Review

Nilesh Zaware* and Michael Ohlmeyer

Recent advances in dibenzo[*b*,*f*][1,4]oxazepine synthesis

Abstract: Dibenzo[*b*,*f*][1,4]oxazepine (DBO) derivatives possess an array of pharmacological activities, and are of growing pharmaceutical interest. Twelve recent synthetic protocols to construct DBO and DBO derivatives have been described in this review. The reported methods include cyclocondensation with two precursors exemplified by substituted 2-aminophenols and substituted 2-halobenzaldehydes, substituted 2-nitro-1-bromobenzene and substituted 2-triazolylphenols, substituted 2-nitro-1-bromobenzene and substituted 2-hydrazonamidophenol, substituted 2-nitro-1-bromobenzene and substituted 2-(aminomethyl)phenol, and 2-aminobenzonitrile and 1,4-dichloro-2-nitrobenzene. Other methods include copper catalysis, 1,3-dipolar cycloaddition, domino elimination-rearrangement-addition sequence, and an Ugi four-component reaction followed by an intramolecular *O*-arylation. These methods will serve as a guide to chemists in developing DBO derivatives of pharmacological interest.

Keywords: copper catalysis; cyclocondensation; dibenzo[*b*,*f*][1,4]oxazepine; dibenzoxazepine; 1,3-dipolar cycloaddition; domino reaction; tricyclic; Ugi four-component reaction (U-4CR).

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Introduction

Three isomeric forms of dibenzoxazepine systems are possible – dibenz[*b*,*f*][1,4]oxazepine (DBO) **1**, dibenz[*b*,*e*][1,4]oxazepine **2**, and dibenz[*c*,*f*][1,2]oxazepine **3** (Figure 1).

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Among tricyclic isomers **1–3**, the DBO ring system **1** is of particular interest because it is found in many physiologically active compounds. Compounds containing chemotype **1** include antidepressants [1], analgesics [2], calcium channel antagonists [3], a histamine H_4 receptor agonist [4], a non-nucleoside HIV-1 reverse transcriptase inhibitor [5], and a lachrymatory agent [6]. This review provides synthetic chemists with an update on the progress in the synthesis of DBO derivatives.

Synthetic strategies to DBOs

In a report by Ghafarzadeh et al. [7], DBO derivatives **6** were synthesized in short reaction time in yields of 78–87% (Scheme 1). Substituted 2-chlorobenzaldehydes **4** were allowed to react with substituted 2-aminophenols **5** under basic conditions in a microwave oven. The simplicity of the reaction and a short reaction time make this method attractive from a practical standpoint.

Sang et al. [8] reported a protocol for the one-pot synthesis of indole/benzimidazole-fused DBOs **9** *via* copper catalysis (Scheme 2). The reaction involves a copper initiated C-N and C-O coupling of 2-halophenols **7** and 2-(2-halophenyl)-1*H*-indoles **8** in one pot. Use of easily available aryl chlorides enhances the practical application of this method. Notably, this transformation involves a Smiles rearrangement (1,5-hydrogen shift) leading to the observed regioselectivity.

Khlebnikov et al. [9] reported synthesis of novel DBO derivatives – dibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepines **18** (Scheme 3). The synthesis involves reaction of imines **10**

