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Mechanochemical Magnesium-Mediated Minisci C–H Alkylation of Pyrimidines with Alkyl Bromides and Chlorides

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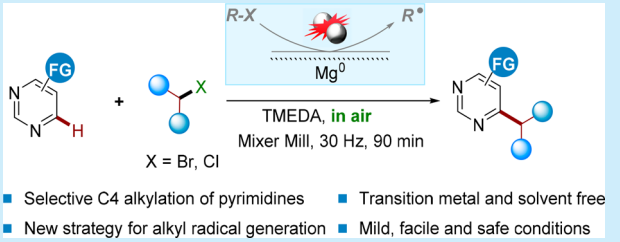
ABSTRACT: A novel method to synthesize 4-alkylpyrimidines by the mechanochemical magnesium-mediated Minisci reaction of pyrimidine derivatives and alkyl halides has been reported. The reaction process operates with a broad substrate scope and excellent regioselectivity under mild conditions with no requirement of transition-metal catalysts, solvents, and inert gas protection. The practicality of this protocol has been demonstrated by the up-scale synthesis, mechanochemical product derivatization, and antimalarial drug pyrimethamine preparation.



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Pyrimidine and its derivatives are a highly significant class of nitrogen-rich heterocyclic compounds that are widely found in natural products, artificial molecules, and pharmaceuticals.[1] Advances in transition-metal-catalyzed C–H activation has simplified the synthesis of heteroarenes;[2] however, the achievement of direct functionalization of pyrimidines remains a challenging goal owing to their innate properties such as they always serve as directing groups[3] and ligands.[4]

In recent years, radical-mediated C–H functionalization has attracted much attention in organic synthesis as it is a promising complement to C–H activation strategy.[5] In particular, Minisci-type reactions offer great opportunities for early- and late-stage functionalization of pharmaceutically relevant molecules.[6] In these reactions, the generation of unstabilized alkyl radicals is crucial to bestow a controlled outcome of the ensuing processes. Alkyl halides as commercially available chemical building blocks appeared as the ideal choice to form such species via homolytic cleavage of a labile C–X bond.[7] Classically, their role as radical precursors for generating carbon radicals is limited to halogen-atom transfer (XAT) strategies based on hazardous tin or silicon reagents.[8] Alexanian and co-workers' recent works[9] employed hybrid organometallic–radical catalysis (single electron activation) to generate alkyl radicals from unactivated alkyl halides. Despite these advances, the use of precious metals/ligands, high temperature, and the inability to add tertiary alkyl radicals to heteroarenes calls for further development of this method. Metallaphotoredox catalysis provided a milder alternative,[10] but introduction of strongly reducing systems was often necessary for alkyl halides with highly negative reduction potentials (Scheme 1a).[11] Therefore, the identification of a reliable chemical strategy for carbon radical generation from unactivated alkyl halides to facilitate the functionalization of pyrimidines still needs to be explored.

Hamdouchi and Garst et al.'s pioneering works[12] on the mechanisms of Grignard reactions indicating alkyl radicals could be generated as an intermediate at the magnesium surface caught our attention (Scheme 1b). Another important information finding by Whitaker[13] showed that unsolvated Grignard reagents could be formed under mechanochemical milling conditions, where highly reactive excess Mg powder can prove to diversify reactions. It was also discovered by Browne and co-workers[14] that the input of mechanical energy was in favor of breaking down the resilient zinc oxide surface, which was also crucial for magnesium activation and boosting the formation of organozinc species without carefully prepared solvents and inert gases (Scheme 1c). Drawing inspiration from these reports and our previous works[15] on mechanochemical reactions[16] with altered selectivity and reactivity, we envisioned that a mechanochemical interaction of alkyl halide reagents with freshly generated magnesium surfaces could offer a straightforward approach to access various alkyl radicals that might be caught by pyrimidines rather than undergoing Grignard reactions. Herein, we reported a mechanochemical magnesium-mediated Minisci reaction of pyrimidines with a variety of primary, secondary, and tertiary alkyl halides, which gave a facile and efficient synthetic method for 4-alkylpyrimidines (Scheme 1d).

