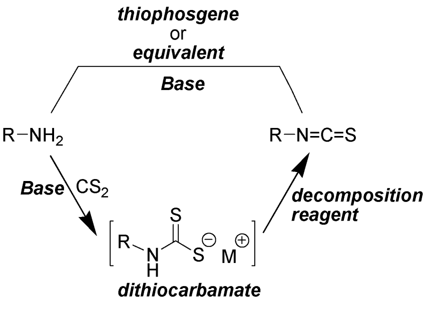
The isothiocyanate moiety is ubiquitous structural unit in a number of biologically active compounds, and is widely used in the synthesis of various sulfur-nitrogen-containing heterocycles or applied as chemoselective electrophiles in bioconjugate chemistry.[1] Numerous methods have been developed for the conversion of amines into isothiocyanates, in which thiophosgene was mostly employed.[2] In view of its high toxicity and incompatibility with many functional groups, various 'thiocarbonyl transfer' reagents were developed as thiophosgene equivalents (Scheme 1), including thiocarbonyl-ditriazole[3] or diimidazole,[4] dipyridylthionocarbonate,[5] *etc.* Most of these reagents are not readily available, and often do not work as desired due to the formation of thiourea as a side product.

On the other hand, it is a fact that the treatment of an amine with carbon disulfide in the presence of a suitable base can easily afford the corresponding dithiocarbamic acid salt, which may be desulfurylated into isothiocyanate when a certain decomposition reagent is employed. Therefore, various decomposition reagents for the desulfurylation of *in situ* generated dithiocarbamates have been developed as alternative approaches, including uronium- and phosphonium-based peptide coupling reagents,[6] triphenylphosphine dibromide,[7] tosyl chloride,[8] dialkyl dicarbonates,[9] and other harsh reagents. Frankly, these methods are efficient enough, but most of them possess drawbacks such as rigorous or hazardous conditions and intractable side reactions. Recently, a relatively green method was reported for the synthesis of various isothiocyanates in aqueous media, but it still involves the use of cyanuric acid as the desulfurylation reagent, and long reaction times with tedious work up were desired.[10]

To circumvent these problems, one of the best alternatives is to carry out these kind of reactions under solvent-free conditions, which can also overcome the instability of isothiocyanates in solution. Among current solvent-free techniques, mechanical ball-milling has recently been contributing more and more to the efficient promotion of various organic reactions in a greener way.[11,12] We have also successfully applied this technique in several transformations in recent years, including Diels–Alder reactions, reductive benzylization, Michael addition and free radical addition reactions.[13] Herein we are keen to report a mechanochemical ball-milling-promoted method for the facile synthesis of various phenyl isothiocyanates, in which just cheap KOH is employed both as base and decomposition reagent, avoiding the use of any other harsh or toxic chemical. And further investigation on the synthesis of symmetrical and unsymmetrical thioureas was also explored.

Firstly, we chose the synthesis of 4-methyl-phenyl isothiocyanate (**3g**) as the model reaction to optimize the reaction conditions. A series of experiments were carried out in solution and under ball milling by varying the base, the solvent and the usage amount of CS_2, and the results are summarized in Table 1.

At first, the reaction was carried out using the reactant CS_2 as solvent, and several common bases were explored. In most cases, the conversion is rather low even after 24 h, giving only trace to



Scheme 1

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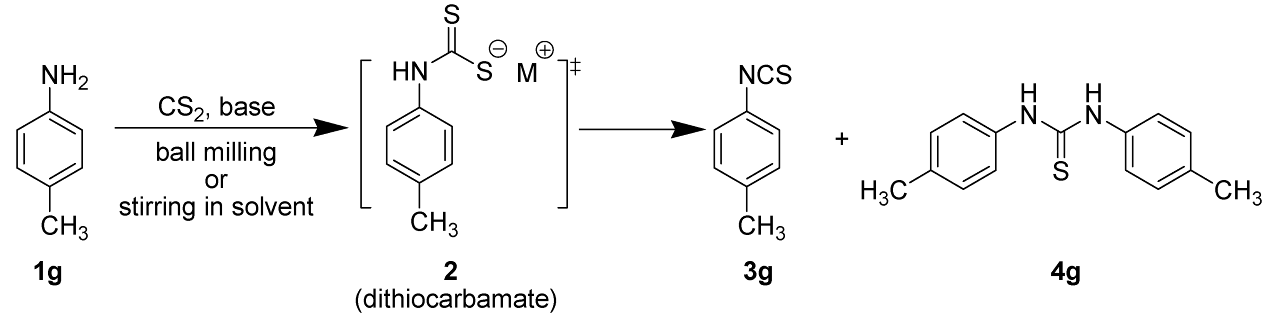
† Electronic supplementary information (ESI) available: Experimental section, characterization details and NMR spectra for all products. See DOI: 10.1039/c3ra43252a

