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Synthesis of 2-imidazolines by co-grinding of *N*-tosylaziridines and nitriles

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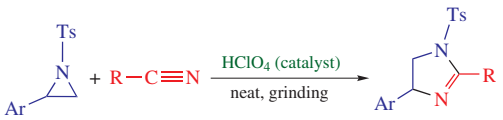
Solvent-free solid-state co-grinding of *N*-tosylaziridines and nitriles in the presence of perchloric acid as the catalyst affords 2-imidazolines in good yields.



Keywords: solvent-free reactions, aziridines, grinding, 2-imidazolines, nitriles, heterocyclization.

Chemical transformations involving mechanochemical (grinding) reactions using a mortar and pestle were initiated a long time ago, however recently, mechanochemistry has attracted much attention because it allows reactions to be promoted under solvent-free conditions.[1]

Imidazolines are considered as important five-membered heterocycles.[2] 2-Imidazolines can be found in natural product chemistry, pharmaceutical chemistry, organic synthesis, coordination chemistry, and homogeneous catalysis. They are useful intermediates for designing molecules with pharmacological activities such as anti-inflammatory,[3] antidiabetic[4] and anticancer[5] and have been applied as synthetic intermediates[6] and auxiliaries[7] or catalysts[8] for asymmetric synthesis.

Several methods are available for the synthesis of 2-imidazolines.[9] Despite the non-typical ways to construct imidazolinium cycle,[9(b),(c)] a traditional route involves the reactions of vicinal diamines and carboxylic acid derivatives.[9(d)–(h)] Aziridines, synthetic equivalents of diamines, were also applied,[9(i)–(l)] in particular, in [3+2] cycloaddition between *N*-tosylaziridines and nitriles.[9(m)–(r)] In continuation of our previous studies on aziridine chemistry,[10] herein we report a simple and convenient procedure for the rapid synthesis of 2-imidazolines by co-grinding of *N*-tosylaziridines and various nitriles in the presence of perchloric acid.†

The required *N*-tosylaziridines were obtained as reported.[11] The optimization of the reaction conditions (Table S1, see Online Supplementary Materials) included variation of acid catalyst and revealed $HClO_4$ to be optimal. With the optimized conditions in hands, various 2-aryl-1-tosylaziridines **1a–h** were reacted with benzonitriles **2a–i** (Scheme 1). The yields of products **3a–z** were generally good to excellent regardless of electron-withdrawing or -donating properties of the substituents in both aryl moieties Ar^1 and Ar^2 (see Scheme 1). The structure of 4-(2-chlorophenyl)-2-(3-methoxyphenyl)-1-tosyl-4,5-dihydro-1*H*-imidazole **3l** was ultimately established by X-ray study (Figure 1).‡

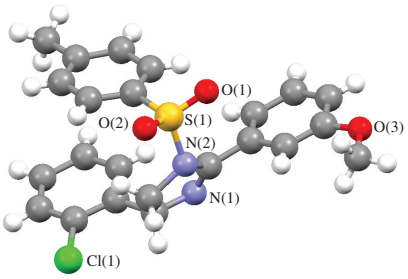
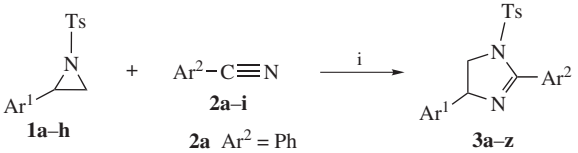


Figure 1 Molecular structure of 4-(2-chlorophenyl)-2-(3-methoxyphenyl)-1-tosyl-4,5-dihydro-1*H*-imidazole **3l**.

† *General procedure for the synthesis of compounds* **3** *and* **5**. A mixture of aziridine **1** (0.25 mmol), nitrile **2** or **4** (0.25 mmol) and perchloric acid (0.25 mmol) was placed in a mortar. The reaction mixture was thoroughly ground at room temperature for 5 min. After completion (TLC) the reaction mixture was diluted with a 1 : 1 water/ethyl acetate mixture (10 ml) and washed with sodium bicarbonate (10 ml) followed by brine solution (10 ml). Then the combined organic layer was dried over anhydrous Na_2SO_4. Evaporation of solvent furnished the crude product which was subjected to column chromatography using ethyl acetate–light petroleum as eluent to obtain the analytically pure product.

‡ *Crystallographic data for* **3l**. Crystals of $C_{23}H_{21}ClN_2O_3S$ (M = 440.93) are monoclinic, space group $P12_11$, at 296(2) K: a = 9.3569(8), b = 10.1481(8) and c = 21.9506(18) Å, β = 90.037(4)°, V = 2084.3(3) Å^3, Z = 2, d_{calc} = = 0.703 g cm^{-3}, λ(MoKα) = 0.71073 Å, F(000) = 460. 60909 reflections were measured and 10722 independent reflections (R_{int} = 0.0754) were used in a further refinement. The refinement converged to wR_2 = 0.2974 and GOF = 1.990 for all independent reflections [R_1 = 0.0978 was calculated against F for 9965 observed reflections with $I > 2\sigma(I)$]. The measurements were performed on a Bruker Apex Smart CCD diffractometer with graphite-monochromated MoKα radiation (λ = 0.71073 Å). The structure was solved by direct methods, and the non-hydrogen atoms were located from the trial structure and then refined anisotropically with SHELXTL using a full-matrix least-squares procedure based on F^2. The hydrogen atom positions were fixed geometrically at calculated distances and allowed to ride on the parent atoms.

