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Use of the Nosyl Group as a Functional Protecting Group in Applications of a Michael/Smiles Tandem Process

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Supporting Information

ABSTRACT: Concise preparations of elaborated polycyclic and heterocyclic systems present in natural products were obtained using the nosyl group as a functional protecting group not only to mask the reactivity of a sensitive moiety but also to provide a structure desired in the final target. The group is transferred to the substrate during deprotection through a novel extension of the Truce–Smiles rearrangement in tandem with a 1,4-addition. This strategy provides access to a ring system laden with valuable functionalities for subsequent manipulations and can serve as a versatile building block for the construction of more complex molecular architectures such as indoles in a manner compatible with the concepts of green chemistry and atom economy.

There is a general understanding that sustainable, environmentally benign routes to synthetic targets should be atom economical[1] and protecting group-free,[2] yet it is often difficult to achieve these ideal conditions when preparing challenging polyfunctional molecules. As a complement of these important strategies, a new approach would envisage the development of "functional protecting groups" that not only mask the reactivity of sensitive ensembles but also carry a moiety desired in the final target and which will be transferred to the substrate at the time of deprotection via an extension of the Truce–Smiles rearrangement,[3] Figure 1. This strategy would provide the benefits of protecting groups while minimizing the need for additional steps and atom waste.

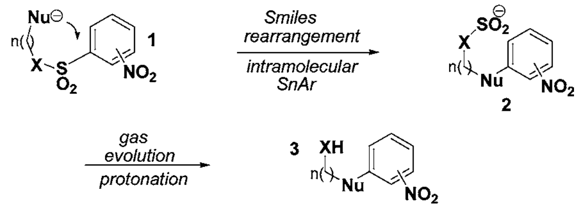

Figure 1. Truce–Smiles transformation.

If the Truce–Smiles transformation opens up several opportunities in synthesis, this powerful tool would offer a plethora of novel synthetic strategies if it were judiciously combined in a tandem manner with another important transformation such as a 1,4-addition that would be triggered by the functional protecting group. Since the Smiles rearrangement majoritarily involves an intramolecular Sn-Aryl process, the aryl moiety has to be electron poor. In this objective, a Fukuyama-type sulfonamide[4] appears to be an ideal functionality where the SO_2 segment would be used as a leaving tether group first and as a single byproduct at the end. Futhermore, the nitro-aryl may be converted into indoles and indolines by a subsequent reduction. It should be noted that many alkaloids such as (+)-kopsihainanine A[5,6] from the kopsia hainanesis family or (+)-tabersonine from the aspidosperma family[7] contain an aryl group connected to an inherently nucleophilic carbon atom, Figure 2.

In this paper, we describe the rapid formation of poly- and heterocyclic systems using the nosyl functionality as a protecting group and to provide a portion of the target molecule. This reaction proceeds under slightly basic (cesium

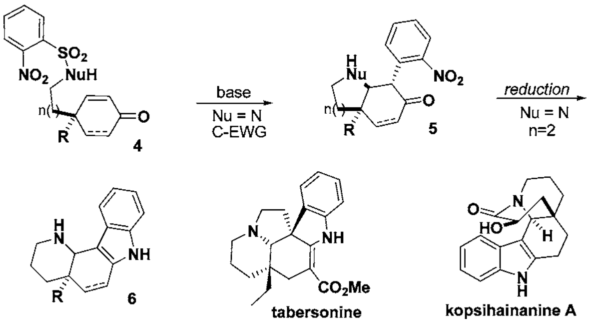

Figure 2. Functional protecting group approach and alkaloids.

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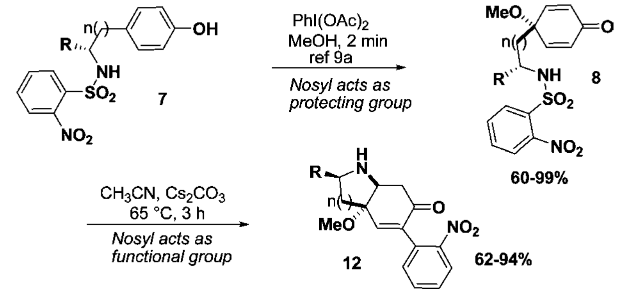
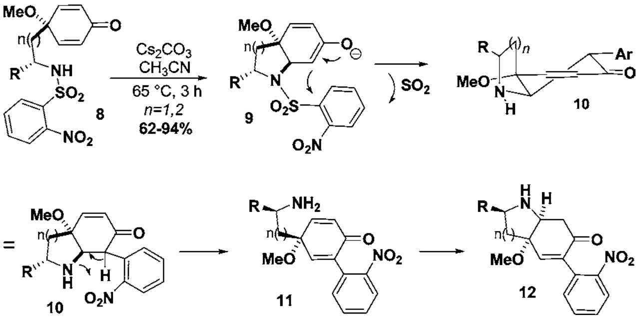
carbonate) conditions at moderate (65 °C) temperatures. Acetonitrile was selected as the solvent due to its identification as an environmentally benign organic solvent by the CHEM21 consortium, with an environmental impact score similar to ethanol.[8] Prochiral dienone starting materials **8** were first employed to delineate the scope, limits, and stereoselectivity of the technique. The dienones were obtained in good yields through a hypervalent iodine activation of phenols[9] in the presence of alcohols[10] (Scheme 1).

