

SYNLETT Spotlight 459

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

2-Halobenzamides

Compiled by Shah Jaimin Balkrishna

Shah Jaimin Balkrishna was born in Vadodara, Gujarat, India in 1984. He received his B.Sc. degree in chemistry (2005) and his M.Sc. degree in organic chemistry (2007) from The Maharaja Sayajirao University of Baroda, India. From 2007 to 2009 he worked as senior scientific assistant at the Zydu Research Centre, Ahmedabad, India. Currently, he is carrying out his Ph.D. studies at the Indian Institute of Science Education and Research (IISER) Bhopal, India under the supervision of Dr. Sangit Kumar. His research interests focus on developing new methodologies for the construction of organoselenium compounds and their use in bromination of alkenes.

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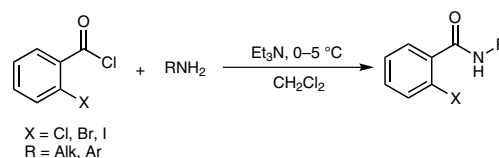


Introduction

2-Halobenzamides are important precursors in organic synthesis to construct various heterocyclic compounds. They exhibit strong intermolecular N–H···O=C hydrogen bonding^{1a} and therefore, most of them are crystalline solids in nature and can be stored for a long period of time. Most of the 2-halobenzamides are soluble in organic solvents, for example, in dichloromethane, chloroform, acetone, methanol, etc.

Preparation

2-Halobenzamide can be easily prepared from the corresponding 2-halobenzoyl chloride and freshly distilled primary amine in the presence of triethylamine.^{1a–e} Dichloromethane, chloroform, tetrahydrofuran, etc. are suitable solvents for this reaction.

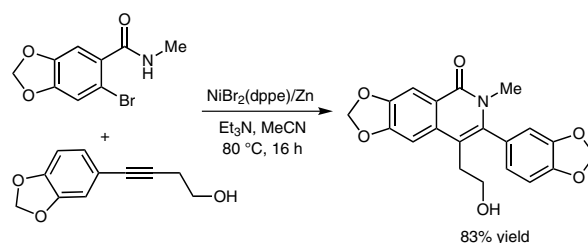


Scheme 1 Synthesis of 2-halobenzamides

Abstracts

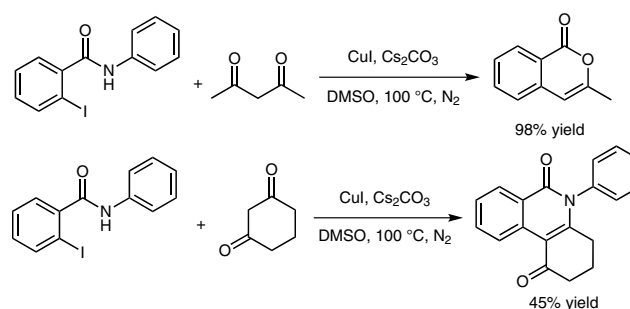
(A) Synthesis of Isoquinolones:

Cheng and colleagues described an efficient nickel-catalyzed method for the synthesis of substituted 1(2*H*)-isoquinolones via annulation of variously substituted 2-halobenzamides with alkynes. The reaction worked well with both internal and terminal alkynes. Here, Ni(II) is reduced to Ni(0) by zinc powder, followed by oxidative addition of 2-halobenzamide to Ni(0) to form a five-membered nickelacycle. The insertion of alkyne gave a seven-membered nickelacycle which upon reductive elimination yielded the isoquinolone.²



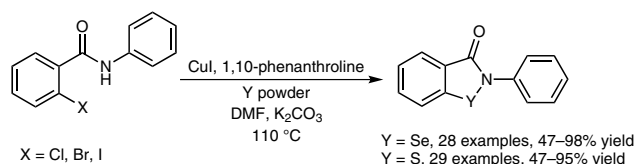
(B) Synthesis of Isocoumarins:

Isocoumarins are well-known heterocyclic scaffolds for the construction of various natural products possessing a wide range of biological activities. Yao and co-workers described an efficient synthesis of isocoumarins by a copper-catalyzed tandem C–C/C–O coupling strategy by utilizing various 2-iodo-*N*-phenylbenzamides and acyclic 1,3-diketones as starting materials.³ By using a cyclic ketone as starting material the isoquinolinone is produced.

