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USE OF 2-BROMOACETYLBENZOFURANS IN HETEROCYCLIC SYNTHESIS (REVIEW)

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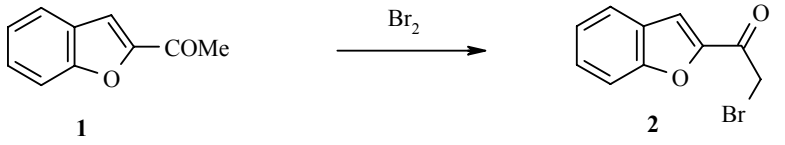
Data on the synthesis of 2-bromoacetylbenzofurans and their reactions are reviewed.

Keywords: 2-acetylbenzofuran, benzofuran, 2-bromoacetylbenzofuran.

2-Bromoacetylbenzofurans are widely used as intermediates in fine organic synthesis. In this article we discuss the methods of preparation and reactions of 1-(benzofuran-2-yl)-2-bromoethanones. The review provides useful and up-to-date data for medicinal chemists.

1. Synthesis

Bromination of 2-acetylbenzofuran **1** in dioxane/ether [1–4] or in carbon disulfide [5] gives 2-bromoacetylbenzofuran **2** in good yield.



1 **2**

Bromination of 2-acetyl-5-chloro-3-methylbenzofuran with bromine in acetic acid gives 2-bromoacetyl-5-chloro-3-methylbenzofuran **3** in good to medium yield [6].

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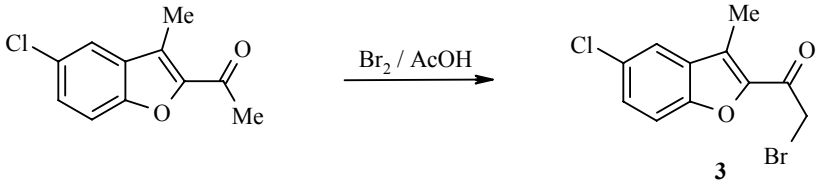
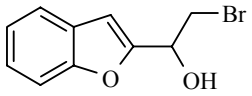


3

2. Reactions

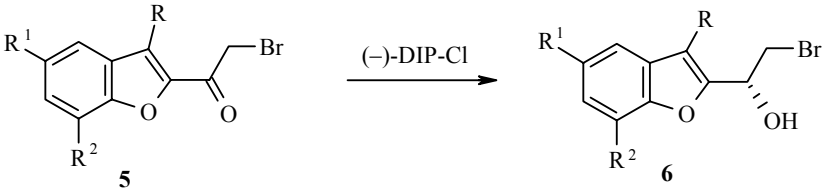
2.1. Reduction

Hydrogenation of 2-bromoacetylbenzofuran with $NaBH_4$ in methanol affords 1-(2-benzofuryl)-2-bromo-1-hydroxyethane **4** in high yield [7].



4

Enantioselective reduction of 2-bromoacetylbenzofurans **5** with (–)-β-chlorodiisopinocampheylborane [(–)-DIP-Cl] gives the bromohydrins (*R*)-**6** [8].

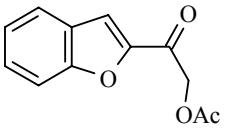


5 **6**

R, R^1 = H, R^2 = Et; R = CH_2CH_2Ph, R^1, R^2 = H

2.2. Reactions with acid salts

Treatment of compound **2** with sodium acetate affords 2-acetoxyacetylbenzofuran **7** in good yield [1]. The reaction of compound **2** with sodium benzenesulfinate gives the corresponding sulfone derivative **8** [9].



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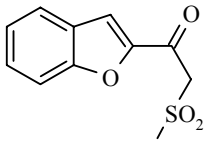
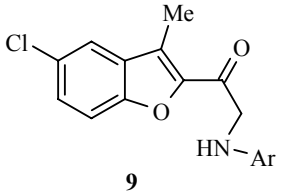


8

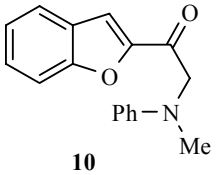
2.3. Reaction with amines

Condensation of 2-bromoacetyl-5-chloro-3-methylbenzofuran **3** with various substituted aromatic amines gives 2-N-arylaminoacetyl-5-chloro-3-methylbenzofurans **9** [6].



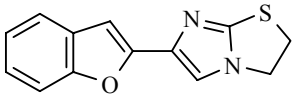
9

N-Methylaniline condenses with compound **2** to give the corresponding amino ketone derivative **10** [2].



