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Alkylation of *N*H-sulfoximines under Mitsunobu-type conditions†

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Previously described approaches for the alkylation of *N*H-sulfoximines typically rely either on transition metal catalysis, or the use of traditional alkylation reagents and strong bases. Herein, we report a straightforward alkylation of diverse *N*H-sulfoximines under simple Mitsunobu-type conditions, despite the unusually high pK_a of the *N*H center.

Sulfoximines, the mono-aza analogues of sulfones, have increasingly emerged as a useful isostere for sulfur-containing, biologically-active molecules.[1] Although the first sulfoximine-containing molecule (methionine sulfoximine (**1**), Fig. 1) was characterized in the 1940s,[2] reports of sulfoximine chemistry in the literature have grown particularly quickly over the past twenty years. Indeed, the total reactions per decade involving a sulfoximine substructure increased nearly 100-fold from the 1990s to the 2010s.[1a] The physicochemical advantages offered to medicinal chemists by the sulfoximine substructure are plentiful and include the potential for chemistry on a basic, nucleophilic nitrogen center (*via* *N*H-sulfoximines), increased solubility in protic solvents compared to sulfones, and the addition of a stereocenter.[3] A number of sulfoximine-containing drug-like small molecules have been reported in the literature, including the rofecoxib analog **2**,[4] and the ataxia telangiectasia and Rad3-related kinase inhibitor AZD6738 (**3**), which has recently entered clinical trials.[5] Sulfoximines have also found use in insecticides; the insect neurotoxin sulfoxaflor (**4**) was approved by the EPA in 2013 [6] (see Fig. 1 for the chemical structures of selected sulfoximine-containing compounds).[1a]

Among other methods, *N*H-sulfoximines are readily synthesized from the corresponding thioethers using PhI(OAc)$_2$ and an ammonia source,[7] and their recent, widespread commercial availability has facilitated explorations around the chemistry available to the nucleophilic *N*H center. Many groups have described *N*-sulfonylation, sulfenylation, phosphorylation, acylation, halogenation, trifluoromethylation, and arylation, among other transformations.[8] It is therefore perhaps surprising that there are comparatively few reports describing the simple *N*-alkylation of *N*H-sulfoximines. To date, such reports rely either on the use of transition metal and/or visible light catalysis,[9] or alkylation conditions involving toxic or strongly basic reagents (which are often limited to methylations and other simple alkyl groups)[4,10] to effect this kind of transformation (Scheme 1). Although many of these studies are encouraging with respect to the high yields with which alkylated *N*H-sulfoximines can be isolated, there exists an unmet need to develop a simple, economical approach that is of greater utility to chemists working in the drug discovery space. These historical limitations of *N*H-sulfoximine alkylations prompted us to consider the following: could this type of functionalization be effected using a simpler, classical approach, specifically Mitsunobu-type chemistry?

The pK_a of the sulfoximine *N*H center is many orders of magnitude beyond the traditionally operable range for Mitsunobu-type chemistry, and, accordingly, such an approach

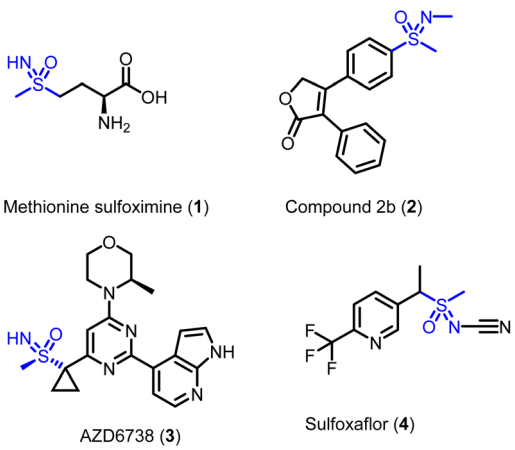

Fig. 1 Chemical structures of selected sulfoximines.

