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# Nucleophilic Aromatic Substitution Reactions in Water Enabled by Micellar Catalysis

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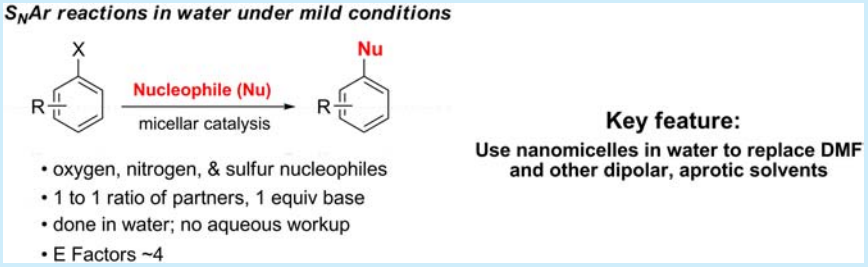
Supporting Information




**ABSTRACT:** Given the huge dependence on dipolar, aprotic solvents such as DMF, DMSO, DMAc, and NMP in nucleophilic aromatic substitution reactions ($S_NAr$), a simple and environmentally friendly alternative is reported. Use of a "benign-by-design" nonionic surfactant, TPGS-750-M, in water enables nitrogen, oxygen, and sulfur nucleophiles to participate in $S_NAr$ reactions. Aromatic and heteroaromatic substrates readily participate in this micellar catalysis, which takes place at or near ambient temperatures.

Of the 1086 unique small molecules approved by the U.S. Food and Drug Administration (FDA), 640 are heterocyclic and contain at least one nitrogen. Of this subset, 97% either contain a 6-membered (379 total) or 5-membered ring (250 total); hence, 5- and 6-membered *N*-heterocycles play key roles within the pharmaceutical industry.[1] One common thread among these arrays can be found in their assemblage, where at least one nucleophilic aromatic substitution reaction ($S_NAr$) is involved.[2] Indeed, an $S_NAr$ reaction is used *once or more* in synthetic schemes en route to the following best-selling[3,4] FDA-approved small molecules: abacavir, imiquimod, erlotinib, levofloxacin, moxifloxacin, pioglitazone, rosiglitazone, pazopanib, febuxostat, itraconazole, ziprasidone, olanzapine, and timolol.[5] A number of these are listed on the World Health Organization's List of Essential Medicines.[6] Clearly, nucleophilic aromatic substitution is an important reaction within industrial circles.[7]

The appeal of the $S_NAr$ reaction lies not only in its atom economy but also its associated metal-free conditions. It is also complementary to traditional cross-coupling reactions, where the better the leaving group (e.g., fluoride) in an $S_NAr$ reaction the more difficult the initial oxidative addition step of a metal-catalyzed cross-coupling.[7] Despite these apparent attributes, a major drawback is that dipolar, aprotic solvents are often required. Remarkably, nearly 50% of DMF, DMAc, NMP, and DMSO usage over the past 14 years comes from $S_NAr$ or $S_N2$ reactions, as disclosed in a recent survey.[8] Significant health issues, however, have been attributed to these solvents, including embryo–fetal development.[9] Therefore, "greener" methods are being sought to replace these solvents,[10] although such alternatives are often found to be toxic with time (e.g., NMP), and still require an aqueous work up adding to the wastewater stream.

While nucleophilic aromatic substitution ($S_NAr$) reactions have been heavily studied in organic media,[7] very limited data exist for related reactions studied under micellar catalysis conditions involving nonionic surfactants. Since organic solvents constitute as much as 85% of total organic waste and nearly 60% of the total waste within the pharmaceutical industry,[11] demonstrating that $S_NAr$ reactions can be effected in limited amounts of recyclable water is meaningful for several reasons: (1) micellar catalysis, by definition, entirely avoids dipolar, aprotic solvents; (2) such an approach may lead to lower reaction temperatures given the high local concentrations that exist within micelles; and (3) routes followed by medicinal chemists during discovery that are environmentally attractive can potentially translate into viable large-scale processes saving development costs and time to market.[10a]

Herein, we report that $S_NAr$ reactions can be performed under aqueous micellar conditions with oxygen-, nitrogen-, and sulfur-based nucleophiles at ambient or slightly evaluated temperatures. This chemistry is in line with several of the "12 Principles of Green Chemistry"[11b] in that (a) coupling partners are oftentimes used at a 1:1 ratio, (b) a "benign-by-design" surfactant, TPGS-750-M,[12] is present but only to the extent of 2 wt %, and (3) high global concentrations are involved (≥0.5 M) with water as the