10

The reaction of 2-amino-4-thiazoline, 2-aminothiazole, and 2-aminobenzothiazole with compound **2** gives dihydroimidazothiazole, imidazothiazole, and imidazobenzothiazole derivatives **11-13**, respectively [11].



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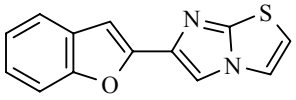

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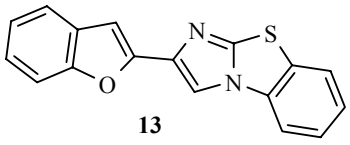
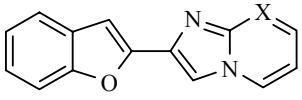


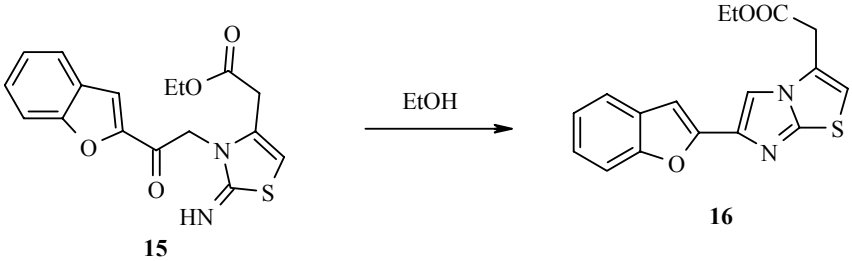
13

Cyclocondensation of 2-aminopyridine and 2-aminopyrimidine with compound **2** affords the imidazo[1,2-*a*]pyridine **14** (X = CH) and imidazo[1,2-*a*]pyrimidine **14** (X = N) derivatives in good yields [12, 13].



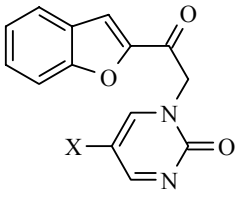
14

The condensation reaction of compound **2** with ethyl 2-aminothiazole-4-acetate (1:1) in acetone affords ethyl 3-(2-benzofuroylmethyl)-2-iminothiazoline-4-acetate **15**, which on refluxing in EtOH cyclizes to give imidazolothiazole derivative **16** [14].



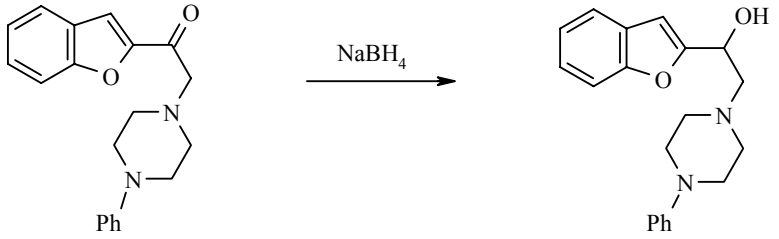
15 **16**

Pyrimidinone derivatives **17** (X = Hal, CF_3) are synthesized by the treatment of compound **2** with 5-substituted 1H-2-pyrimidinones [15].



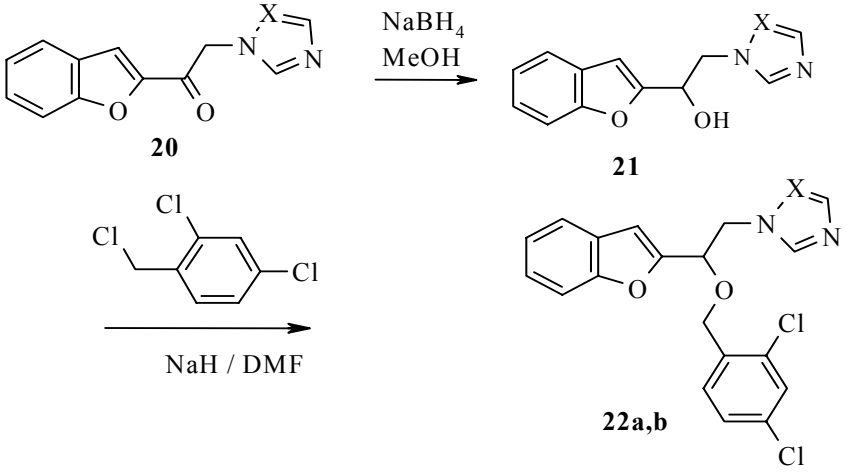
17

1-(Benzofuran-2-yl)-2-(4-phenylpiperazin-1-yl)ethanone **18** and 1-(benzofuran-2-yl)-2-(4-phenylpiperazin-1-yl)ethanol **19** have been synthesized by the reaction of compound **2** with N-phenylpiperazine followed by $NaBH_4$ reduction [16].



