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Solvent-free mechanochemical and one-pot reductive benzylizations of malononitrile and 4-methylaniline using Hantzsch 1,4-dihydropyridine as the reductant†

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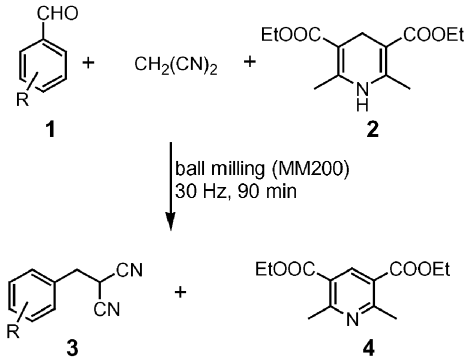
Under mechanical milling conditions, direct reductive benzylizations of malononitrile and 4-methylaniline by aromatic aldehydes were achieved using a Hantzsch 1,4-dihydropyridine as the reductant.

Chemical hydrogenations of double bond-containing compounds including imines, benzylidenemalononitriles and various other α,β-unsaturated systems often involve the use of metal catalysts[1] or stoichiometric amount of metal hydrides.[2] In these cases there are some drawbacks, such as the use of expensive and even toxic metals, relatively low chemoselectivity and so on. To circumvent these problems one of the best alternatives is to apply organoreductants, which have been arousing great interest in recent years.[3] As a typical example among these organoreductants, Hantzsch 1,4-dihydropyridine (HEH), which possesses excellent reducibility, has been investigated to a great extent.[4] But in most cases it was used as model of hydride-reduction cofactor NAD(P)H to mimic biological reductions of various unsaturated compounds. Tremendous efforts were made to study mainly the mechanistic details of these systems[5] and relatively little attention has been paid to the application of HEH as a reducing agent in organic synthesis. In recent years there have been some developments in this field,[6,7] especially with the most recent applications in the selective reduction of α,β-unsaturated aldehydes.[3a,8] Although these attempts have achieved good to excellent results, there are still some limitations, including the use of organic solvents, the need of excessive HEH or protection under an inert atmosphere and relatively long reaction times. In the course of our study on mechanical organic synthesis[9] we were inspired to perform these reactions using a mechanical milling technique, which supplies a completely solvent-free and thus environmentally friendly condition. Traditionally, benzyl malononitriles and anilines were synthesized by the reduction of benzylidene malononitriles and anilines, which should be prepared in advance due to the susceptibility of the aldehydes to common metal-containing reductants. In this communication, we report a direct reductive benzylization process in which a mixture of an aldehyde and malononitrile (or 4-methylaniline) and is directly treated with Hantzsch 1,4-dihydropyridine in a one-pot fashion, under mechanical milling conditions.

The direct reductive benzylization of malononitrile (Scheme 1) was investigated first. In a typical procedure, a mixture of aldehyde **1** (0.5 mmol), malononitrile (0.5 mmol) and Hantzsch 1,4-dihydropyridine **2** (0.51 mmol) was introduced, together with a stainless ball of 7.0 mm diameter, into a stainless jar (5 mL).The same mixture was also introduced into a second, parallel jar. The two reaction vessels were closed and fixed on the vibration arms of a ball-milling apparatus (Retsch MM200 mixer mill, Retsch GmbH, Haan, Germany) and were vibrated vigorously at a rate of 1800 rounds per minute (30 Hz) at room temperature for 90 min. The results are summarized in Table 1.



Scheme 1

Table 1 Direct reductive benzylization of malononitrile by various aromatic aldehydes using HEH **2** as the reductant

Product **3**	R	Yield (%)[a],([b])
3a	4-Cl	97 (82)
3b	4-Br	98 (83)
3c	4-NO_2	98 (87)
3d	4-CN	98 (86)
3e	3-NO_2	98 (86)
3f	2-NO_2	98 (71)
3g	3,4-Cl	95 (54)
3h	2,4-Cl	98 (72)
3i	H	68 (—)
3j	4-$N(CH_3)_2$	0

[a] Isolated yield from direct separation of the reaction mixtures by flash column chromatography over silica gel with petroleum ether–ethyl acetate as the eluent. [b] Isolated yield from the following procedure: the reaction mixtures were immersed in 20 mL of diluted hydrochloric acid (5%) with the aid of ultrasonic irradiation, then the desired solid products were collected by Büchner filtration, washed with H_2O and dried in a desiccator.