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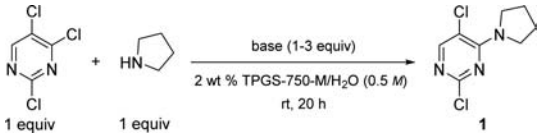
bulk medium. Moreover, the aqueous medium can be directly recycled without removal from the reaction vessel and without affecting subsequent reactions. These attributes, taken together, add up to low *E* factors,[13] indicative of minimal waste production.

Initial model studies employed a pyrimidine trichloride and pyrrolidine in equal amounts. The anticipated $S_NAr$ reaction took place at room temperature in nanoreactors derived from TPGS-750-M in water. Several bases were found to assist with this displacement reaction to product **1**, as illustrated in Table 1.

**Table 1. Selected Experimental Data from Initial Screening**




| entry | base | yield[a] (%) |
|---|---|---|
| 1 | $Et_3N$ (3 equiv) | 75 |
| 2 | $K_2CO_3$ (3 equiv) | 86 |
| 3 | $K_2CO_3$ (1.5 equiv) | 96[b] |
| 4 | DIPEA (3 equiv) | >99[b] |
| 5 | $K_3PO_4$ (1 equiv) | 88 (>99)[b] |

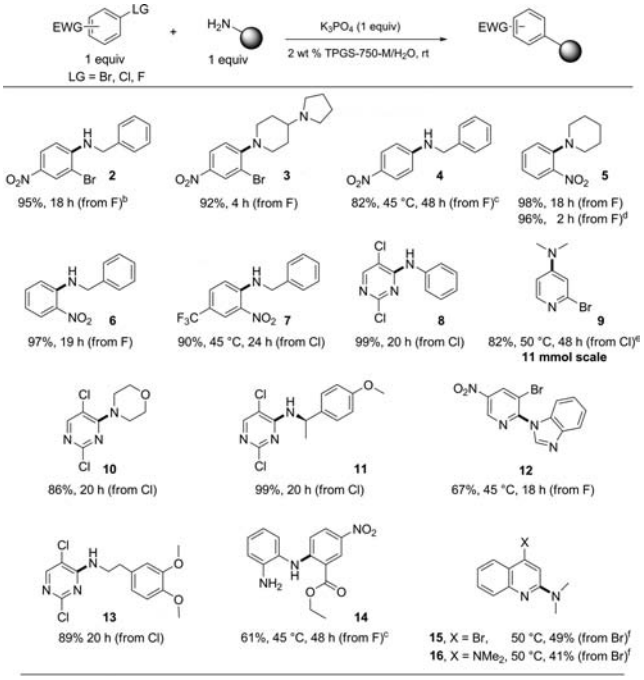
[a]Isolated yield after purification via flash chromatography. [b]Conversion based on consumption of 2,4,5-trichloropyrimidine via GC−MS.

Other bases, such as substituted pyridines (e.g., 2,6-lutidine), quaternary ammonium hydroxide salts, and KO-*t*-Bu were inefficient. Strongly basic conditions led to competitive addition of hydroxide as the nucleophile. "On water" experiments (i.e., run in the absence of surfactant) were occasionally successful, although with crystalline educts, the surfactant was crucial to prevent clumping and provide a more even, homogeneous-like mixture. A surfactant loading beyond 2 wt % offered little advantage. In fact, higher loadings for these particular reactions can lead to a more viscous medium, resulting in inefficient stirring. Overall, both tertiary alkylamine and inorganic bases can be utilized. Since only 1 equiv of $K_3PO_4$ suffices, it was chosen to further explore substrate scope.