Table 1 Optimization of the reaction conditions for synthesis of 4-methyl-phenyl isothiocyanate (**3g**)[a]



Entry	CS_2 (equiv.)	Base	Solvent	Time	Product (yield)[b]
1	Solvent	Na_2CO_3	CS_2	24 h	**3g** (trace)
2	Solvent	K_2CO_3	CS_2	24 h	**3g** (trace)
3	Solvent	NaOH	CS_2	24 h	**3g** (36%) + **4g** (trace)
4	Solvent	KOH	CS_2	24 h	**3g** (41%) + **4g** (trace)
5	Solvent	^{t}BuOK	CS_2	24 h	**3g** (45%) + **4g** (trace)
6	Solvent	Et_3N	CS_2	24 h	**2** (major) + **3g** (28%) + **4g** (22%)
7	5.0	KOH	CH_2Cl_2	24 h	**3g** (10%) + **4g** (trace)
8	5.0	KOH	THF	24 h	**3g** (22%) + **4g** (16%)
9	5.0	KOH	CH_3COCH_3	24 h	**3g** (16%) + **4g** (25%)
10	5.0	KOH	CH_3OH	24 h	**3g** (11%) + **4g** (36%)
11	5.0	KOH	DMF	24 h	**3g** (trace) + **4g** (45%)
12	5.0	KOH	DMSO	24 h	**3g** (trace) + **4g** (49%)
13	5.0	Et_3N	ball milling	40 min	**2** (major) + **3g** (26%)
14	5.0	Na_2CO_3	ball milling	40 min	**3g** (57%) + **4g** (trace)
15	5.0	K_2CO_3	ball milling	40 min	**3g** (61%) + **4g** (trace)
16	5.0	NaOH	ball milling	40 min	**3g** (92%)
17	5.0	^{t}BuOK	ball milling	40 min	**3g** (86%)
18	***5.0***	***KOH***	***ball milling***	***40 min***	***3g (98%)***
19	3.0	KOH	ball milling	40 min	**3g** (58%) + **4g** (27%)
20	***1.0***	***KOH***	***ball milling***	***40 min***	***3g (trace) + 4g (93%)***

[a] Reactions were carried out with 4-methylaniline **1g** (10.0 mmol), CS_2 (designated usage) and base (10.0 mmol) at room temperature; 1800 rpm (30 Hz) vibration frequency for ball-milling and 15 mL solvent for stirring in solution. [b] Determined by HPLC analysis based on 4-methylaniline.

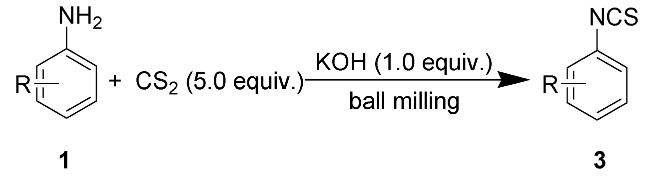
very poor yields for **3g** (entries 1–5, Table 1). This inefficacy may be due to the insolubility of the base in non-polar CS_2. Although the case of Et_3N afforded almost complete conversion, the reactant **1g** was mainly converted into dithiocarbamate **2** (entry 6, Table 1). Herein the chemoselectivity is somewhat different from the similar reaction of fullerene in solution.[14]

