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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
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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.

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.\(^1\) By using a cyclic ketone as starting material the isoquinolinolone is produced.
(C) Synthesis of Chalcogen–N Heterocycles:
Kumar and co-workers described a copper-catalyzed methodology for the construction of heterocyclic compounds bearing a Se–N or S–N bond. 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. 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 K₂O-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. Larock and co-workers described the synthesis from 2-halobenzamides and ortho-(trimethylsilyl)aryl triflate in the presence of a palladium catalyst. CsF is used as fluoride source to generate benzene. A toluene–acetonitrile solvent ratio of 4:1 is important to get high yields of the desired products.

(F) Synthesis of 3-Methylisoindolin-1-ones:
Ma and co-workers reported a CuI/L-proline-catalyzed coupling of 2-bromobenzamides with terminal alkynes to cyclize into 3-methylisoindolin-1-ones. The reaction works equally well in DMF/DMSO solvents.

(G) Synthesis of Dibenzoxazepinones:
A copper-catalyzed domino reaction between 2-iodobenzamides and 2-bromophenols by using K₂PO₄ 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.

References