A wide range of nitrogen-based nucleophiles was examined, with most reactions taking place at room temperature using a 1:1 ratio of each partner, along with 1 equiv of $K_3PO_4$ (Scheme 1). Electron-deficient arenes bearing nitro, $CF_3$, chloro, and bromo groups were sufficient to activate the ring toward substitution, affording the desired products containing piperidine (**3**, **5**), pyrrolidine (**1**), benzylamine (**2**, **4**, **6**, **7**), and aniline derivatives (**14**) on the aromatic/heteroaromatic core. 2,4,5-Trichloropyrimidine reacted selectively at the 4-position (as in the model studies with pyrrolidine; see **1**) at room temperature in high yields with aniline, morpholine, $\alpha$-substituted benzylic amines, and phenethylamine derivatives to arrive at adducts **8**, **10**, **11**, and **13**, respectively. Additionally, a substituted 2-fluoropyridine reacted with benzoimidazole as nucleophile to give the highly functionalized product **12**, albeit at 45 °C and in modest yield. Although 1:1 ratios of partners are sufficient, increasing the amount of nucleophile to 2 equiv significantly decreases reaction time. Also, if the nucleophile is a liquid, using more than 1 equiv may aid with homogeneity of the reaction medium (e.g., **5**).

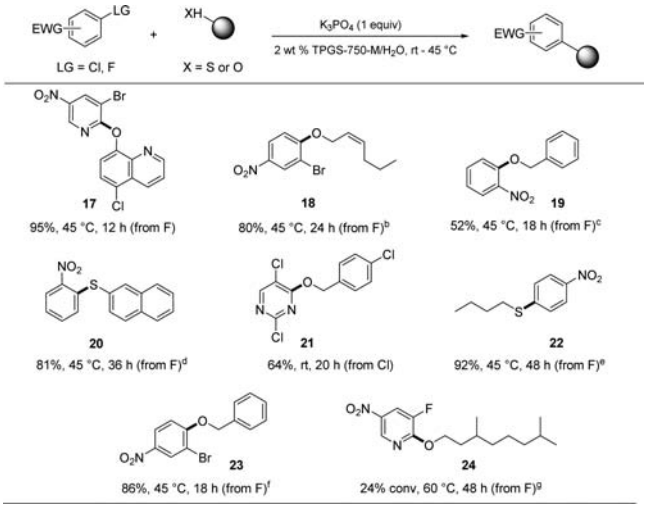
Oxygen- and sulfur-based nucleophiles are also amenable to these $S_NAr$ couplings, although both are less reactive than nitrogen. Hence, mild heating to 45 °C was required in most cases (Scheme 2). Benzylic alcohols worked well (**19**, **21**, **23**), along with hydroxylated heteroaromatics (**17**). Alkanols were

**Scheme 1. Scope of $S_NAr$ Reactions Using Nitrogen-Based Nucleophiles**




[a]Conditions: 0.2 mmol scale, 2 wt % TPGS-750-M/$H_2O$ (0.4 mL, 0.5 M). [b]0.5 mmol scale. [c]0.5 mmol scale, amine nucleophile (1.1 equiv), $K_3PO_4$ (1.1 equiv). [d]Amine nucleophile (2.0 equiv). [e]Reaction "on water" containing 40 wt % of the amine. [f]0.5 mmol scale, reaction "on water" containing 40 wt % of the amine.

**Scheme 2. $S_NAr$ Reactions of Alcohols and Thiols as Nucleophiles**




[a]Conditions: 0.2 mmol scale, 2 wt % TPGS-750-M/$H_2O$ (0.4 mL, 0.5 M). [b]NaO-*t*-Bu (3 equiv). [c]Nucleophile (2.0 equiv), NaO-*t*-Bu (2 equiv). [d]0.5 mmol, nucleophile (1.1 equiv), $K_3PO_4$ (1.1 equiv). [e]0.5 mmol scale, base (2.2 equiv), 1.1 equiv of thiouronium salt as a nonvolatile source of butanethiol. [f]KO-*t*-Bu (3 equiv). [g]Nucleophile (2.0 equiv), 10 mol % of DMAP.

troublesome, requiring the presence of DMAP (10 mol %) as well as heating to 60 °C. These more forcing conditions still produced the anticipated product although in low levels of conversion (24%, by GC−MS). Using NaO-*t*-Bu was necessary



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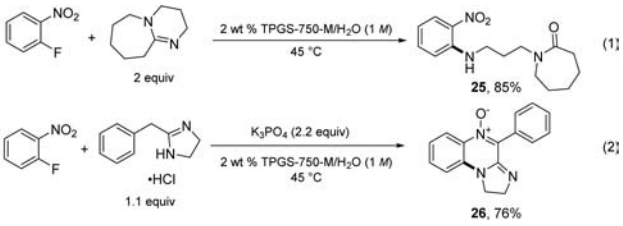
with the *Z*-allylic alcohol precursor to product **18** due to its lower acidity. No isomerization to the corresponding *E*-isomer was observed. Thiols such as 2-naphthylthiol and *n*-butylthiol afforded the expected sulfides **20** and **22**, respectively. The latter was introduced via its thiouronium salt to avoid volatility issues.