We commenced our studies with *N*-pyrimidylindole (**1a**) and 2-bromopropane (**2a**). The former is a challenging radical receptor because of the possibility of the radical addition

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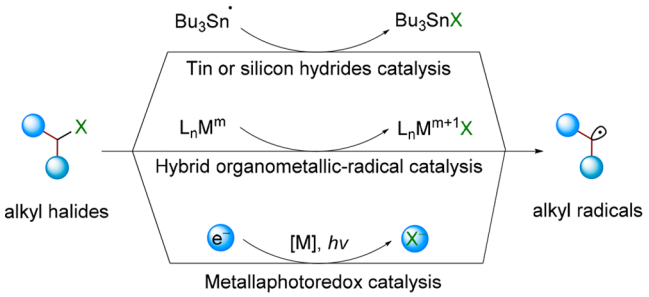
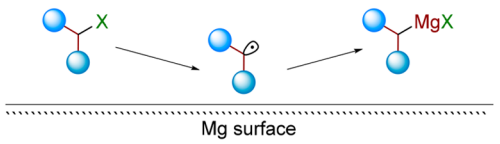
Scheme 1. Background and Reaction Design of This Work

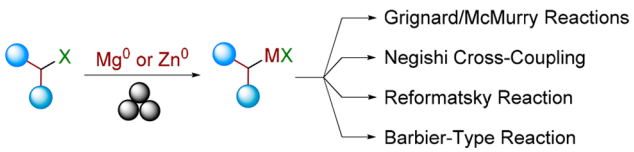
a) Typical methods for the generation of carbon radicals from alkyl halides



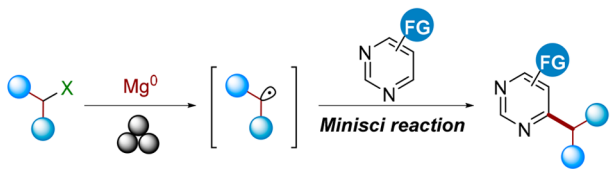
b) The generation of radical R• via the formation of RMgX



c) The formation of organometallic species via mechanochemical

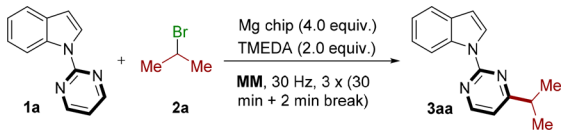


*d) **This work:** New approach to access alkyl radicals via mechanochemical*



occurring at the indole ring.[17] However, as part of our optimization, we particularly sought to identify a mechanochemical strategy that would be selective for the position of pyrimidine even in the presence of other active heterocycles. We first examined the magnesium chip as a radical initiator under the preferred milling conditions[18] without specific inert gas protection, which delivered the desired product **3aa** in moderate yield with excellent regioselectivity (Table 1, entry 1; Table S1). Subsequently, the control experiments revealed that both the magnesium and the additive *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) were essential for this transformation (entries 2 and 3), while reducing their dosages led to lower yields (entries 4 and 5). The magnesium forms were next tested, in contrast to previous work,[14] and obvious influences on the product yields were found (entry 6). Smaller particle size magnesium was probably inclined to the formation of Grignard reagents rather than affording radicals. Several nitrogen-containing bases, including triethylamine, *N*,*N*′-dimethyl-1,2-ethanediamine (DMEDA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were screened in a bid to improve the yield, yet all of these failed to afford higher yields (entry 7; Table S1). However, liquid-assisted grinding[19] using either tetrahydrofuran or 1,4-dioxane gave comparable results (entry 8). It should be noted that all the transformations precluded the use of glovebox or Schlenk-line techniques, which is indispensable for moisture- and/or oxygen-sensitive reagents.[20]

Table 1. Optimization of Mechanochemical Magnesium-Mediated Minisci Reaction between 1a and 2a



entry	deviation from standard conditions	3aa[a] (%)
1	none	61
2	without Mg chip	nr
3	without TMEDA	15
4	3.0 equiv instead of 4.0 equiv of Mg chip	38
5	1.0 equiv instead of 2.0 equiv of TMEDA	32
6	Mg foil/powder instead of Mg chip	36/17
7	Et_3N/DMEDA/DBU instead of TMEDA	19/44/46
8[b]	THF/1,4-dioxane as LAGs	51/51

[a]Yield of isolated product. [b]LAGs (20 μL, η = 0.3 [V (liquid; μL)/m (solid reagents; mg)]) was added. MM = Mixer Mill.

