

Solution-Phase Parallel Synthesis of Aryloxyimino Amides via a Novel Multicomponent Reaction among Aromatic (*Z*)-Chlorooximes, Isocyanides, and Electron-Deficient Phenols

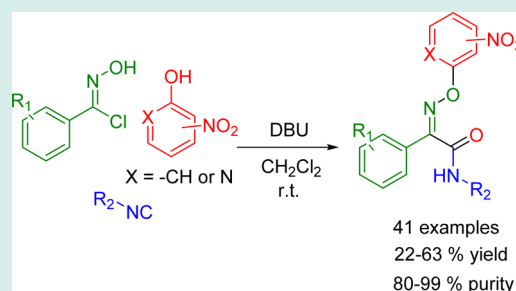
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Supporting Information

ABSTRACT: A library of 41 aryloxyimino amides was prepared via solution phase parallel synthesis by extending the multicomponent reaction of (*Z*)-chlorooximes and isocyanides to the use of electron-deficient phenols. The resulting aryloxyiminoamide derivatives can be used as intermediates for the synthesis of benzo[*d*]isoxazole-3-carboxamides, dramatically reducing the number of synthetic steps required by other methods reported in literature.



KEYWORDS: multicomponent reactions, isocyanides, (*Z*)-chlorooximes, aryloxyiminoamides, benzo[*d*]isoxazole-3-carboxamides

In addition to providing excellent organic chemistry training for many chemists, the discovery of novel multicomponent reactions (MCRs)¹ can give direct access to uncharted territories of chemical space or simplify the synthesis of well-known medicinally active compounds.² Among all the multicomponent reactions presently known, those mediated by isocyanides³ have had greatest success in attracting the interest of chemists and several important novel transformations have emerged over the last decades.⁴ The peculiar ability of the divalent carbon of isocyanides to react first with electrophiles and subsequently with nucleophiles, is the key property enabling and sustaining the multicomponent process. For this reason the identification of *novel electrophilic partners*⁵ constitutes a starting point for the discovery of new isocyanide mediated MCRs. Our recent discovery that nitrile *N*-oxide species (generated in situ from (*Z*)-chlorooximes) are good electrophilic partners for isocyanides with which they form a transient nitrilium ion adduct that can be intercepted by both external and internal nucleophiles has led to the discovery of novel multicomponent reactions⁶ and to an innovative synthesis of medicinally important α -arylketamide amides.⁷

As a continuation of our previous studies, we questioned whether an electron deficient phenol could be a good nucleophile third component to intercept the nitrilium ion affording aryloxyiminoamides. After formation of the imidate, the hydroxyl group of the oxime, which is properly positioned, thanks to the stereoselective addition of isocyanide to the nitrile *N*-oxide,⁸ should trigger a Smiles rearrangement,⁹ in a manner reminiscent of the Passerini–Smiles reaction developed by

Prof. El Kaïm.¹⁰ In this case, a six-membered transition state should occur,¹¹ contrary to the typical Smiles rearrangement which forms a five-membered transition state (Scheme 1).

To test our hypothesis, we chose (*Z*)-phenylchlorooximes (1){1}, pentylisocyanide (2){3}, and *p*-nitrophenol (3){1}. The last component was reported as being more problematic than *o*-nitrophenol in favoring the Smiles rearrangement, and so presented a good challenge for reaction development and optimization. Indeed, *p*-nitrophenol has been shown to be less reactive in the Ugi–Smiles,¹² and completely non reactive in the Passerini–Smiles rearrangement.¹⁰

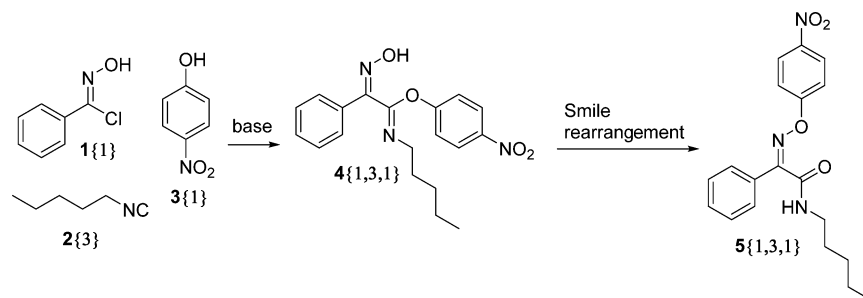
When the reaction was carried out in the presence of 2 equiv of triethylamine (TEA), in dichloromethane at room temperature (2 h), we obtained a mixture from which the desired product (5) {1,3,1} and the imidate (4) {1,3,1} could be separated with yields of 14% and 20%, respectively. These two compounds were easily identified via ¹³C NMR (see Supporting Information). The result did not change when the reaction was heated at reflux in toluene (6 h). We reasoned that the difficulty in triggering the Smiles rearrangement could be due to the inability of TEA (p*K*_a = 10.65) to fully deprotonate the oxime (p*K*_a = 10.78). The use of 2 equiv of potassium *tert*-butoxide (p*K*_a = 18) did not, however, improve the result. Under such conditions the reaction was not clean and we were able to isolate the desired compound (5) {1,1,1} only in very low yield

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Scheme 1. Three-Component Synthesis of Aryloxyimino Amide (5)



(less than 10%). We therefore searched for a base stronger than TEA but weaker than *t*-BuOK, and we opted for 2 equiv of DBU ($pK_a = 12$) which allowed us to isolate desired product (5) {1,1,1} in 20% yield and without observing the formation of the imidate.

