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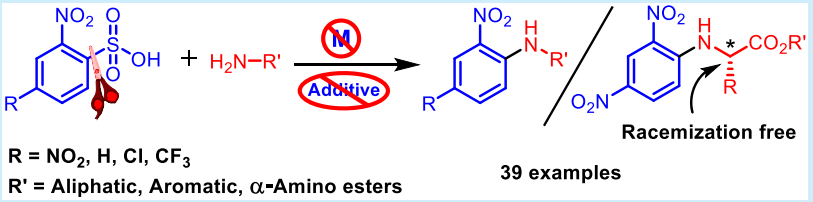
Synthesis of *o*-Nitroarylamines via Ipso Nucleophilic Substitution of Sulfonic Acids

Srinivasa Rao Manne, Jyoti Chandra, and Bhubaneswar Mandal*

Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, India 781039

Supporting Information

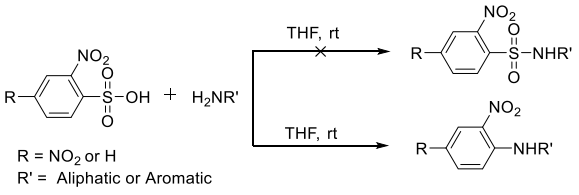


ABSTRACT: A mild, efficient, and eco-friendly method for the synthesis of *o*-nitroarylamine from *o*-nitroaryl sulfonic acid via ipso nucleophilic aryl substitution by amine is described. The products have been obtained with good yields at room temperature without the assistance of any metal, activating agent, or toxic oxidant. This method is useful for racemization-free synthesis of *N*-aryl amino acid esters.

The arylamine moiety is an important functional group present in many biologically active natural products[1] and medicinally important compounds.[2] They are widely used in the synthesis of fine chemicals, dyes, materials with special properties,[3] and polymers.[4] Because of the diverse applications of arylamines, numerous strategies have been developed for the construction of the aryl−nitrogen bond.[5] N-Arylation of amines is usually performed by palladium- or copper-catalyzed cross-coupling of aryl halides with amines,[6] the copper-catalyzed Ullmann-type coupling of aryl halides with aryl amines,[7] and Chan−Lam coupling of aryl boronic acids with aryl amines.[8] The palladium-catalyzed coupling reactions have some limitations in large-scale synthesis, such as the use of expensive palladium catalysts and the use of elevated temperatures in the reaction.[9] Alternatively, copper-mediated aryl coupling reactions are widely used on an industrial scale, due to inexpensive copper salts and a straightforward approach. However, this protocol also suffers from the requirement for a stoichiometric or large amount of copper salts, production of a significant amount of a toxic copper-based effluent, a high temperature, and a longer reaction time.[10] Therefore, it is always desirable to develop a transition metal-free method for the synthesis of arylamines. In this respect, few reports have described the transition metal-free couplings between primary or secondary amines and aryl halides.[11] Also, various electrophiles such as aryl boronic acids and their derivatives,[12] diaryliodonium salts,[13] Sanger's reagent,[14] and *o*-silylaryl triflates[15] are also used for direct nucleophilic aromatic substitution reactions with an amine.

For our research in medicinal chemistry, we required the conversion of aromatic sulfonic acid to the corresponding sulfonamide and sulfonate ester, which was previously achieved by activating sulfonic acids[16] and by direct coupling.[17] Thus, we reacted aromatic sulfonic acid **1a** with an amine in THF; unexpectedly, we obtained an arylamine instead of the desired sulfonamide. It is worth mentioning that such a reaction with an alcohol instead of an amine efficiently generated the corresponding sulfonate ester at an elevated temperature.[17] To the best of our knowledge, there is no report in the literature concerning the metal-free aryl amine synthesis from *o*-nitrobenzenesulfonic acids. This protocol (Scheme 1) requires neither the performance of the reaction at a high temperature nor expensive and air-sensitive phosphine ligands that are often required for palladium chemistry.