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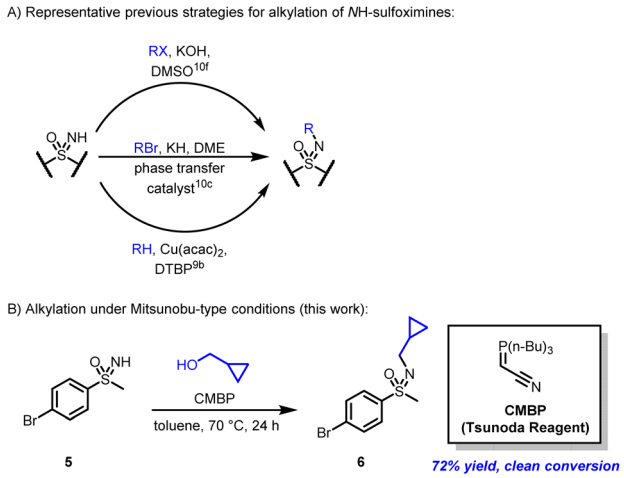


Scheme 1 Alkylation strategies for *N*H-sulfoximines.

would not obviously be applicable for the functionalization of *N*H-sulfoximines (pK_a's < 11 traditionally tolerated, sulfoximine *N*H pK_a = 24 in DMSO[11]). However, the advent of next-generation, electron-rich azodicarboxylates including 1,1′-(azodicarbonyl)dipiperidine (ADDP) and tetramethylazodicarboxamide (TMAD or diamide)[12] has allowed for select poorly acidic nucleophiles to participate in this type of alkylation reaction. Additionally, reports describing the "all in one" phosphorane reagents (cyanomethylene)trimethylphosphorane (CMMP) and (cyanomethylene)tributylphosphorane (CMBP, Scheme 1),[13] detail the alkylations of numerous unconventional and low-acidity nucleophiles including pyrazoles, carbon nucleophiles, amines, and alcohols.[14] CMBP, or the Tsunoda reagent, is particularly attractive due to its commercial availability, high thermal stability compared to the azodicarboxylates, and relative stability compared to CMMP.[13] We therefore wondered if this reagent might affect the alkylation of racemic *N*H-sulfoximine **5** using cyclopropylmethanol (Scheme 1).

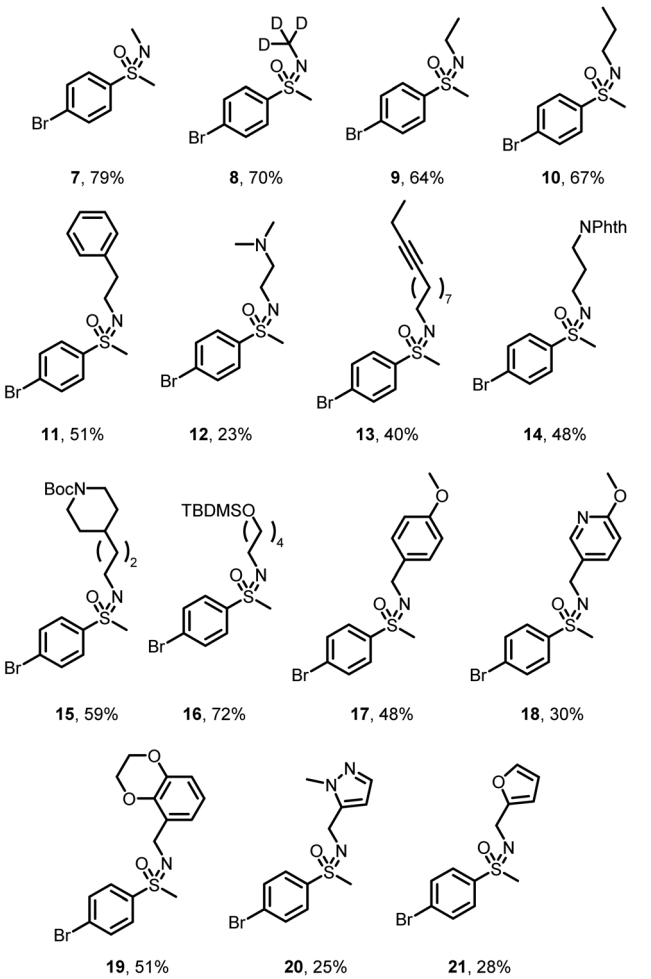
While an initial reaction using ADDP and P(*n*-Bu)$_3$ proved unsuccessful toward this end (Table 1, entry 1), we were gratified to observe the desired sulfoximine **6** in relatively low yield using CMBP under similar thermal conditions originally described by Tsunoda and others (entry 2, 30%).[13b,14c] A survey of lower temperatures (entries 3–6) revealed 70 °C to be optimal (entry 5, 72% isolated yield). Replacement of toluene with alternative solvents (entries 7–9) proved detrimental; no desired product was observed when the reaction was run in DCE under identical conditions (entry 8). Additionally, shortened reaction times were also counterproductive (entry 10), as were changes in reaction concentration (entries 11 and 12). We therefore selected the conditions described in entry 5 to probe the substrate scope of this reaction. Overall, we were encouraged by the operational simplicity of these conditions (minimal reagents without the need for an aqueous workup) as well as the clean conversion (primary isolated byproduct is typically starting material **5**, Scheme 1).