Under the optimized conditions, we set out to explore the generality of this method against a variety of unactivated alkyl halides. As shown in Scheme 2a, primary bromoalkanes carrying long chain and sterically hindered alkyl as well as functionalizable alkenyl groups were compatible with this mild protocol, generating corresponding products in synthetically acceptable yields (**3ab**−**3ag**), despite the low stability and nucleophilicity of primary alkyl radicals[21] which made them the challenging reactants in Minisci reactions. Comparatively, the alkylation reactions of secondary and tertiary alkyl bromides produced higher yields, where both cyclic and noncyclic alkyl radicals were well tolerated. We were pleased to find that inexpensive and widely available alkyl chlorides (**2a**′, **2c**′, **2l**′, and **2m**′) could also be used in this reaction, and even higher yields were obtained in some cases (**3ac** and **3la**). To the best of our knowledge, no successful examples of Minisci C−H alkylation of alkyl chlorides have been reported thus far, owing to the strong C−Cl bond strength.[22] Thus, the current mechanochemical process provides a cost-efficient route for the application of alkyl chlorides in organic synthesis.

Following this, the substrate scope of pyrimidines was evaluated (Scheme 2b). It was observed that *N*-pyrimidylindoles bearing electron-withdrawing or electron-donating groups at the 2-, 3-, 4-, 5-, or 6-positions on the indole ring afforded the corresponding products (**3ba**−**3fa**) in satisfactory yields. Interestingly, the substrates that possess electron-enriched indoles produced higher yields (compare **3ba**−**3ca** vs **3da**−**3fa**). The structure of **3da** (CCDC 2087972) was unambiguously confirmed by single-crystal X-ray analysis. To further demonstrate the regioselectivity of this mechanochemical Minisci reaction, diverse 2-substituted pyrimidines containing (hetero)arenes, aromatic amines, and alkylamines **1g**−**1r** were tested, and the results showed that only C4 alkylation of pyrimidines occurred in all cases. Of note, the mechanochemical conditions allowed the introduction of the sensitive amino group (**3ra**), which provides synthetic handles for further derivatization and application in drug synthesis.[23] Moreover, the reaction was not restricted to substituted pyrimidines, as pyridines were also suitable substrates. 2-Methylpyridine **1s**, pyridine **1t**, and 4-methoxylpyridine **1u** furnished the desired alkylation products (**3sl**, **3ta**, and **3up**) with 71%, 66%, and 62% yields, respectively. It should be noted that the former two showed excellent C4 position