The results from entries 1–6 prompted us to use KOH as the best base to promote this transformation in polar solvents or under ball milling condition. The results from entries 7–12 in Table 1 demonstrated that the more polar the solvent, the higher the conversion of the aniline, and stronger polarity favored the formation of thiourea **4g**. In general, all solution cases furnished poor conversion and chemoselectivity. In contrast, ball milling conditions accelerated the conversion significantly. That is, the aniline **1g** was almost completely consumed in very short time (40 min), whatever base was employed (entries 13–18, Table 1). The rapid conversion of the current solid-state procedure may be ascribed to an enhanced reaction rate resulting from ultimately high concentrations of reactants with no use of solvent, and the high mechanical energy that can greatly enforce the reaction. Furthermore, it should be noted that the basicity of the bases has an obvious effect on the chemoselectivity. For examples, organic base Et_3N still favored the formation of dithiocarbamate **2** (entry 13, Table 1), similar to the result from solution case (entry 6, Table 1). The strong inorganic base KOH gave almost quantitative yield (entry 18, Table 1). On the other hand, the usage amount of CS_2 is crucial for the reaction selectivity (entries 18–20, Table 1). Excessive (5.0 equiv) CS_2 is both necessary and also enough for highly selective generation of the desired product **3g**. Further reducing the usage of CS_2 led to the formation of byproduct thiourea **4g**.

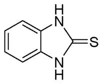
Inspired by the above-described results as summarized in Table 1, we then employed KOH and 5.0 equivalents of CS_2 under ball milling conditions to access a wide variety of phenyl isothiocyanates from anilines bearing different substituents. Under this mechanically-promoted condition, the reactions proceeded cleanly without intermediate work-up and left no, or only traces of, byproducts. The detailed results are outlined in Table 2.

As can be seen from Table 2, anilines containing *ortho*, *meta* and *para* substituents are all smoothly converted into the corresponding isothiocyanates in good yields in a relatively short

Table 2 Mechanochemical synthesis of phenyl isothiocyanates **3** from anilines **1** and CS_2 promoted by KOH[a]



Entry	R	Product **3**	Time (min)	Yield (%)[b]
1	H	**3a**	40	85
2	2-Me	**3b**	40	92
3	2-OMe	**3c**	40	91
4	2-Cl	**3d**	70	71
5	3-Me	**3e**	45	93
6	3-Cl	**3f**	90	72
7	4-Me	**3g**	40	96
8	4-OMe	**3h**	40	95
9	4-Br	**3i**	60	83
10	4-Cl	**3j**	90	75
11	4-NO_2	**3k**	90	61
12	3,4-Cl	**3l**	90	52
13	2-NH_2	**4l**	40	97

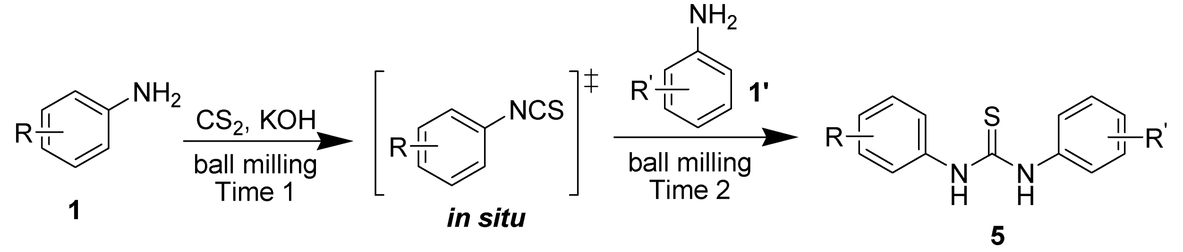


[a] Reactions were carried out with aniline **1** (10.0 mmol), CS_2 (50.0 mmol) and KOH (10.0 mmol) at room temperature at a vibration frequency of 30 Hz. [b] Isolated yield combined from two parallel runs *via* Retsch MM400 ball miller, by direct separation of the reaction mixtures through short column chromatography.

time (within 1.5 h), except that 1,2-diaminobenzene exclusively afforded the corresponding thiourea **4l** (entry 13). Specifically for anilines bearing electron-donating substituents, just 40–45 min were needed for complete conversion and almost quantitative formation of the desired products **3**. For anilines bearing electron-withdrawing substituents, the corresponding isothiocyanates could still be obtained in moderate to good yields, although relatively long reaction times were needed. Under traditional solution conditions, anilines bearing strong electron-withdrawing substituents are very difficult to be transformed into in the corresponding isothiocyanates unless harsh conditions or decomposition reagent is employed. For example, a mixture containing 4-nitrophenyl amine **1k** (10.0 mmol), KOH (10.0 mmol) and CS_2 (20 mL) was stirred at room temperature for 48 h, and only a trace of product **3k** was detected. But in this protocol, ball milling for 90 min could afford 61% isolated yield in the presence of just 5.0 equivalents of CS_2. In all cases, the desired products **3** were isolated directly from the resulting reaction mixtures just through short column chromatography eluted with hexane/ethyl acetate (v/v = 20 : 1), thus the work up procedure is very simple.