An unexpected observation was made when DBU was explored as a potential base to aid in solubilization of highly crystalline material. This bicyclic amidine participated as a nucleophile, after which it underwent ring opening, yielding in the presence of water a substituted lactam **25** (eq 1). 2-




Benzylimidazoline was also prone, as a nucleophile, toward displacement of fluoride, arriving ultimately at **26**. Thus, after removal of the acidic proton at the benzylic position in the initial adduct, an intramolecular addition to the *o*-nitro group led to nitrone **26** (eq 2). Only a minor amount of the ring-opened product was observed in this case.

To demonstrate the potential for nonionic surfactants in water to serve as a replacement for DMF in $S_NAr$ reactions, side-by-side comparisons of reaction rates were conducted for several combinations of educt and nucleophile, as shown in Figure 1.

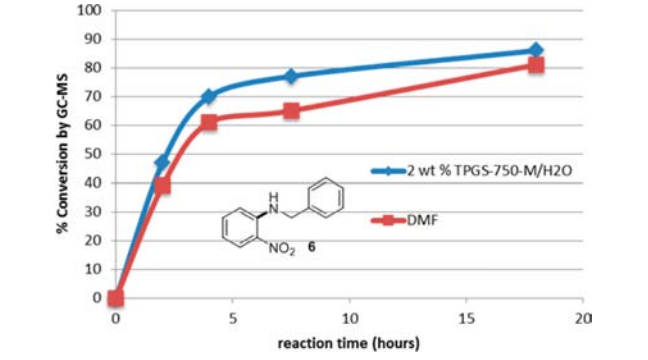
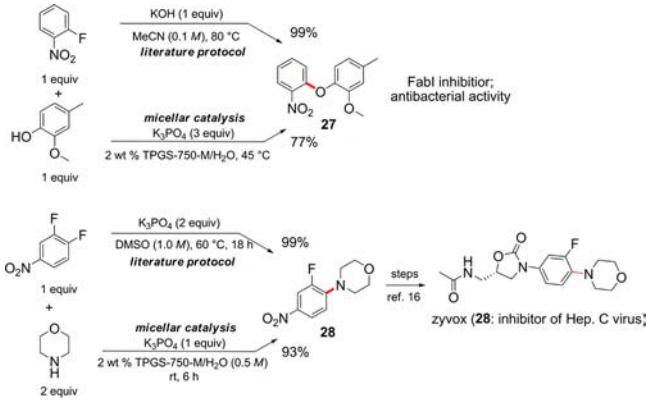



**Figure 1.** Comparison of rates of $S_NAr$ reactions in 2 wt % of TPGS-750-M/$H_2O$ vs DMF (see the Supporting Information for additional substrates).

Using nanomicelles consisting of TPGS-750-M (2 wt %) in water leads to reaction rates that are roughly comparable to those observed to DMF. Whereas some reactions were faster under micellar conditions (e.g., Figure 1; see Supporting Information), others were found to be slower, although the overall conversion in each case is essentially equal to that in pure DMF. These data suggest that designer surfactants of the appropriate nanoreactor size and shape, such as found with TPGS-750-M, can function in place of DMF as a medium for $S_NAr$ reactions.

Applications of our micellar conditions focused on two examples: (1) an antibacterial and known FabI inhibitor, **27**, and (2) compound **28**, known as an inhibitor of hepatitis C virus replication.[14] The former could be prepared in our surfactant solution at 45 °C, whereas the literature procedure involves a dilute solution of MeCN at 80 °C to achieve the desired product (Scheme 3).[15] Morpholine adduct **28** could be formed in high yield at ambient temperatures, a known intermediate en route to zyvox, effective against bacterial infections.[16]

**Scheme 3. Literature Comparisons Traditional vs Micellar Conditions**




A third example shown in Figure 2 is also an intermediate en route to an FDA-approved drug: seroquel, used to treat