We found that all the aldehydes were not reduced under these conditions; that is, the reduction was completely selective for aldehyde-derived benzylidene malononitriles. From Table 1 it can be seen that in most cases the reactions afforded exclusively the redox products **3** and **4** in nearly quantitative yields. The desired products, benzyl malononitriles **3**, were isolated from direct separation of the reaction mixtures by flash column chromatography. Most of them could also be obtained by following a more straightforward and easy work-up procedure, as shown in Table 1, which may be more practical without regard to the relatively lower yields. Furthermore, this reaction system exhibits a significant substituent effect, which can be easily understood from the fact that the aldehydes bearing electron-withdrawing groups show obviously higher reactivities than

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† Electronic supplementary information (ESI) available: melting point for compounds **3** and **5**, and spectral data for compounds **3f–3h**, **5g** and **5h**. See http://www.rsc.org/suppdata/ob/b5/b502662h/.

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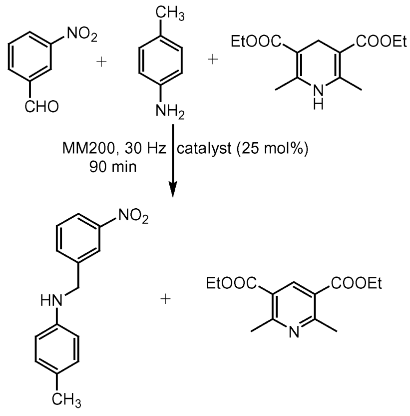
those without substituents or bearing electron-donating groups. For example, benzaldehyde afforded only 68% of product **3i** and 4-dimethylaminobenzaldehyde did not give any desired product. It is worth pointing out that the Hantzsch 1,4-dihydropyridine employed here also acted as a base to catalyze the Knoevenagel condensation step, similar to that catalyzed by piperidine.[10] To confirm this point we have carried out controlled reactions of aldehydes with malononitrile in the absence of and in the presence of a catalytic amount (5 mol%) of HEH **2** under the same conditions, which afforded only trace and quantitative amount of benzylidene malononitriles, respectively.

To further investigate the reactivity of HEH **2** as a reducing agent in organic synthesis, we extended its applications to imines. However, the reaction hardly proceeded without the addition of any additive. To improve this poorness, we have investigated the addition of various Lewis acids. The catalytic effect of several Lewis acids (25 mol%) on the one-pot mechanical reduction of *in situ* generated imine (3-nitro-benzylidene-*p*-tolylamine) from 3-nitrobenzaldehyde and 4-methylaniline with HEH **2** (Scheme 2) for 90 min was examined to sort out the best catalyst, and the results are listed in Table 2.



5a

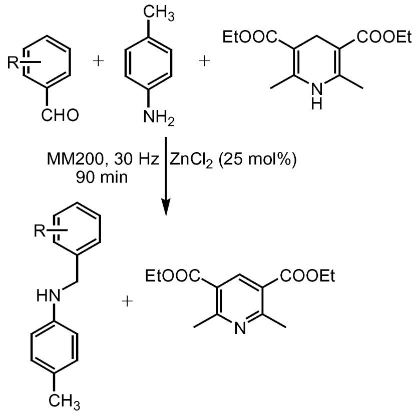
Scheme 2

Table 2 Catalytic activity of various Lewis acids in the reducion of *in situ* generated 3-nitro-benzylidene-*p*-tolylamine using HEH **2** as the reductant