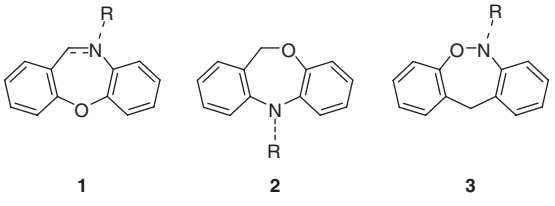
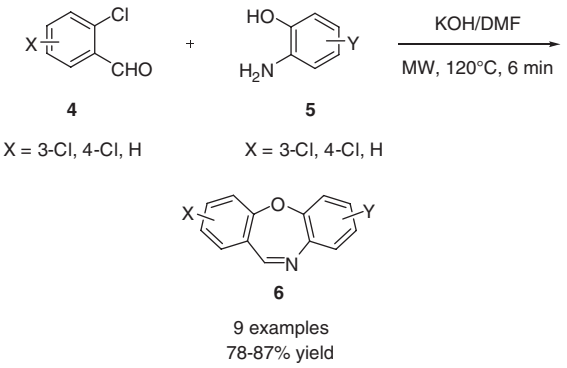
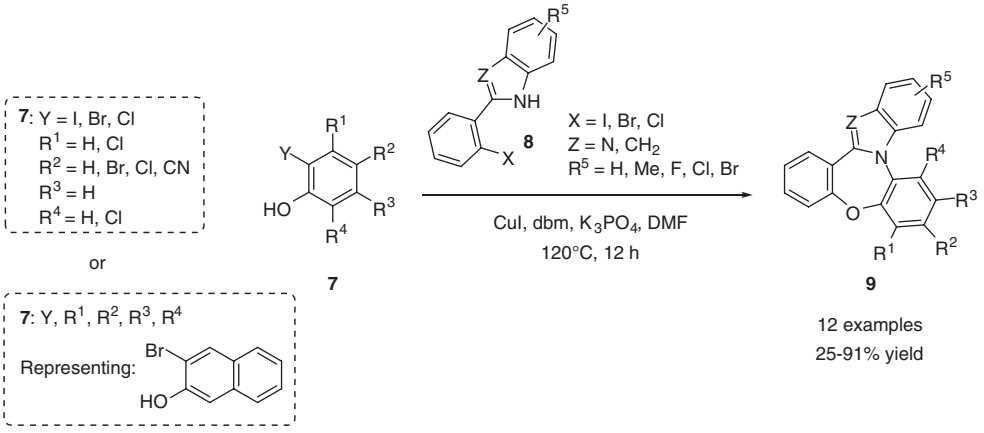


Figure 1 Isomeric forms of dibenzoxazepine systems.

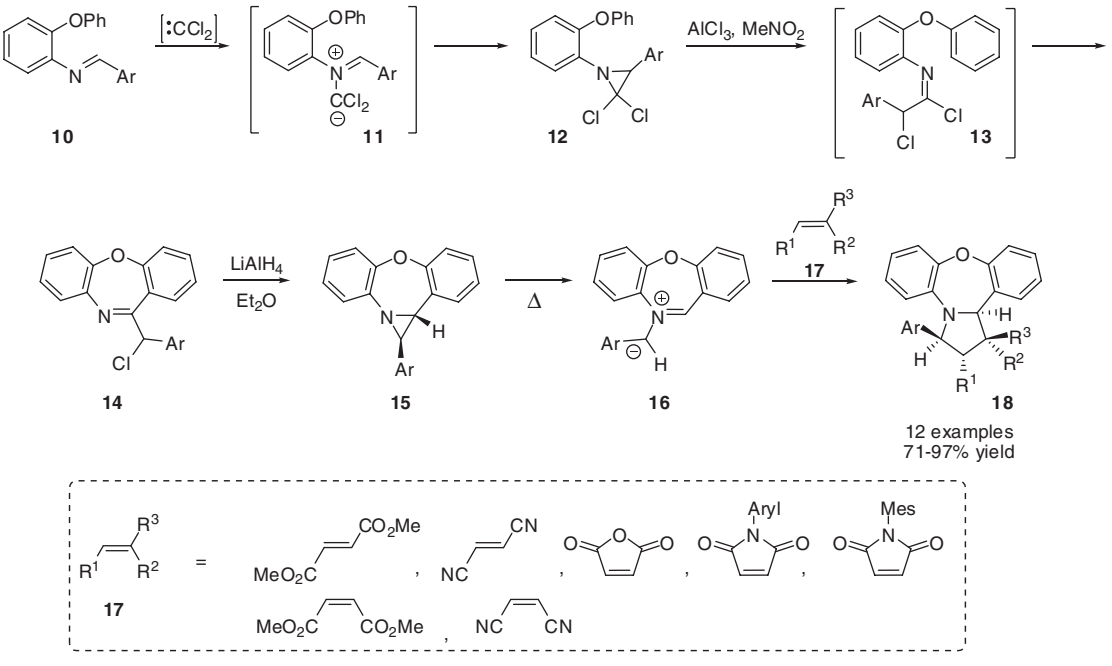


Scheme 1 Microwave-induced formation of DBO derivatives **6**.