Scheme 1. Synthesis of Arylamine from *o*-Nitrobenzenesulfonic Acid



For optimization of the reaction condition, synthesis of *N*-cyclohexyl-2,4-dinitroaniline (**3a**) from the reaction of 2,4-dinitrobenzenesulfonic acid with cyclohexylamine was examined, and the results are outlined in Table 1. We screened a variety of solvents, such as CH_3CN, H_2O, DCM, $CHCl_3$, EtOAc, DMF, MeOH, and THF. In the case of THF, we observed a moderate yield (entry 8) of the product. To improve the yield of the product, we added various bases such as DMAP, DBU, DABCO, and DIPEA. However, no change in the product yield (entries 9−12) was noted. Use of excess base

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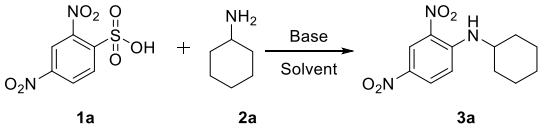
Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

entry	solvent	amine (equiv)	base (equiv)	yield (%)[b]
1	CH_3CN	1	–	22
2	H_2O	1	–	20
3	DCM	1	–	25
4	$CHCl_3$	1	–	26
5	EtOAC	1	–	24
6	DMF	1	–	21
7	MeOH	1	–	23
8	THF	1	–	44
9	THF	1	DMAP(1)	42
10	THF	1	DBU(1)	45
11	THF	1	DABCO(1)	44
12	THF	1	DIPEA(1)	45
13	THF	1	DIPEA(2)	44
14	THF	1	DIPEA(3)	44
15	THF	1	DIPEA(4)	42
16	THF	2	–	73
17	THF	3	–	94
18	THF	4	–	96

[a]For the reactions, 2,4-dinitrobenzenesulfonic acid (**1a**) (0.5 mmol), cyclohexylamine (**2a**, varied amount), and a base were stirred for 30 min at room temperature. [b]Isolated yield.

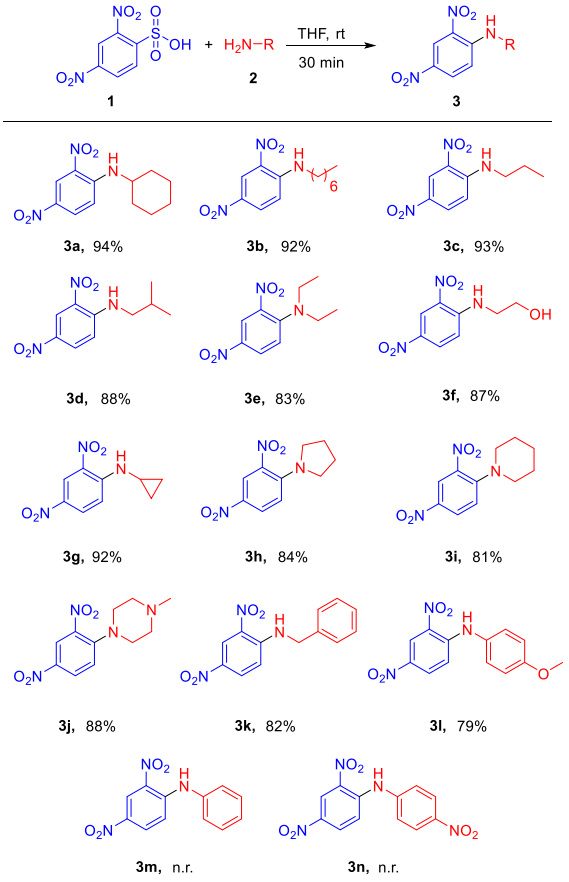
(DIPEA) also did not improve the yield of the reaction (entries 13−15). However, increasing the amount of amine from 2 to 4 equiv improved the yield of the desired product from 74 to 96% (entries 16−18). Therefore, 3 equiv of amine and THF as a solvent was considered as the optimal condition.

The scope of the reaction between 2,4-dinitrobenzenesulfonic acid (**1a**) and various amines (Scheme 2) was investigated under the optimized conditions. The reactions worked well with primary and secondary amines, and the products were obtained in good yields (**3a−e**). In the case of *β*-amino alcohol (**3f**), the amine group was found to be arylated selectively with good yield but the hydroxyl group remained intact. Further, we achieved arylation on heterocyclic compounds such as pyrrolidine, piperidine, and 1-methylpiperazine (**3h−j**) and an electron-rich aromatic aniline such as 4-methoxyaniline (**3l**). However, arylation did not take place on neutral and electron deficient aromatic amines such as aniline and 4-nitroaniline (**3m** and **3n**).

Next, the scope of the methodology was explored with substituted sulfonic acids. The reactions worked well with mono (*ortho*) and dinitro substituents but did not work without an *o*-nitro substituent (Table S1). A moderate yield was obtained when the nitro group in the *para* position was replaced with other electron-withdrawing groups, e.g., CF_3 and Cl (Scheme 3).