*N*H-Sulfoximine **5** can be alkylated with a wide variety of alcohols to give substituted sulfoximines **7**–**21** in moderate to high yields (Scheme 2, 23–79%). Simple aliphatic alcohols

Table 1 Optimization of reaction conditions[a]

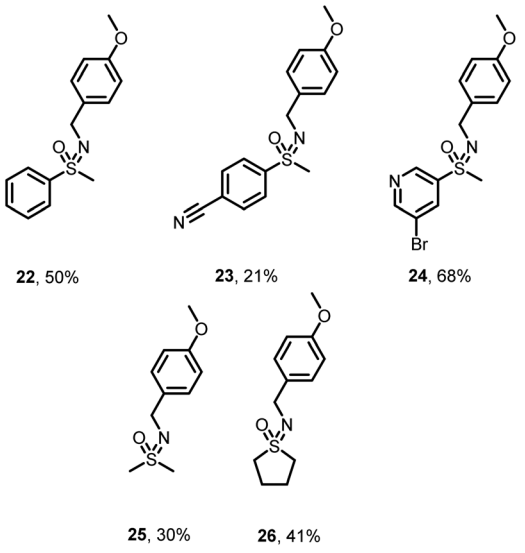
Entry[a]	Reagent(s)	Solvent	Temp. (°C)	Time (h)	M	Yield[b] (%)
1	P(*n*-Bu)$_3$ (1.5 eq.), ADDP (1.5 eq.)	THF	r.t.	2	0.2	0[c]
2	CMBP	Toluene	120	24	0.2	30
3	CMBP	Toluene	r.t.	24	0.2	37
4	CMBP	Toluene	50	24	0.2	56
5	**CMBP**	**Toluene**	**70**	**24**	**0.2**	**72 ± 1**[d]
6	CMBP	Toluene	90	24	0.2	49
7	CMBP	THF	70	24	0.2	40
8	CMBP	DCE	70	24	0.2	0[c]
9	CMBP	MeCN	70	24	0.2	46
10	CMBP	Toluene	70	3	0.2	55
11	CMBP	Toluene	70	24	0.1	52
12	CMBP	Toluene	70	24	0.4	64

[a] Unless otherwise stated, reactions run under an N_2 atmosphere in a sealed vessel with cyclopropylmethanol (2 eq.) and CMBP (2 eq.). [b] Isolated yield. [c] Reaction was monitored by LCMS, and no isolation was attempted. [d] Average of 2 independent experiments.



Scheme 2 Scope of the Mitsunobu-type alkylation of *N*H-sulfoximines with **5**. Standard reaction conditions: **5** (1 eq.), alcohol (2 eq.), CMBP (2 eq.), toluene (0.2 M), 70 °C, 24 h. Isolated yields after column chromatography.

(**7**–**11**) were well tolerated under the reaction conditions, furnishing the corresponding substituted sulfoximines in high yields. Of note is deuterated sulfoximine **8**, which is readily synthesized from methanol-d_4 in a comparable yield to the other short chain aliphatic substrates (70%). More complex aliphatic systems (**12**–**16**) were also tolerated under the reaction conditions, including strongly basic amines (**12**), internal alkynes (**13**), and a variety of common protecting groups (**14**–**16**). Benzylic alcohols also readily yielded the corresponding *N*-benzyl sulfoximines, although these systems were observed to be sensitive to ring electronics. Whereas electron-withdrawing groups generally led to lower isolated yields (no desired *N*H-alkylation product was observed using (4-nitrophenyl)methanol), electron rich systems were readily isolated in moderate yields (**17**–**19**). Both 5- and 6-membered heteroaromatic systems, including pyrazole **20** and furan **21**, were compatible with these conditions, and we were encouraged by the amenability of this reaction to these useful drug-like motifs. In parallel with our survey of compatible alcohols, we also explored variations on *N*H-sulfoximine **5** (Scheme 3) using (4-methoxyphenyl)methanol as a coupling partner. We found that a variety of *N*H-sulfoximines were well tolerated under the reaction conditions including bromopyridine **24** (68% isolated yield), and simple aliphatic *N*H-sulfoximines **25** and **26** (30% and 41% isolated yields, respectively). As observed with the alcohol substrate scope, electron-withdrawing modifications on the aryl *N*H-sulfoximine tended to diminish isolated yields (21% for benzonitrile **23**). Although yields remained modest in some cases of alcohols with higher complexity, we were encouraged by the structural diversity of the *N*H-sulfoximines obtainable under these conditions, with many drug-like motifs tolerated.