In this case, as with TEA, heating the reaction at 80 °C in toluene (6 h) did not change the yield. Reasoning that, while the formation of the nitrile *N*-oxide species required an equimolar amount of base, the Smiles rearrangement occurring after the addition of *p*-nitrophenol to the nitrilium ion could proceed in the presence of a catalytic amount of base. Thus, by reducing the amount of DBU to 1.2 equiv in dichloromethane (room temperature, overnight) we were able to isolate the product in 37% yield. Again, the imidate was not isolated. Such yield represented a notable advance, since as already discussed above, *p*-nitrophenol is a particularly challenging reactant for this type of rearrangement.

We were pleased to find the aryloxyimino amide to be stable, in particular with respect to a potential Beckmann rearrangement because of the presence of a nitrophenol leaving group. No sign of Beckmann product could be detected after refluxing in toluene for several hours. As there is in literature only one precedent for the synthesis of aryloxyimino amides,¹³ with the optimized conditions for this novel multicomponent reaction in our hands, and after verifying that both the work up and the chromatographic purification were experimentally easy, we explored the generality of this transformation by employing it in the combinatorial parallel synthesis of a library of compounds. Three aryl-(*Z*)-chlorooximes 1{1–3} bearing either electron-deficient or electro-donor substituents, three isocyanides 2{1–3}, and five electron-deficient arenes 3{1–5} were used (Figure 1). By combination of these reagents in a three-component reaction a library of 45 compounds should be obtained.

To optimize the management of such a large number of reactions and minimize the chances of trivial operator errors (such as miscalculations which could compromise the outcome of some of the reactions), we wrote the computer program MCRcombiS, able to manage large amounts of data and quickly output the correct quantities/concentrations of reagents (mmol, mg/mL, etc.) to be used in each reaction. This program is now freely available for noncommercial use.¹⁴ The results obtained are shown in Figure 2 (see in the Supporting Information Table S1 the structures of all the synthesized compounds along with yields and purity).

The reactions proceeded efficiently and only in four cases we were not able to isolate the desired aryloxyimino amide. The reaction does not seem to be very sensitive to steric or electronic factors. In order to evaluate their purity all the final compounds were analyzed by HPLC-UV-MS (see Supporting

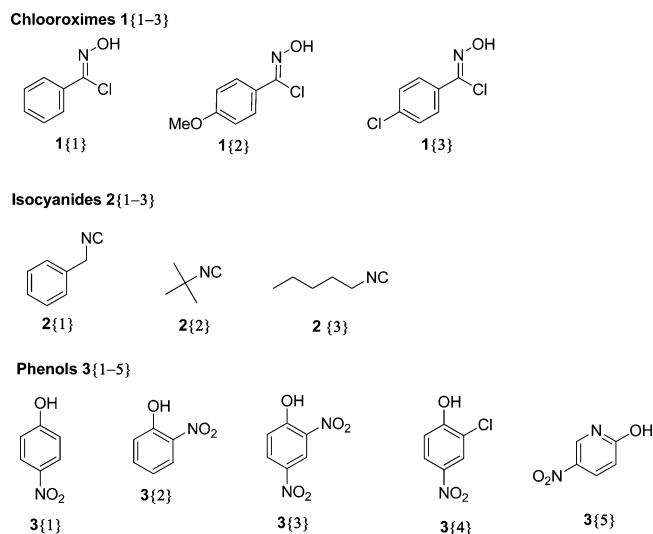


Figure 1. Building blocks used.

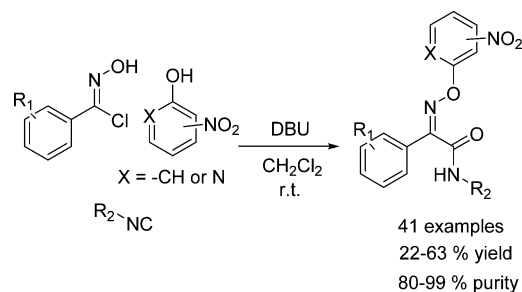
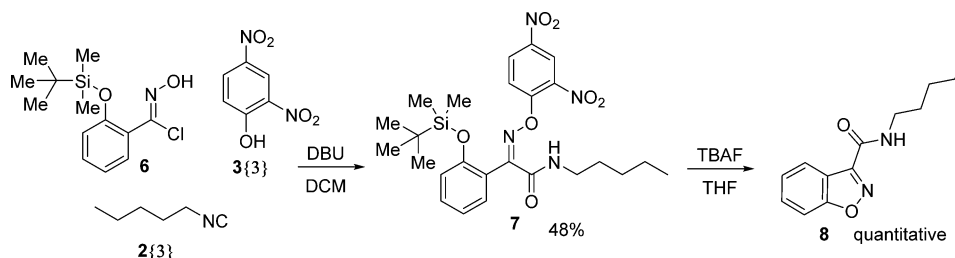


Figure 2. General scheme of the aryloxyiminoamides synthesized.