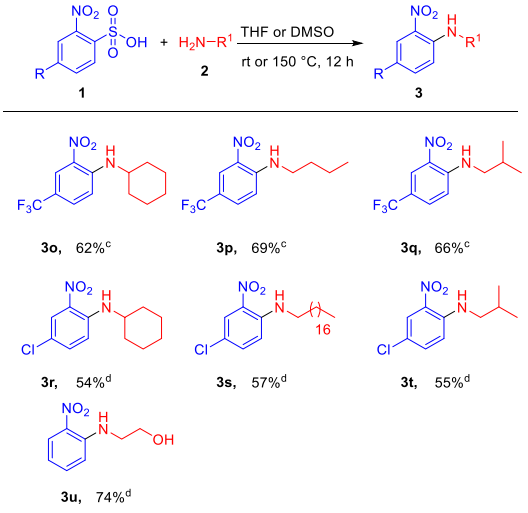
Next, the scope of this protocol was extended to various amino acid esters. The reactions of amino acid esters with 2,4-dinitrobenzenesulfonic acid progressed efficiently with good yields, including reaction with the sterically hindered amino acid methyl esters [**5a−h** (Scheme 4)]. Also, the reactions worked well with the *tert*-butyl esters of alanine, phenylalanine, and proline (**5i−m**). This method was compatible with a C-terminal unprotected amino acid (**5n**) and the side chain amino group of amino acids (**5o**). In addition, the reaction was

Scheme 2. Facile N-Arylation of Amines with 2,4-Dinitrobenzenesulfonic Acid[a,b]



[a]Reaction conditions: 2,4-dinitrobenzenesulfonic acid (**1a**, 0.5 mmol), amine (1.5 mmol), reaction time of 30 min. [b]Isolated yields with respect to sulfonic acid. n.r., no reaction.

Scheme 3. Facile N-Arylation of Amines with Substituted *o*-Nitrobenzenesulfonic Acids[a,b]



[a]Reaction conditions: sulfonic acid (0.5 mmol), amine (1.5 mmol). [b]Isolated yield with respect to the sulfonic acid. [c]Stirred the reaction mixture for 12 h at room temperature in THF as the solvent. [d]Stirred the reaction mixture for 12 h at 150 °C in DMSO as the solvent.

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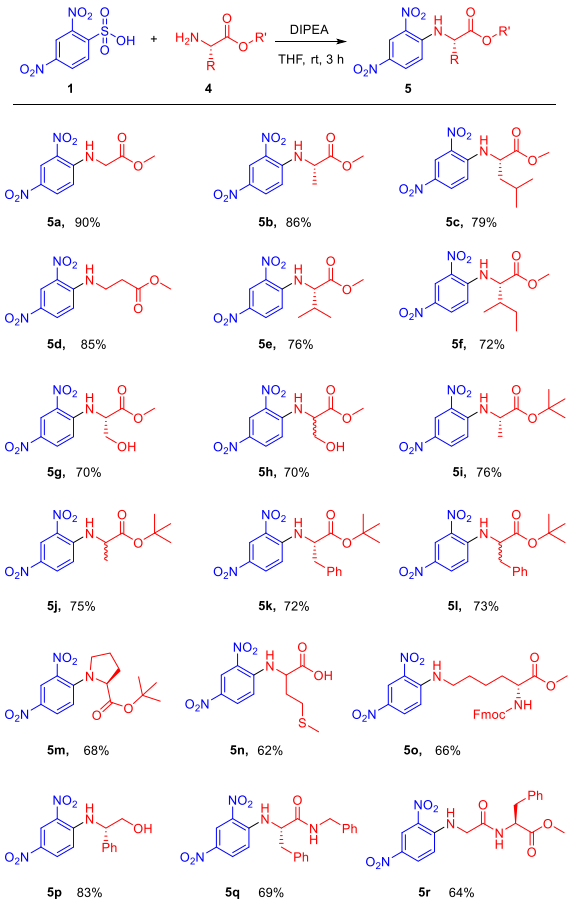
Scheme 4. Facile N-Arylation of the Amino Acids[a,b]



[a]For the chiral products, the ee was ≥99% based on the chiral HPLC data (Supporting Information). Reaction conditions: 2,4-dinitrobenzenesulfonic acid (**1a**, 0.5 mmol), amino acid (1.5 mmol), DIPEA (1.5 mmol), reaction time of 3 h. [b]Isolated yield with respect to the sulfonic acid.