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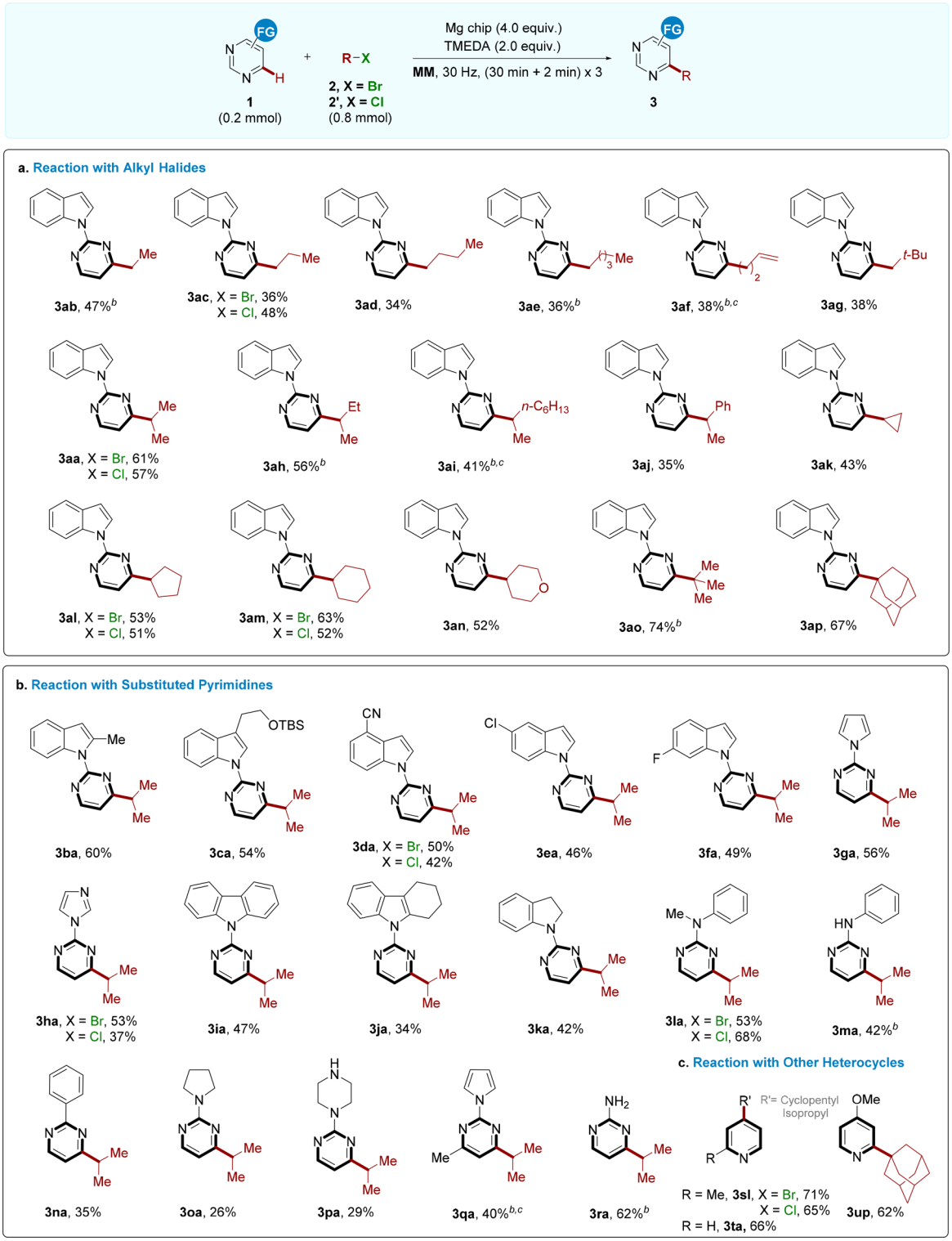
Scheme 2. Mechanochemical Magnesium-Mediated Minisci Reaction between 1 and Alkyl Bromides and Chlorides[a]



[a]All yields are isolated yields. [b]Milling at 30 Hz for [4(30 min + 2 min break)]. [c]**2** (1.0 mmol), Mg chip (5.0 equiv).

selectivity, which is a sharp contrast to solution chemistry[24] where mixed products were commonly encountered and C6 alkylation was preferred.

The practicality of this protocol has also been demonstrated (Scheme 3). The scale-up experiment showed that the efficiency of the multimillimolar reaction was not significantly compromised (for details, see the Supporting Information). Gratifyingly, the Minisci reaction products could undergo derivatizations through mechanochemical base metal catalyzed C−H functionalizations (Scheme 3a). In this context, we achieved the first $MnCl_2$-catalyzed indole C2 alkylation with in situ generated organomagnesium under solvent-free conditions, which provided expedient access to biisopropylated *N*-pyrimidylindole **4a**. The reaction features notably (1) nonpre-