Information). Thus, the application of this novel multicomponent reaction to combinatorial synthesis afforded 41 of the expected 45 compounds with an overall success rate for this library of 93% and an average purity of 93%, after a simple silica gel filtration. Four compounds [5{1,3,5}, 5{2,3,1}, 5{2,3,5}, and 5{3,3,5}] were found to be mixtures of *Z* and *E* isomers of the oxime, detected by both ¹H NMR and HPLC, while six compounds [5{1,1,1}, 5{1,2,1}, 5{1,1,2}, 5{2,2,1}, 5{2,1,2}, and 5{2,2,2}] showed the presence of less than 5% of the *E* isomer visible only by HPLC. In this case, the *E*-isomer was easily removed by crystallization.

Aryloxyimino amides are interesting compounds per se, but we were also intrigued by their potential use as intermediates for further synthetic transformations. As an example, we explored the synthesis of benzo[*d*]isoxazole-3-carboxamides, a well-known scaffold in medicinal chemistry, which usually requires a long and tedious synthesis (8 steps).¹⁵ As it has been

Scheme 2. Synthesis of Benzo[*d*]isoxazole-3-carboxamides

demonstrated that S_N2 reactions can occur at the sp^2 nitrogen of oximes,¹⁶ we reasoned that the aryloxyimino amide **7**, derived from the (*Z*)-chlorooxime of salicylaldehyde (**6**) may, after hydroxyl deprotection, trigger an intramolecular S_N2 type reaction affording benzo[*d*]isoxazole-3-carboxamides (**8**) (Scheme 2). We were pleased to find that, when TBAF was used to cleave the silyl protecting group, the desired transformation occurred in quantitative yield.¹⁷

In conclusion, we reported here the discovery of a novel multicomponent reaction among (*Z*)-chlorooximes, isocyanides and electron-deficient arenes. The oxime-mediated Smiles rearrangement drives the reaction from the less stable imidates toward the formation of stable amides. The reaction is robust enough to be used in a combinatorial process, and one example of use as a synthetic intermediate for the preparation of a 3-substituted benzo[*d*]isoxazole was demonstrated, raising the possibility of a shorter synthetic pathway for the production of this heterocycle. We are currently investigating the biological properties of this hitherto unreported class of compounds and the result of such study will be reported in due course.

EXPERIMENTAL PROCEDURES

Solvents and Reagents. Commercially available solvents and reagents were used without further purification. Dichloromethane was dried by distillation over P_2O_5 and stored over activated molecular sieves (4 Å). When needed, the reactions were performed in oven-dried glassware under a positive pressure of dry nitrogen.

Chromatography. Column chromatography was performed on silica gel 60 (Kieselgel 230–400 mesh ASTM) using the indicated eluents. Thin layer chromatography (TLC) was carried out on 5 × 20 cm plates with a layer thickness of 0.25 mm (Silica gel 60 F254). When needed they were visualized using $KMnO_4$ reagent.

Spectra. Infrared spectra were recorded on a FT-IR with absorption maxima (ν_{max}) recorded in wavenumbers (cm^{-1}). NMR spectra were recorded using a 300 or 400 MHz spectrometer. Chemical shifts (δ) are quoted in parts per million and referenced to the residual solvent peak. The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; hept, heptet; m, multiplet; br, broad singlet. Coupling constants (*J*) are reported in Hertz (Hz). HRMS were recorded on ORBITRAP mass spectrometer equipped with an ESI source. Melting points were determined and remain uncorrected. Chlorooximes **1{1}**, **1{2}**, and **1{3}** are not new, and they were prepared following literature procedure.¹⁸

General Preparation of Aryloxyimino Amides. The chlorooxime (1 equiv) was dissolved in dry dichloromethane and isocyanide (1 equiv), phenol (1.1 equiv), and DBU (1.2

equiv) were added. The reaction was stirred at room temperature under a nitrogen atmosphere until all the chlorooxime was consumed (typically overnight as judged by TLC). The reaction mixture was concentrated under reduced pressure, and the crude material was purified by column chromatography.

ASSOCIATED CONTENT

Supporting Information

Structures of all compounds synthesized, spectroscopic data, copies of 1H and ^{13}C NMR, HPLC spectra and list of aryloxyimino amides synthesized. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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