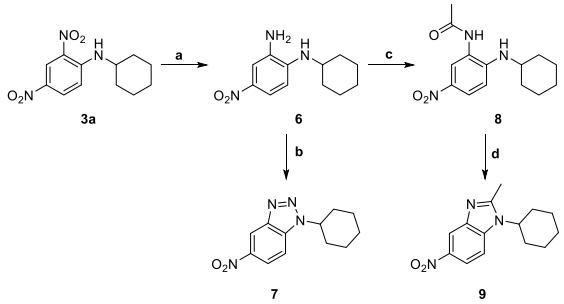
compatible with dipeptides,[18] and the arylation was accomplished successfully with a good yield (**5r**).

All of the products were almost pure and did not require any column chromatography. The chemical structures of compounds **3d** and **5f** were further confirmed by X-ray crystallographic analysis (Figures S132 and S133).

Racemization is a crucial factor in the synthesis of *N*-aryl amino acid esters. At first, we performed arylation with the methyl esters of DL- and L-serine using our protocol [**5g** and **5h** (Figures S84 and S85, respectively)] as serine is known to be an amino acid highly prone to racemization. There was no sign of racemization in the HPLC profile of the L-isomer. Furthermore, we synthesized two other sets of L and DL derivatives of alanine and phenylalanine [**5i–l** (Figures S89, S90, S94, and S95, respectively)] and found no detectable racemization during the amination reaction. Therefore, the current method can be used for N-arylation of amino acid esters and peptides without detectable racemization.

The *o*-nitroarylamines obtained can be used to prepare important compounds. For example, the regioselective reduction of the *o*-nitro group of compound **3a** gave the *p*-nitrophenyldiamine derivative **6**, which is a key intermediate for the synthesis of the benzotriazole[19] and benzimidazole[20] derivatives (Scheme 5) that exhibit interesting medicinal properties.[21]

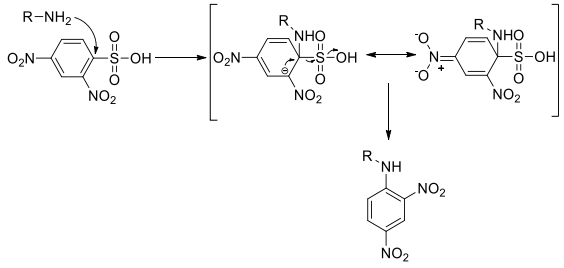
Scheme 5. Synthesis of Benzotriazole and Benzimidazole[a]



[a]Reagents and conditions: (a) $Na_2S·9H_2O$, S, EtOH, H_2O, 100 °C, 2 h; (b) $NaNO_2$, AcOH, H_2O, 4 °C, 2 h; (c) AC_2O, NMI, 2 h; (d) HCl, EtOH, 70 °C, 4 h.

A plausible pathway was postulated on the basis of the existing literature (Scheme 6).[22] The reaction proceeded

Scheme 6. A Plausible Mechanism for the Formation of Arylamine



smoothly with electron deficient aromatic sulfonic acids having electron-withdrawing substituents on the benzene ring, but the desired product was not obtained with benzenesulfonic acid that was either unsubstituted or substituted with an electron-donating group. Aliphatic sulfonic acids also did not react. Therefore, it is possible that the reaction proceeded via ipso nucleophilic aromatic substitution [$^{i}S_NAr$ (Scheme 6)] by the formation of a Meisenheimer complex.[23] The Meisenheimer complex was stabilized by the presence of the electron-withdrawing groups. Furthermore, no reaction was observed in the absence of the *o*-nitro group, which can account for the higher rates of the reactions with *ortho*-substituted aromatic sulfonic acids by stabilization of the Meisenheimer complex via the *ortho* effect.[22b]

In conclusion, a direct method for the synthesis of *o*-nitroarylamine without using any transition metal catalyst was presented. The main advantages of this method include the short reaction time, good yields, the high product purity, and operational simplicity. Additionally, no racemization could be detected during amination with chiral amino acid esters.

■ ASSOCIATED CONTENT

Supporting Information

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General experimental details and characterization data of the compounds (PDF)

Accession Codes

CCDC 1580047 and 1586476 contain 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.

AUTHOR INFORMATION

Corresponding Author

*E-mail: bmandal@iitg.ac.in.

ORCID

Bhubaneswar Mandal: 0000-0003-3435-5443

Notes

The authors declare no competing financial interest.

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