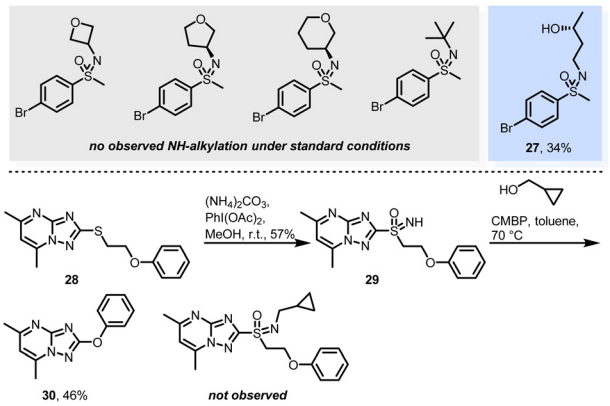


Scheme 3 *N*H-Sulfoximine scope of the Mitsunobu-type alkylation. Standard reaction conditions: *N*H-sulfoximine (1 eq.), (4-methoxyphenyl)methanol (2 eq.), CMBP (2 eq.), toluene (0.2 M), 70 °C, 24 h. Isolated yields after column chromatography.

As shown in Scheme 4, secondary alcohols were not tolerated under these reaction conditions, and only trace desired *N*-alkylated sulfoximine products were observed in such cases. Although there is some precedent in the literature for Mitsunobu-type reactions using tertiary alcohols,[15] an attempted reaction with *tert*-butanol was also unsuccessful. This robust chemoselectivity for primary alcohols was successfully leveraged to generate *N*-alkylated sulfoximine **27**, in which **5** was cleanly reacted with (*R*)-butane-1,3-diol without the need for additional protection steps (Scheme 4). No additional reactivity of the secondary alcohol was observed under these conditions.

In order to further understand the potential applications of this chemistry to additional drug-like motifs, *N*H-sulfoximine **29** was first generated from known erythropoietin-mimetic **28**,[7,16] which was subsequently subjected to the optimized alkylation conditions (Scheme 4). Intriguingly, compound **30** was isolated as the major product of the Mitsunobu alkylation for this specific substrate. Presumably, this occurs through α-deprotonation, potentially mediated by the phosphorane species, to form a vinyl sulfoximine with liberation of a phenolate anion. Nucleophilic aromatic substitution (S_NAr) at the 2-position of the dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidine bicycle would then generate **30** after elimination of a vinylsulfinamide.[17] This reactivity raises unique possibilities for the development of new aromatic substitution chemistry *via* controlled sulfoximine eliminations. For example, although β-eliminations of *N*-substituted sulfoximines have been previously disclosed,[18] the one-pot aromatic substitution reaction described here could allow for the development of new sulfoximine-deletion chemistry within a given substrate (whether occurring through β-elimination or a different pathway).

In summary, we have described an operationally simple alkylation of diverse *N*H-sulfoximines using the versatile and underutilized Tsunoda reagent. These conditions allow for alkylations of *N*H-sulfoximines that are otherwise challenging under standard base-mediated S_N2-type conditions, and can



Scheme 4 Limitations and unexpected reactivity of *N*H-sulfoximine alkylations. The alkylation of *N*H-sulfoximines under the standard conditions is highly chemoselective for primary alcohols (top). Unexpected sulfoximine elimination chemistry on a drug-like scaffold (bottom).

be applied to the straightforward alkylation of diverse systems. The key advantages of this method include operational simplicity, high functional group tolerance compared to previous reports, and use of easily handled and widely available reagents. Further studies on the reactivity of additional drug-like molecules under similar conditions, with an emphasis on the further characterization of competing sulfoximine elimination pathways, are ongoing in our laboratory and will be reported in due course.

Author contributions

A. M. B. conceived this work and performed synthetic chemistry with C. J. D., D. C. S., and J. L. A. M. B. wrote the manuscript with input and revisions from all authors.

Conflicts of interest

There are no conflicts to declare.

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