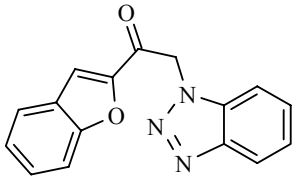
18 **19**

1-(2-(2,4-Dichlorobenzyloxy)-2-(benzofuran-2-yl)ethyl)-1H-imidazole **22a** (X = CH) or 1-(2-(2,4-dichlorobenzyloxy)-2-(benzofuran-2-yl)ethyl)-1H-1,2,4-triazole **22b** (X = N) are prepared by the reaction of compound **2** with 1H-imidazole or 1H-1,2,4-triazole, which leads to azole ketones **20**. Reduction with $NaBH_4$ gives secondary alcohols **21**, which are converted into the target compounds by etherification with 2,4-dichloro-1-(chloromethyl)benzene [17].



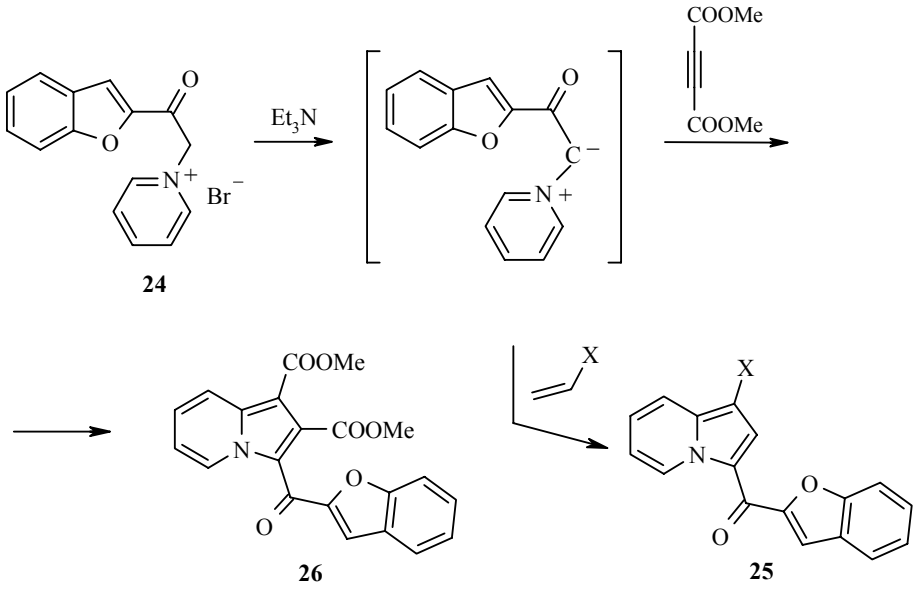
20 **21** **22a,b**

The reaction of compound **2** with 1H-benzotriazole gave 1-(benzofuran-2-yl)-2-(benzotriazol-1-yl)ethanone **23** in high yield [18].



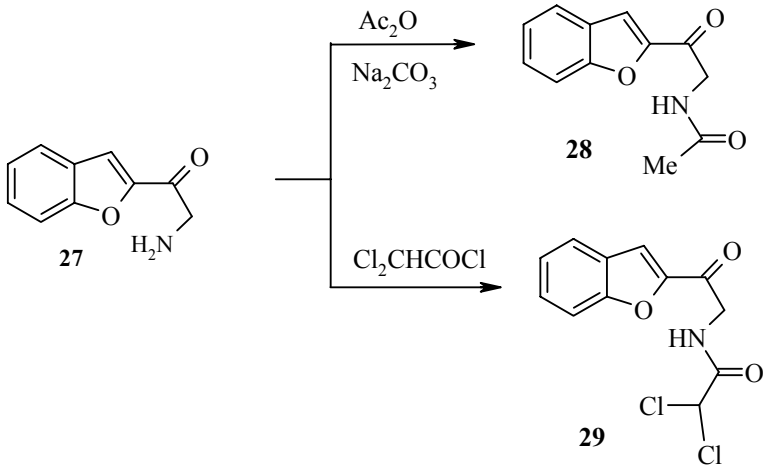
23

The reaction of compound **2** with pyridine produces the corresponding pyridinium bromide **24**. The latter reacted with some activated alkenes and acetylenes to give the indolizine derivatives **25** (X = CN, COOMe) and **26**, respectively [22].