Considering the fact that isothiocyanates are easy to react with amino groups, we were inspired to directly add some other anilines (equal equiv.) into those almost quantitatively *in situ* generated isothiocyanates (**3e**, **3g**, **3h**) for a one-pot synthesis of unsymmetrical thioureas. Gratifyingly, all the afterward added anilines **1′** proceeded through a "click"[15] reaction sequence within one hour, affording the unsymmetrical thiourea **5** in almost quantitative yield (Table 3). The products were obtained just through immersing the resulting reaction mixtures in diluted HCl with the aid of ultrasonic irradiation and Büchner filtration. In contrast, the traditional synthesis of unsymmetrical thioureas

Table 3 Mechanochemical one-pot synthesis of unsymmetrical phenylthioureas **5** by addition of phenyl amines **1′** on *in situ* generated isothiocyanates[a]



Entry	R	R′	Product **5**	Time 1 (min)	Time 2 (min)	Yield (%)[b]
1	4-Me	2-Me	**5a**	40	35	89
2	4-Me	3-Me	**5b**	40	35	92
3	4-Me	4-OCH_3	**5c**	40	30	95
4	4-Me	4-Br	**5d**	40	45	92
5	4-Me	4-Cl	**5e**	40	60	87
6	4-Me	H	**5f**	40	40	94
7	4-OMe	4-Cl	**5g**	40	60	90
8	4-OMe	3-Cl	**5h**	40	60	89
9	4-OMe	2-Cl	**5i**	40	75	85
10	4-OMe	4-Br	**5j**	40	60	94
11	3-Me	4-OMe	**5k**	45	40	96
12	3-Me	4-Br	**5l**	45	60	91

[a] Reactions were carried out with aniline **1** (10.0 mmol), CS_2 (50.0 mmol), KOH (10.0 mmol) and afterward added aniline **1′** (10.0 mmol) at room temperature at a vibration frequency of 30 Hz. [b] Isolated yield combined from two parallel runs.

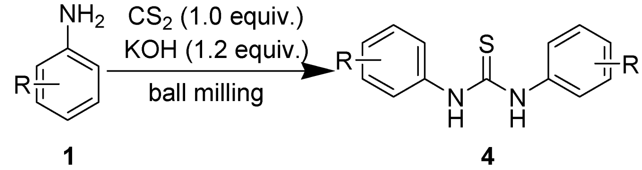
often involves preliminary preparation and handing of isothiocyanates, which is somewhat tedious and hazardous.

On the other hand, the result from entry 20 in Table 1 demonstrated that the symmetrical thiourea was almost exclusively generated when the usage amount of CS_2 was reduced to 1.0 equivalent. This result prompted us to attempt other anilines for the synthesis of various symmetrical phenyl thioureas, and satisfactory results were also achieved as shown in Table 4.

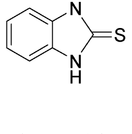
As expected, the yields of the products are significantly affected by the nature of the amines, similarly to those in the transformation to isothiocyanates. That is, anilines bearing electron-rich substituents are good substrates for this process and show higher reactivity than those bearing electron-deficient groups. To demonstrate the utility and substrate scope of this methodology, 1,4-phenylenediamine was also attempted to synthesize the corresponding bis-isothiocyanate and further conversion into symmetrical and unsymmetrical thioureas. Unfortunately, the results were rather complicated with very poor chemoselectivity.