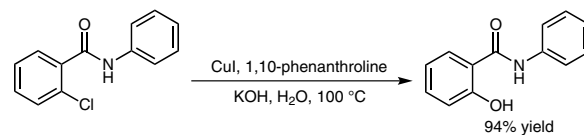


(C) *Synthesis of Chalcogen-N Heterocycles:*

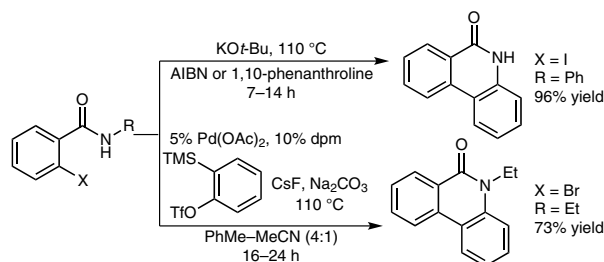
Kumar and colleagues described a copper-catalyzed methodology for the construction of heterocyclic compounds bearing a Se-N or S-N bond.⁴ 2-Halobenzamides are treated with elemental selenium or sulfur in the presence of CuI catalyst and K₂CO₃ as base.

(D) *Synthesis of 2-Hydroxybenzamides:*

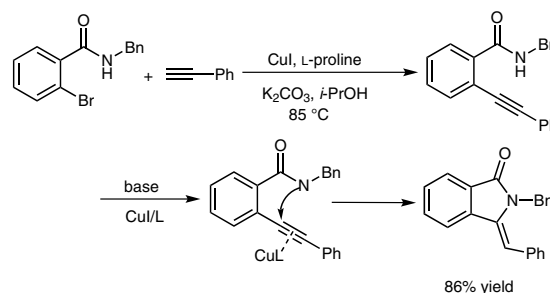
The 2-hydroxybenzamide motif has a wide range of biological activities. Kumar and co-worker described an efficient methodology for the synthesis of 2-hydroxybenzamides from the corresponding 2-chlorobenzamides by using CuI/1,10-phenanthroline.⁵ This is the first report of a copper-catalyzed hydroxylation in neat water.

(E) *Synthesis of Phenanthridinones:*

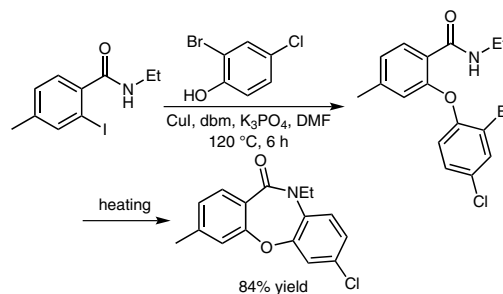
Synthesis of phenanthridinones is described from 2-halobenzamides in the presence of KO^t-Bu by using a catalytic amount of 1,10-phenanthroline or AIBN. The reaction proceeds through a radical mechanism as it is progressing smoothly in the presence of the radical initiator AIBN. Moreover, the presence of the radical was confirmed by EPR spectroscopy.⁶ Larock and co-workers described the synthesis from 2-halobenzamides and *ortho*-(trimethylsilyl)aryl triflate in the presence of a palladium catalyst.⁷ CsF is used as fluoride source to generate benzyne. A toluene-acetonitrile solvent ratio of 4:1 is important to get high yields of the desired products.

(F) *Synthesis of 3-Methylisindolin-1-ones:*

Ma and co-workers reported a CuI/L-proline-catalyzed coupling of 2-bromobenzamides with terminal alkynes to cyclize into 3-methylisindolin-1-ones. The reaction works equally well in DMF/DMSO solvents.⁸

(G) *Synthesis of Dibenzoxazepinones:*

A copper-catalyzed domino reaction between 2-iodobenzamides and 2-bromophenols by using K₃PO₄ as base resulted in dibenzoxazepinones. The reaction sequence started with a copper-catalyzed Ullmann coupling followed by a base-mediated Smiles rearrangement and a final ring-closing process to give the desired product.⁹



References

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