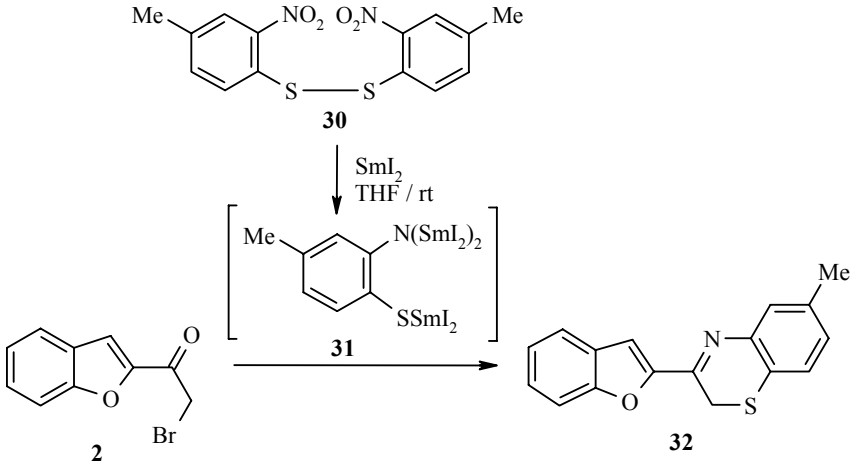
24 **26** **25**

When compound **2** is treated with hexamethylenetetramine in dry chloroform and the formed quaternary salt hydrolyzed with concentrated hydrochloric acid at room temperature the amino ketone **27** is produced. Acetylation of the latter compound with acetic anhydride gives the acetamide derivative **28**. On the other hand, when the amine hydrochloride **27** is treated with dichloroacetyl chloride, it gives the corresponding dichloroacetamide derivative **29** in good yield [19].



27 **28** **29**

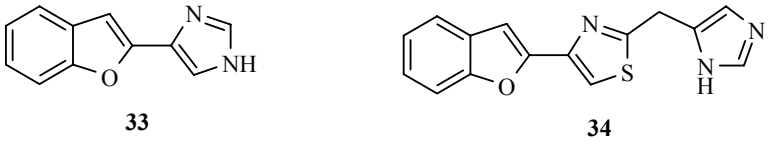
Treatment of bis(*o*-nitrophenyl)disulfides **30** with samarium(II) iodide leads to simultaneous reduction of the nitro groups and reductive cleavage of the S–S bond to form the active intermediate **31**. The intermediate **31** reacts smoothly with compound **2** at room temperature to afford 2H-1,4-benzothiazine derivative **32** in good yield [6].



2.4. Reaction with amide derivatives

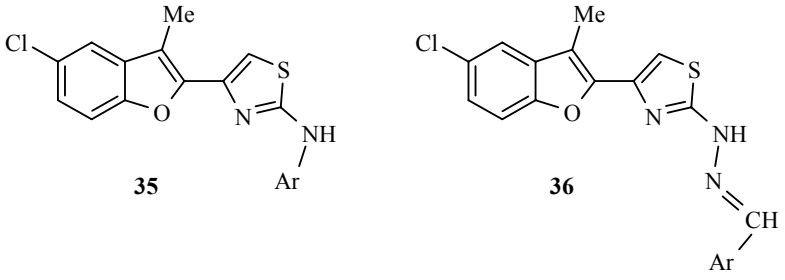
The reaction of compound **2** with formamide results in the formation of 2-(4-imidazolyl)benzofuran **33** [20].

The reaction of compound **2** with 2-(1H-imidazol-5-yl)ethanethioamide afforded 4-(2-benzofuryl)-2-(imidazol-4-ylmethyl)thiazole **34** [20].

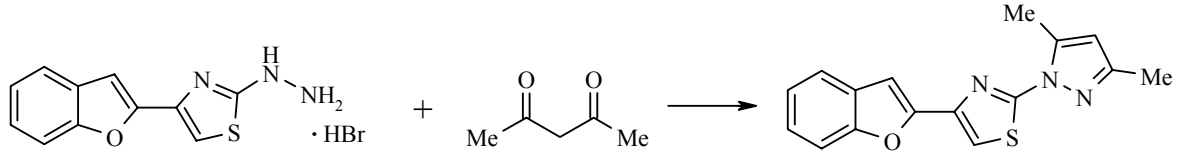


2.5. Reaction with thioureas

The reaction of 2-acetyl-5-chloro-3-methylbenzofuran with various substituted aryl thioureas in ethanol gives N-aryl-4-(5-chloro-3-methylbenzofuran-2-yl)thiazol-2-amines **35**, while its reaction with arylidene thiosemicarb-azides in ethanol produces 2-arylidenehydrazino-4-(5'-chloro-3'-methylbenzofuran-2'-yl)thiazoles **36** [23].