Scheme 1. Rapid Elaboration of Polycyclic Systems



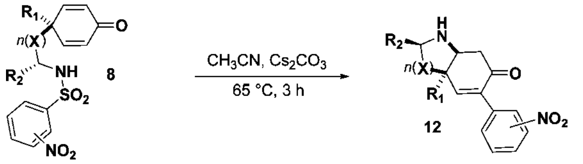
Surprisingly, activation of **8** in the presence of cesium carbonate yields enone **12** rather than **10** (or **5** described in Figure 2). This may be the result of a retro-aza-Michael[11] reaction on intermediate **10** promoted by its conjugated enolate form under basic conditions. The process would terminate with a 1,4-addition on the second double bond leading to **12** which also appears to be a valuable synthetic scaffold. In this instance, adduct **5** (Figure 2, or compound **10**) would be present only as an intermediate but would explain the stereoselectivity[12] obtained through an envelope- (n = 1) or chair- (n = 2) like transition state during the process. A potential mechanism is depicted in Scheme 2.

Scheme 2. Proposed Mechanism of the Michael–Smiles Process



Compound **12** represents an interesting scaffold containing a pyrrolidine or a piperidine moiety as well as a cyclohexanone functionality connected to an electron-withdrawing nitroaryl group. This core may be obtained in good yield from phenol **7** in only two steps (Scheme 1). The transformation was extended to several other substrates to investigate the scope of the new process (Table 1). Interestingly, good diastereoselectivity observed by NMR (1:19 dr) and controlled by the methyl ester was obtained when a tyrosine derivative was used (R = CO_2Me, **12e** and **12f**) to yield the 5-membered ring. Examples including alkyl chains connected through an ether linkage and an asymmetric center to develop a diastereoselective pathway were also tested. We were pleased to observe that formation of the 6-membered ring **12k** occurred with good selectivity.[12] However; the process was not effective for the formation of seven membered rings.

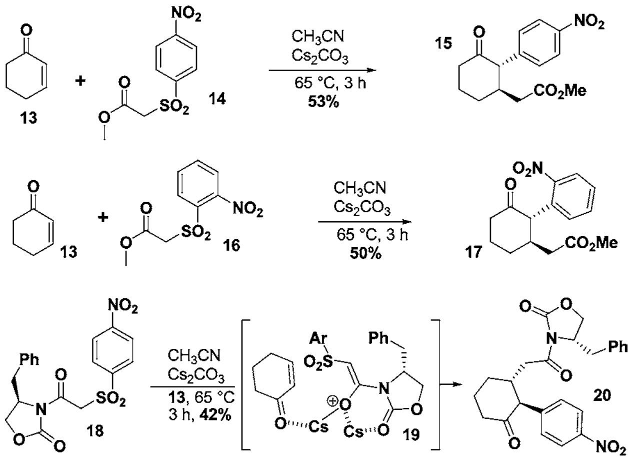
Table 1. Formation of Pyrrolidine or Piperidine Moieties



entry	n	X	NO_2	R_1	R_2	yield (%)
a	1	CH_2	ortho	OMe	H	90
b	1	CH_2	ortho	OEt	H	86
c	1	CH_2	para	OMe	H	82
d	2	CH_2	ortho	OMe	H	94
e	1	CH_2	ortho	OMe	CO_2Me	62
f	1	CH_2	ortho	OEt	CO_2Me	63
g	2	CH_2	para	OMe	H	73
h	1	CH_2	ortho-para	OMe	H	64
i	1	CH_2	ortho	NHAc	H	76
j	1	$O{-}CH_2$	ortho	Et	H	75
k	1	$O{-}CH_2$	ortho	Et	Me	73

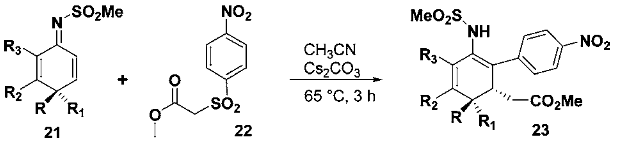
This approach is not limited to intramolecular reaction of sulfonamides and may be extended to carbon-based nucleophile **14** or **16** in an intermolecular pathway. No retro-Michael process is observed in the presence of carbon-based nucleophiles, probably due their higher pK_a. The same reaction may be performed in the presence of the *ortho*- or *para*-nitro adducts to produce α-β-disubstituted cyclohexanones **15** and **17** in similar yields. A diastereoselective route[13] to **25** was investigated using **18** as an Evans derivative of **14**. This transformation yielded **20** in 42% yield with excellent diastereoselectivity (>1:19 dr),[12] demonstrating the feasibility of an asymmetric version of the Michael–Smiles tandem process (Scheme 3). Compound **19** represents a potential transition state of this stereoselective transformation.