Entry	Catalyst (25 mol%)	Yield (%)
1	None	Trace
2	$CeCl_3 \cdot H_2O$	52
3	$NiCl_2 \cdot 6H_2O$	48
4	$ZnCl_2$	98
5	$CuSO_4 \cdot 5H_2O$	28
6	$Cu(OAc)_2 \cdot H_2O$	34
7	$Co(OAc)_2 \cdot 4H_2O$	37
8	p-CH_3–$C_6H_4SO_3H$	88
9	H_3BO_3	39

It can be seen from Table 2 that all the additives can promote the reaction to a certain extent, but it is obvious that $ZnCl_2$ (entry 4) and *p*-toluene sulfonic acid (entry 8) demonstrate superior catalytic activity among them. This result prompted us to select $ZnCl_2$ as the catalyst for further study; that is, we used $ZnCl_2$ to catalyze the direct mechanical benzylization of 4-methylaniline by various aldehydes with HEH **2** as the reductant for 90 min (Scheme 3).

The experimental procedure is similar to that of malononitrile as discussed above, except that products **5** were obtained just by column chromatography since they are more inclined to change in the presence of HCl. As expected, very good results were achieved and are summarized in Table 3. Here again, the same significant substituent effect was observed, just as that observed in the reactions of malononitrile.



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Scheme 3

Table 3 Direct reductive benzylization of 4-methylaniline by various aromatic aldehydes using HEH **2** as the reductant

Product **5**	R	Yield (%)[a]
5a	3-NO_2	98
5b	4-Br	96
5c	4-NO_2	95
5d	4-CN	96
5e	4-Cl	94
5f	2-NO_2	95
5g	2,4-Cl	97
5h	3,4-Cl	98
5i	H	62
5j	4-$N(CH_3)_2$	0

[a] Isolated yield from direct separation of the reaction mixtures by flash column chromatography over silica gel with petroleum ether–ethyl acetate as the eluent.

It is known that Hantzsch 1,4-dihydropyridine **2** is prone to oxidation even in the presence of air. On the other hand, traditional reactions involving HEH **2** were most commonly performed in organic solvents and the reaction time was very long. Therefore, treatment of these reactions often used largely excessive HEH or inert gases such as nitrogen and argon. In the present protocol, all the reactions were performed under solid-state conditions without any organic solvent at room temperature, the reaction time was relatively short (90 min) and 1.02 molar equivalent of HEH is enough to promote the reaction completely, even without protection by any inert gas.

In summary, we present here the first example of Hantzsch 1,4-dihydropyridine used in mechanochemical organic synthesis. The present work has successfully developed a more straightforward method for the synthesis of benzyl malononitriles and anilines. There is no need for the separation of the *in situ* generated benzylidene malononitriles and *p*-tolylamines and good to excellent yields of benzylated products can still be achieved in a one-pot process. Furthermore, the reductant Hantzsch 1,4-dihydropyridine demonstrates a complete selectivity, for there is no reduction of any other functional group such as aldehyde, nitro or cyano groups. All of these advantages make this protocol a promising and thus appealing alternative both in academic research and in practical processes.

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Notes and references

1 (*a*) M. A. Esteruelas and L. A. Oro, *Chem. Rev.*, 1998, **98**, 577–588; (*b*) G. Zassinovich, G. Mestroni and S. Gladiali, *Chem. Rev.*, 1992, **92**, 1051–1069.

2 (*a*) B. C. Ranu and S. Samanta, *Tetrahedron*, 2003, **59**, 7901–7906; (*b*) T. Suwa, E. Sugiyama, I. Shibata and A. Baba, *Synlett*, 2000, 556–558.

3 (*a*) J. W. Yang, M. T. Hechavarria Fonseca and B. List, *Angew. Chem., Int. Ed.*, 2005, **44**, 108–110; (*b*) M. R. Acocella, O. G. Mancheno, M. Bella and K. A. Jørgensen, *J. Org. Chem.*, 2004, **69**, 8165–8167; (*c*) R. M. Kellog, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 8, p. 79–106.