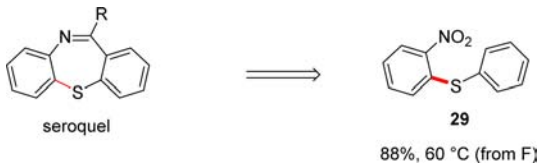
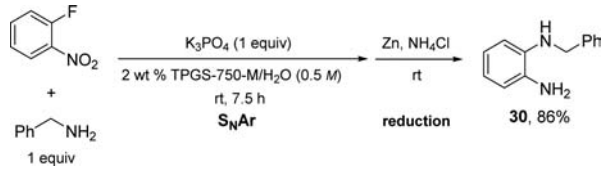



**Figure 2.** Intermediate toward FDA-approved drug utilizing an $S_NAr$ reaction.

schizophrenia, bipolar disorder, or depression.[16] Intermediate **29** was isolated in high yields using a 1:1 ratio of coupling partners and 1 equiv of $K_3PO_4$ as base at 60 °C.

Typically, an arene poised for an $S_NAr$ reaction is activated by an electron-withdrawing group that is either carried through subsequent steps and contained within the final product or is utilized directly. A nitro group serving in this capacity is oftentimes viewed as an amine equivalent, subject to reduction as needed. A one-pot sequence involving an initial $S_NAr$ reaction followed by $NO_2$ reduction occurs smoothly, where after C−N bond formation Zn and $NH_4Cl$ can simply be added to the reaction vessel to reduce the nitro group giving **30** in 86% overall yield (Scheme 4).[17]

**Scheme 4. One-Pot $S_NAr$/Nitro Group Reduction in Water at rt**




Lastly, due to "in flask" extraction of the aqueous micellar reaction media, the amount of organic solvent produced as waste is dramatically reduced, as quantified by *E* Factors.[13] Moreover, the reaction medium can be reused to generate a different product from an $S_NAr$ reaction, as illustrated in Table 2. Following an initial displacement by benzylamine, product **2** was extracted with a minimum of EtOAc and isolated in 90% yield.



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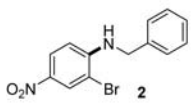
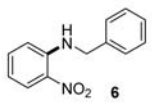
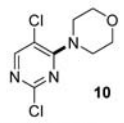
**Table 2. *E* Factors and Recycling Study**

| initial reaction | 1st recycle | 2nd recycle |
|---|---|---|
|  |  |  |
| 90%, rt, 24 h (from F)[a] | 93%, rt, 8 h (from F)[b] | 80%, rt, 6 h (from Cl)[a] |

| based on | *E* Factors | | |
|---|---|---|---|
| | reaction | first recycle | second recycle |
| total organic solvent | 4.1 | 4.6 | 4.8 |
| aqueous waste included | 7.7 | 4.6 | 4.8 |

[a]Conditions: amine (1 equiv), $K_3PO_4$ (1 equiv), 2 wt % TPGS-750-M/$H_2O$. [b]Conditions: amine (1.5 equiv), $K_3PO_4$ (1 equiv), 2 wt % TPGS-750-M/$H_2O$.

Additional base and different coupling partners were then added to the vial for use in the first recycle of the original water/surfactant mixture. This approach results in *E* Factors, based on organic solvent used, in the range of only 4−5 for each step. With water included in the calculation, an *E* Factor of only 7.7 was initially obtained. These values, however, drop to that based on organic solvent used per extraction, as no additional water needs be invested in subsequent cycles.

In summary, micellar catalysis has been shown to enable nucleophilic aromatic substitution reactions to be performed in water under mild conditions. These micelles in water serve as nanoreactors that can be viewed as a "green" replacement for dipolar, aprotic solvents such as DMF, which is one of several commonly used for such bond constructions. Oxygen-, nitrogen-, and sulfur-based nucleophiles all participate in these $S_NAr$ reactions. Opportunities also exist for tandem processes that take place in a single pot. Lastly, given the complete absence of organic solvent in the reaction medium, along with in-flask extraction and recycling, the green nature of this chemistry is evidenced by the associated low *E* Factors. Further reports from these laboratories that illustrate the potential of designer surfactants in water to "get organic solvents out of organic reactions" will be forthcoming.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02240.

Experimental procedures, additional comparison of rates (DMF vs TPGS-750-M), references for reported $S_NAr$ reactions utilized in FDA-approved drugs, and full spectral data for all compounds (PDF)

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### Notes

The authors declare no competing financial interest.

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