CCDC 1910227 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.



1a–h **2a–i** **3a–z**

1a Ar^1 = Ph
1b Ar^1 = 2-MeC_6H_4
1c Ar^1 = 3-MeC_6H_4
1d Ar^1 = 2-ClC_6H_4
1e Ar^1 = 3-ClC_6H_4
1f Ar^1 = 4-ClC_6H_4
1g Ar^1 = 3-BrC_6H_4
1h Ar^1 = 4-BrC_6H_4

2a Ar^2 = Ph
2b Ar^2 = 3-MeC_6H_4
2c Ar^2 = 4-MeC_6H_4
2d Ar^2 = 3-$MeOC_6H_4$
2e Ar^2 = 2-ClC_6H_4
2f Ar^2 = 3-ClC_6H_4
2g Ar^2 = 4-ClC_6H_4
2h Ar^2 = 2-FC_6H_4
2i Ar^2 = 4-FC_6H_4

3	Ar^1	Ar^2	Yield (%)		Ar^1	Ar^2	Yield (%)
a	Ph	Ph	95	**n**	2-ClC_6H_4	4-ClC_6H_4	91
b	Ph	3-$MeOC_6H_4$	74	**o**	2-ClC_6H_4	2-FC_6H_4	89
c	Ph	2-ClC_6H_4	63	**p**	2-ClC_6H_4	4-FC_6H_4	89
d	Ph	3-ClC_6H_4	53	**q**	3-ClC_6H_4	3-$MeOC_6H_4$	85
e	Ph	4-ClC_6H_4	65	**r**	4-ClC_6H_4	3-$MeOC_6H_4$	81
f	Ph	2-FC_6H_4	61	**s**	3-BrC_6H_4	Ph	76
g	2-MeC_6H_4	3-$MeOC_6H_4$	74	**t**	3-BrC_6H_4	4-MeC_6H_4	86
h	3-MeC_6H_4	3-$MeOC_6H_4$	68	**u**	3-BrC_6H_4	3-$MeOC_6H_4$	84
i	3-MeC_6H_4	2-FC_6H_4	55	**v**	4-BrC_6H_4	Ph	80
j	2-ClC_6H_4	Ph	92	**w**	4-BrC_6H_4	3-MeC_6H_4	80
k	2-ClC_6H_4	3-MeC_6H_4	78	**x**	4-BrC_6H_4	3-$MeOC_6H_4$	82
l	2-ClC_6H_4	3-$MeOC_6H_4$	74	**y**	4-BrC_6H_4	2-FC_6H_4	76
m	2-ClC_6H_4	3-ClC_6H_4	87	**z**	4-BrC_6H_4	4-FC_6H_4	74

Scheme 1 *Reagents and conditions*: i, $HClO_4$ (cat.), neat, grinding, 5 min.

The similar reaction of representative aziridines **1a**,**d**,**f**,**h** with aliphatic **4a**,**b** or cinnamic **3c** nitriles (Scheme 2) afforded also the desired imidazolines **5a–g** in good yields.

The practical applicability of the procedure developed was demonstrated on the gram scale with the model reactants **1a** and **2a** (Scheme S1, see Online Supplementary Materials), when product **3a** was obtained in 92% yield.

Based on our previous works on aziridines[10] and published data,[9(m),(o)] a probable mechanistic pathway may be proposed (Scheme 3). In the presence of perchloric acid, protonated aziridine **A** was formed and underwent ring-opening to form a stable benzylic carbocation **B** which on further reaction with nitrile led to imidazolines **3** or **5**.

In conclusion, we have demonstrated a simple, solvent-free, energy efficient, clean and high yielding procedure for the synthesis of 2-imidazoline derivatives. This protocol is also applicable to a gram-scale synthesis.

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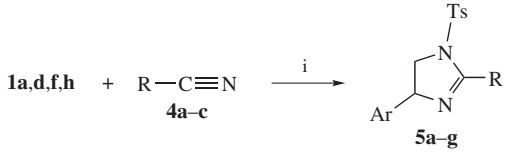
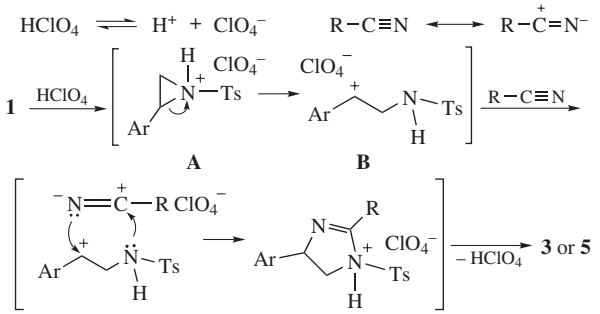


1a,**d**,**f**,**h** **4a–c** **5a–g**

4a R = Me
4b R = $(CH_2)_3Cl$
4c R = CH=CHPh

5a Ar = Ph, R = Me, 57%
5b Ar = 2-ClC_6H_4, R = Me, 84%
5c Ar = Ph, R = $(CH_2)_3Cl$, 59%
5d Ar = 2-ClC_6H_4, R = $(CH_2)_3Cl$, 80%
5e Ar = 2-ClC_6H_4, R = CH=CHPh, 82%
5f Ar = 4-ClC_6H_4, R = CH=CHPh, 78%
5g Ar = 4-BrC_6H_4, R = CH=CHPh, 70%

Scheme 2 *Reagents and conditions*: i, $HClO_4$ (cat.), neat, grinding, 5 min.



Scheme 3

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.03.019.

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