4 For reviews, see: (*a*) R. Lavilla, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1141–1156; (*b*) D. M. Stout, *Chem. Rev.*, 1982, **82**, 223–243.

5 (*a*) X.-Q. Zhu, H.-R. Li, Q. Li, T. Ai, J.-Y. Lu, Y. Yang and J.-P. Cheng, *Chem. Eur. J.*, 2003, **9**, 871–880; (*b*) S. J. Garden, C. R. W. Guimarães, M. B. Corréa, C. A. F. de Oliveira, A. D. Pinto and R. B. de Alencastro, *J. Org. Chem.*, 2003, **68**, 8815–8822; (*c*) X.-Q. Zhu, H.-L. Zou, P.-W. Yuan, Y. Liu, L. Cao and J.-P. Cheng, *J Chem. Soc., Perkin Trans. 2*, 2000, 1857–1861; (*d*) X.-Q. Zhu, Y.-C. Liu and J.-P. Cheng, *J. Org. Chem.*, 1999, **64**, 8980–8981.

6 For application as chiral NAD(P)H models, see: (*a*) J. Li, Y.-C. Liu, J.-G. Deng, X.-Z. Li, X. Cui and Z. Li, *Tetrahedron: Asymmetry*, 2000, **11**, 2677–2682; (*b*) N. Kanomata and T. Nakata, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1207–1211; (*c*) A. Ohno, A. Tsutsumi, Y. Kawai, N. Yamazaki, Y. Mikata and M. Okamura, *J. Am. Chem. Soc.*, 1994, **116**, 8133–8137; (*d*) Y. Combret, J. Duflos, G. Dupas, J. Bourguignon and G. Queguiner, *Tetrahedron: Asymmetry*, 1993, **4**, 1635–1644; (*e*) K. Skog and O. Wennerstrom, *Tetrahedron Lett.*, 1992, **33**, 1751–1754.

7 For recent examples, see: (*a*) T. Itoh, K. Nagata, M. Miyazaki, H. Ishikawa, A. Kurihara and A. Ohsawa, *Tetrahedron*, 2004, **60**, 6649–6655; (*b*) B.-L. Zhang, X.-Q. Zhu, J.-Y. Lu, J.-Q. He, P. G. Wang and J.-P. Cheng, *J. Org. Chem.*, 2003, **68**, 3295–3298; (*c*) J. Zhang, M.-Z. Jin, W. Zhang, L. Yang and Z.-L. Liu, *Tetrahedron Lett.*, 2002, **43**, 9687–9689; (*d*) H. W. Lee, B. Y. Kim, J. B. Ahn, H. J. Son, J. W. Lee, S. K. Ahn and C. I. Hong, *Heterocycles*, 2002, **57**, 2163–2173; (*e*) S. Torchy, G. Corrdonnier, D. Barbry and J. J. Vanden Eynde, *Molecules*, 2002, **7**, 528–533.

8 S. G. Ouellet, J. B. Tuttle and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 32–33.

9 For a review, see: G.-W. Wang, “Fullerene Mechanochemistry”, in *Encyclopedia of Nanoscience and Nanotechnology*, ed. H. S. Nalwa, American Scientific Publishers, Stevenson Ranch, 2004, vol. 3, pp. 557–565; for mechanochemical non-fullerene reactions, see: (*a*) Z. Zhang, C.-B. Miao, G.-W. Wang, Y.-W. Dong and Y.-B. Shen, *Chem. Commun.*, 2004, 1832–1833; (*b*) Z. Zhang, Y.-W. Dong, G.-W. Wang and K. Komatsu, *Synlett*, 2004, 61–64; (*c*) Z. Zhang, Y.-W. Dong, G.-W. Wang and K. Komatsu, *Chem. Lett.*, 2004, **33**, 168–169.

10 S. Abdallahelayoubi, F. Texierboullet and J. Hamelin, *Synthesis*, 1994, 258–260.