In conclusion, an environmentally friendly method has been developed for facile transformation of phenyl amines into isothiocyanates and thioureas by using a mechanochemical ball-milling technique. Cheap KOH is employed both as base and decomposition reagent, avoiding the use of any other harsh or toxic chemical. Phenyl amines bearing both electron-rich and electron-deficient substituents could give desired products in good to excellent yields. Furthermore, some *in situ* generated isothiocyanates can directly "click" with other amines to afford unsymmetrical thioureas in a straightforward way. This protocol is fast, clean and of low cost, and the work-up procedure is very simple and safe. These advantages make it a very efficient and green alternative to traditional methods for the synthesis of aromatic isothiocyanates and thioureas. Under this mechanochemical condition, it can be reasonably anticipated that various thiocarbonyl compounds or sulfur-nitrogen-containing heterocycles would be obtained if a suitable nucleophile was employed in addition with such *in situ* generated isothiocyanates in a one-pot way. Work in this direction is under investigation.

Table 4 Mechanochemical synthesis of symmetrical phenylthioureas **4** from anilines **1** and CS_2 promoted by KOH[a]



Entry	R	Product 3	Time (min)	Yield (%)[b]
1	H	**4a**	45	86
2	2-CH_3	**4b**	45	84
3	2-OCH_3	**4c**	50	87
4	2-Cl	**4d**	90	74
5	3-CH_3	**4e**	50	88
6	3-Cl	**4f**	75	75
7	4-CH_3	**4g**	40	93
8	4-OCH_3	**4h**	40	95
9	4-Br	**4i**	60	82
10	4-Cl	**4j**	80	77
11	4-NO_2	**4k**	90	43[c]
12	2-NH_2	**4l**	40	97



[a] Reactions were carried out with aniline **1** (5.0 mmol), CS_2 (5.0 mmol) and KOH (6.0 mmol) at room temperature at a vibration frequency of 30 Hz. [b] Isolated yield combined from two parallel runs. [c] Isolated yield from column chromatography.

We are grateful to financial support from National Natural Science Foundation of China (21242013, 20902002).

Notes and references

1 (*a*) Y.-S. Zhang, T. Li and V. Gonzalez, *Mol. Cancer Ther.*, 2003, **2**, 1045–1052; (*b*) D. Xiao, V. Vogel and S. V. Singh, *Mol. Cancer Ther.*, 2006, **5**, 2931–2945; (*c*) J. M. G. Fernández, C. O. Mellet, J. L. J. Blanco, J. F. Mota, A. Gadelle, A. Coste-Sarguet and J. Defaye, *Carbohydr. Res.*, 1995, **268**, 57–71; (*d*) A. K. Mukerjee and R. Ashare, *Chem. Rev.*, 1991, **91**, 1–24, and references therein.

2 (*a*) E. Dyer and T. B. Johnson, *J. Am. Chem. Soc.*, 1932, **54**, 777–787; (*b*) G. M. Dyson and H. J. George, *J. Chem. Soc. Trans.*, 1924, **125**, 1702–1708.

3 C. Larsen, K. Stelliou and D. N. Harpp, *J. Org. Chem.*, 1978, **43**, 337–339.

4 C. Larsen and D. N. Harpp, *J. Org. Chem.*, 1981, **46**, 2465–2466.

5 S. Kim and K. Y. Yi, *Tetrahedron Lett.*, 1985, **26**, 1661–1664.

6 (*a*) U. Boas, H. Gertz, J. B. Christensen and P. M. H. Heegaard, *Tetrahedron Lett.*, 2004, **45**, 269–272; (*b*) U. Boas, B. Pedersen and J. B. Christensen, *Synth. Commun.*, 1998, **28**, 1223–1228.

7 P. Molina, M. Alajarin and H. Tamiaki, *Synthesis*, 1982, 596–597.

8 (*a*) R. Wong and S. J. Dolman, *J. Org. Chem.*, 2007, **72**, 3969–3971; (*b*) H. Stephensen and F. Zaragosa, *J. Org. Chem.*, 1997, **62**, 6096–6097.

9 H. Munch, J. S. Hansen, M. Pittelkow, J. B. Christensen and U. Boas, *Tetrahedron Lett.*, 2008, **49**, 3117–3119.

10 N. Sun, B. Li, J.-P. Shao, W.-M. Mo, B.-X. Hu, Z.-L. Shen and X.-Q. Hu, *Beilstein J. Org. Chem.*, 2012, **8**, 61–70.