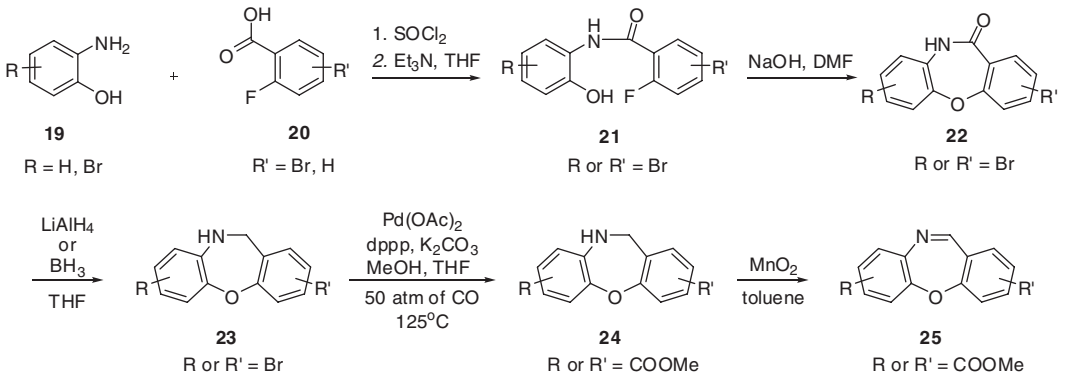
with dichlorocarbene to afford 2,2-dichloroaziridines **12** through intermediate **11**. *gem*-Dichloroaziridines isomerize to imidoylchlorides in the presence of Lewis acids, which are also well-known catalysts for Friedal-Crafts acylation. Hence, treating **12** with $AlCl_3$ leads to domino reactions – azirdine ring opening followed by Friedal-Crafts acylation – to afford oxazepines **14**. Compounds **14** were treated with $LiAlH_4$ to afford aziridinobenzooxazepines **15**. Heating compounds **15** in anhydrous toluene or under solvent-free conditions in presence of dipolarophiles **17** at 140°C furnished the target dibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepines **18** in yields of 71–97% from **15**.



Scheme 2 Synthesis of indole/benzimidazole-fused DBOs **9** *via* copper catalysis.



Scheme 3 Synthesis of dibenzo[*b*,*f*]pyrrolo[1,2-*d*][1,4]oxazepines **18** *via* formation of aziridines followed by 1,3-dipolar cycloaddition of dibenzoxazepinium ylides **16** with alkenes **17**.



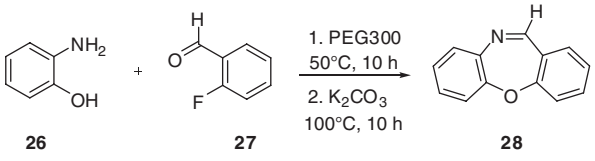
Scheme 4 Synthesis of DBO derivatives **25** by benzamide formation followed by intramolecular S_NAr.

Gijsen et al. [10] reported a series of substituted DBOs (Scheme 4) as potent TRPA1 receptor antagonists. The synthesis involves a benzamide formation from anilines **19** and benzoic acids **20**, followed by an intramolecular S_NAr to install the tricyclic scaffold **22**. Reduction of cyclic amides **22** gave the brominated 10,11-dihydro-DBOs **23**, which were transformed in two steps to the target DBOs **25**.