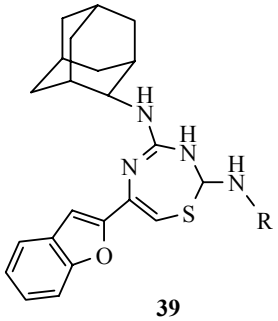


Treatment of compound **2** with thiosemicarbazide affords 1-[4-(benzofuran-2-yl)thiazol-2-yl]hydrazine hydrobromide **37** [22]. Subsequent cyclocondensation of compound **37** with acetylacetone yields 1-[4-(benzofuran-2-yl)thiazol-2-yl]-3,5-dimethyl-1H-pyrazole **38** [24, 25].



37 38

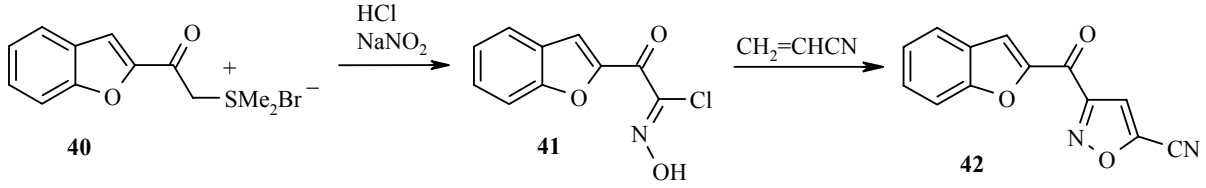
Several 2-aminoadamantane derivatives bonded to a thiadiazepine moiety **39** are prepared by cyclization of thioureas (R = alkyl, alicyclic, or aryl) with 2-bromoacetylbenzofuran **2** [26].



39

2.6. Reaction with dimethyl sulfide

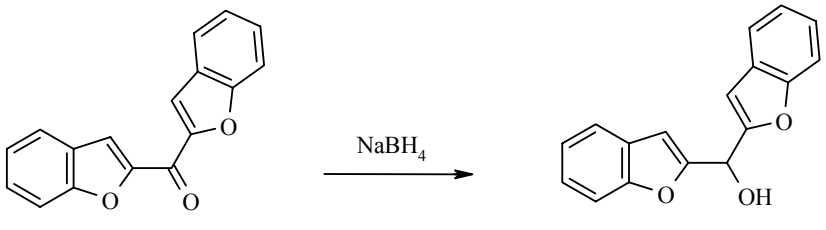
The reaction of compound **2** with dimethyl sulfide gave the corresponding sulfonium salt **40,** which upon treatment with nitrous acid gives benzofuroyl hydroxymoyl chloride **41**. The latter is treated with acrylonitrile to give the isoxazoline derivative **42** [2].



40 41 42

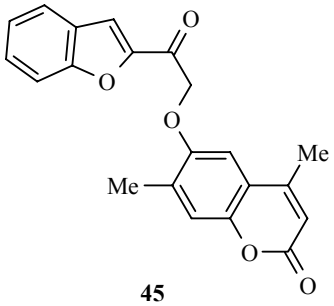
2.7. Reaction with phenols and thiols

Treatment of compound **2** with salicylaldehyde in acetone solution gives bisbenzofuran-2-yl-methanone **43** in the presence of NaH as a neutralizing base, which was then reduced to its alcohol derivative **44** by $NaBH_4$ in dioxane [27].



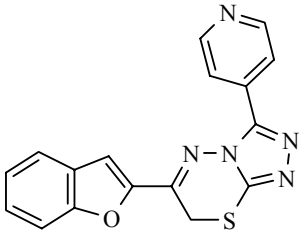
43 44

Benzopyranone derivative **45** is prepared by the reaction of compound **2** with 6-hydroxy-4,7-dimethyl-2H-chromen-2-one in the presence of potassium carbonate [28].



45

6-(2-Benzofuryl)-3-(4-pyridyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine **46** was formed by the reaction of **2** with the sodium salt of 4-amino-5-mercapto-1,2,4-triazole -3-(4-pyridyl)- [29].



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