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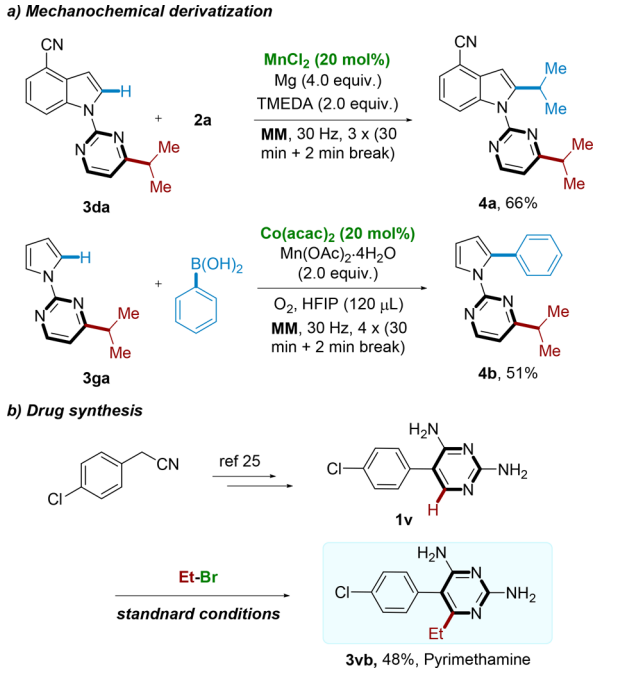
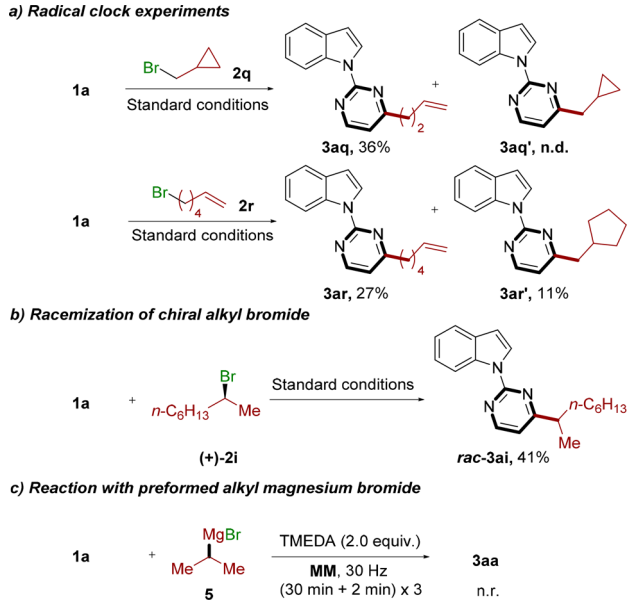
Scheme 3. Demonstration of Synthetic Utility



Scheme 4. Mechanistic Studies



cious Mn(II) catalysis without exogenous Grignard reagents, ligands, and oxidants and (2) easy-to-handle and high stability process with no requirement of inert gases and carefully prepared solvents. Another example was the mechanochemical pyrrole C2 arylation by cobalt catalysis using isopropylated pyrimidine as directing group. Further application in the synthesis of pyrimethamine, an antimalarial drug, elucidated the reliability and robustness of this method (Scheme 3b). Using a recently developed intermediate, **1v** was prepared in a developed procedure by Liu and co-workers[25] in three steps from 4-chlorobenzyl cyanide. Subsequent ethylation of **1v** with bromoethane under the standard conditions afforded the desired product in 48% yield.

Some control experiments have been performed to gain insights into the reaction mechanism (Scheme 4). First, the radical clock reactions starting from substrates **2q** and **2r** were performed to give the ring-opening product **3aq** and the cyclization product **3ar′**, respectively (Scheme 4a), revealing that the formation of carbon-centered radicals can be potentially operative. No product formation was observed from the reaction of **1a** and **2a** in the presence of radical scavengers, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and butylated hydroxytoluene (BHT) (for details, see the Supporting Information). Further, the chiral bromoalkane (+)-**2i** underwent racemization under the standard conditions to yield a product *rac*-**3ai** (Scheme 4b). The above results suggested that this protocol advances via a radical pathway. Additionally, we attempted to use the preformed Grignard reagents **5** as alkylation reagents, but no product was observed (Scheme 4c). Thus, the in situ generation of alkyl magnesium halides in the reaction mechanism can be excluded. In accordance with the widely accepted mechanism,[25,26] this mechanochemical magnesium-mediated C−H alkylation would conduct a radical-chain process.

In summary, we have developed a mechanochemical regioselective Minisci reaction for the construction of diversely functionalized pyrimidines via unprecedentedly magnesium-mediated generation of alkyl radical from commercially available alkyl halides. This strategy enabled the conversion of a wide range of primary and secondary and tertiary alkyl bromides and even alkyl chlorides under mild conditions. Mechanistic studies provided strong support for a radical-chain process, whereas in situ generation of alkyl magnesium halides could be excluded. The scale-up reactions, base metal catalyzed, mechanochemical product derivatization as well as antimalarial drug pyrimethamine synthesis elucidated the reliability and utility of the developed protocol, offering intriguing opportunities for rapid expansion of nitrogen-containing molecular complexity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02241.

Experimental procedures, X-ray crystallography data, characterization data, and NMR spectra of the products (PDF)

Accession Codes

CCDC 2087972 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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