11 For some reviews, see: (*a*) S.-E. Zhu, F. Li and G.-W. Wang, *Chem. Soc. Rev.*, 2013, DOI: 10.1039/C3CS35494F; (*b*) G.-W. Wang, *Chem. Soc. Rev.*, 2013, DOI: 10.1039/c3cs35526h; (*c*) J. Huot, D. B. Ravnsbæk, J. Zhang, F. Cuevas, M. Latroche and T. R. Jensen, *Prog. Mater. Sci.*, 2013, **58**, 30–75; (*d*) R. B. N. Baig and R. S.Varma, *Chem. Soc. Rev.*, 2012, **41**, 1559–1584; (*e*) 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. Waddell, *Chem. Soc. Rev.*, 2012, **41**, 413–447; (*f*) A. Stolle, T. Szuppa, S. E. S. Leonhardt and B. Ondruschka, *Chem. Soc. Rev.*, 2011, **40**, 2317–2329; (*g*) G. Kaupp, *CrystEngComm*, 2009, **11**, 388–403; (*h*) B. Rodríguez, A. Bruckmann, T. Rantanen and C. Bolm, *Adv. Synth. Catal.*, 2007, **349**, 2213–2233.

12 For most recently selected examples, see: (*a*) G.-P. Fan, Z. Liu and G.-W. Wang, *Green Chem.*, 2013, **15**, 1659–1664; (*b*) C. B. Aakeröy and A. S. Sinha, *RSC Adv.*, 2013, **3**, 8168–8171; (*c*) M. Jorres, S. Mersmann, G. Raabe and C. Bolm, *Green Chem.*,

2013, **15**, 612–616; (*d*) J.-B. Yu, Z.-H. Li, K.-Y. Jia, Z.-J. Jiang, M.-L. Liu and W.-K. Su, *Tetrahedron Lett.*, 2013, **54**, 2006–2009; (*e*) N. Mukherjee, S. Ahammed, S. Bhadra and B. C. Ranu, *Green Chem.*, 2013, **15**, 389–397; (*f*) I. Y. Jeon, H. J. Choi, S. M. Jung, J. M. Seo, M. J. Kim, L.-M. Dai and J. B. Baek, *J. Am. Chem. Soc.*, 2013, **135**, 1386–1393; (*g*) J.-B. Yu, Z.-H. Li and W.-K. Su, *Synth. Commun.*, 2013, **43**, 361–374; (*h*) M. Pascu, A. Ruggi, R. Scopelliti and K. Severin, *Chem. Commun.*, 2013, **49**, 45–47; (*i*) Z. Liu, G.-P. Fan and G.-W. Wang, *Chem. Commun.*, 2012, **48**, 11665–11667; (*j*) G.-W. Wang and J. Gao, *Green Chem.*, 2012, **14**, 1125–1131.

13 (*a*) Z. Zhang, Z.-W. Peng, M.-F. Hao and J.-G. Gao, *Synlett*, 2010, 2895–2898; (*b*) Z. Zhang, J. Gao, J.-J. Xia and G.-W. Wang, *Org. Biomol. Chem.*, 2005, **3**, 1617–1619; (*c*) Z. Zhang, Y.-W. Dong, G.-W. Wang and K. Komatsu, *Synlett*, 2004, 61–64; (*d*) Z. Zhang, Y.-W. Dong, G.-W. Wang and K. Komatsu, *Chem. Lett.*, 2004, **33**, 168–169; (*e*) Z. Zhang, G.-W. Wang, C.-B. Miao, Y.-W. Dong and Y.-B. Shen, *Chem. Commun.*, 2004, 1832–1833.

14 G.-W. Wang, J.-X. Li, Y.-J. Li and Y.-C. Liu, *J. Org. Chem.*, 2006, **71**, 680–684.

15 (*a*) V. Štrukil, M. D. Igrc, L. Fábián, M. Eckert-Maksić, S. L. Childs, D. G. Reid, M. J. Duer, I. Halasz, C. Mottillo and T. Friščić, *Green Chem.*, 2012, **14**, 2462–2473; (*b*) V. Štrukil, D. Margetić, M. D. Igrc, M. Eckert-Maksić and T. Friščić, *Chem. Commun.*, 2012, **48**, 9705–9707; (*c*) V. Štrukil, M. D. Igrc, M. Eckert-Maksić and T. Friščić, *Chem.–Eur. J.*, 2012, **18**, 8464–8473.