Scheme 3. Intermolecular Application of Carbon-Based Nucleophiles



The transformation has also been extended to dienimines **21**[14] in the presence of the carbon-based nucleophile **22**. As described in Scheme 3, no retro-Michael process occurred and the direct formation of the α-β-disubstituted adducts **23** was observed. It should be noted that the products were isolated in their enamine form, probably as the result of conjugation induced by the nitro-aryl segment, Table 2.

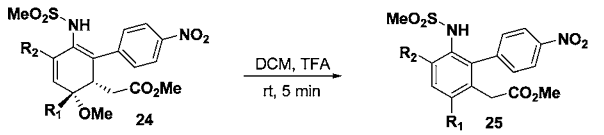
Table 2. Carbon-Based Michael−Smiles Process on Dienimines



entry	R	R_1	R_2	R_3	yield (%)
a	Et	OMe	H	H	57
b	*n*-Pr	OMe	H	H	52
c	CH_2CO_2Me	OMe	H	H	49
d	OMe	OMe	CH=CH−CH=CH		79
e	O−CH_2−CH_2−O		CH=CH−CH=CH		62

The approach may also be used to yield *ortho-meta*-disubstituted anilines through a 1,4-addition−Smiles-aromatization process. Indeed, slightly acidic conditions promoted elimination of methanol, leading to anilines **25**. This method is tolerant of spectator functionalities such as alcohols and esters, Table 3.

Table 3. Formation of Polysubstituted Anilines



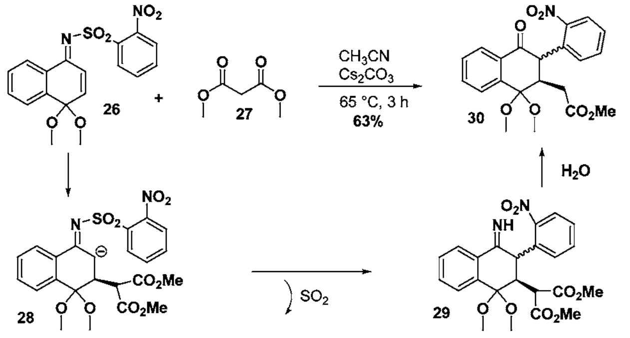
entry	R_1	R_2	yield (%)
a	Et	H	83
b	*n*-Pr	H	85
c	Me	Me	60[a]
d	CH_2OH	H	66[a]
e	CH_2CO_2Me	H	88

[a] Directly obtained from their **21** derivatives.

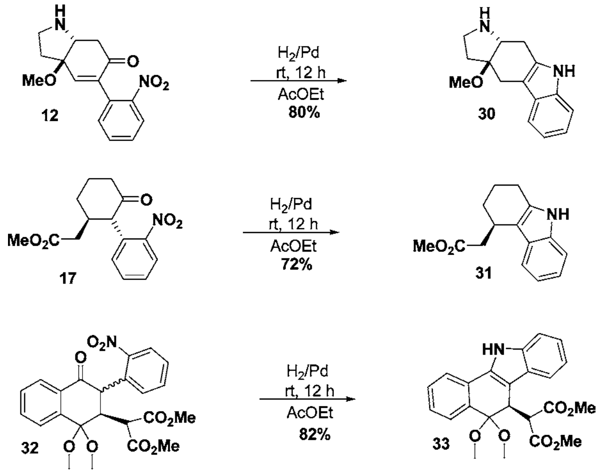
In addition, the migrating aryl segment may be introduced on the Michael acceptor moiety to afford a mixture of diastereomers **30** through a similar Michael−Smiles process. Indeed, a 1,4-addition on enimine **26** generated an aza-enolate **28** which triggered the Smiles rearrangement leading to the *α,β*-disubstituted cyclohexanone **30** in 63% yield, Scheme 4.

It should be noted that the nosylamide protecting group transferred during the "Smiles deprotecting step" produces an aryl-nitro segment that can act as a precursor for a variety of structures. As an example of the potential of this approach, the nitro-aryls may be converted into indoles, which are important bioactive functionalities present in numerous bioactive products, by reduction with hydrogen on palladium.[15] This method was also employed to transform the mixture of diastereomers **30** into a single indole **33** in good yield, Scheme 5.

Scheme 4. Michael Acceptor Moiety as the Trigger Process



Scheme 5. Indole Formation



In summary, a novel tandem Michael−Smiles process has been developed based on the use of a functional protecting group that not only masks the reactivity of sensitive groups but also carries a moiety desired in the final product. This strategy requires mild conditions to enable the rapid formation of functionalized cores and provide a new means of accessing indoles, and releases only sulfur dioxide by gas evolution. This approach is not restricted to nitrogen-based nucleophiles, but may also be extended to carbon-based nucleophiles. Direct applications of this novel approach in total synthesis of natural products are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02105.

Experimental procedures and spectral data for key compounds (PDF)

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Notes

The authors declare no competing financial interest.

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