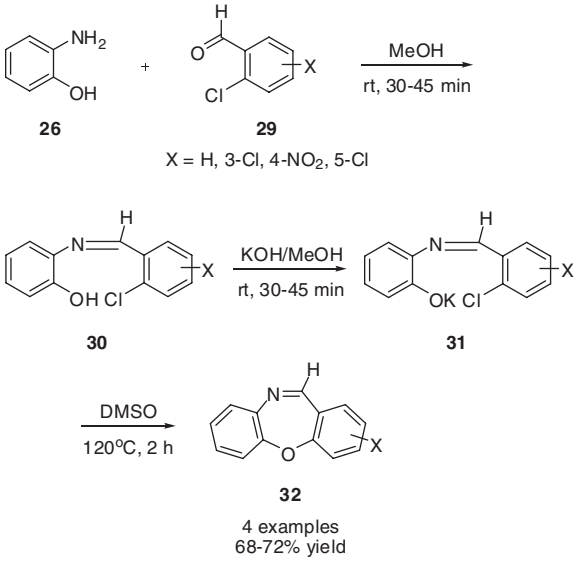
Fakhraian and Nafary [11] investigated conditions for a two-step, one-pot preparation of **28** (Scheme 5). The best result (89% yield) was obtained when 2-aminophenol **26** was first dissolved in PEG(300) at 50°C, and after addition of 2-fluorobenzaldehyde **27**, the solution was stirred for 10 h at 50°C to facilitate Schiff base formation, followed by addition of potassium carbonate and continuing the reaction for 10 h at 100°C. Jorapur et al. [12] also reported the same conversion using PEG(400) instead with the best yield of 89%.

In a novel method to synthesize DBO derivatives developed by Gutch and Acharya [13], 2-aminophenol **26** was condensed with substituted 2-chlorobenzaldehydes **29**. The condensed products **30** were converted to the potassium salts **31**, which, in turn, were cyclized in dimethyl sulfoxide (DMSO) at 120°C to afford target DBOs **32** in yields of 68–72% (Scheme 6).

Miyata et al. [14] investigated the domino reaction of tricyclic alkoxyamine **33** with ethylmagnesium bromide to afford DBO **35** as the minor product (23%) (Scheme 7) and 11-ethyl-10,11-dihydrodibenzo[*b*,*f*][1,4]oxazepine **34**



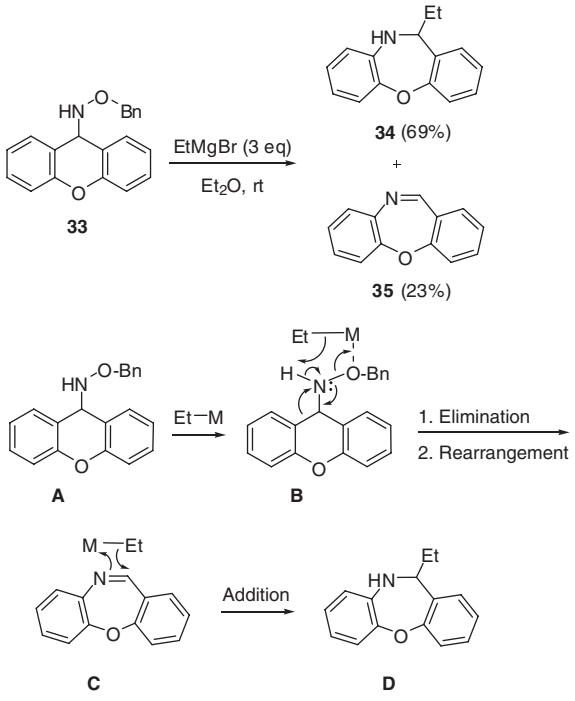
Scheme 5 Synthesis of DBO derivatives **28** from 2-aminophenol **26** and 2-fluorobenzaldehyde **27** using PEG300 and potassium carbonate.



Scheme 6 Synthesis of DBO derivatives **32** from 2-aminophenol **26** and substituted 2-chloroacetaldehyde **29**.

as the major product. Changing the EtMgBr stoichiometry from 3 to 4 equiv or using other Grignard reagents (PhMgBr, allylMgBr, vinylMgBr) gave rise only to products analogous to **34** in 81–94% yields. The reaction involves a domino elimination-rearrangement-addition sequence from the *N*-alkoxy(arylmethyl)amine **A** in the presence of organometallic reagents to afford the target product **D**.

Xing et al. [15] established a general and efficient one-pot synthesis of highly functionalized DBOs *via* microwave-assisted one-pot Ugi four-component reaction (U-4CR) and intramolecular *O*-arylation (Scheme 8). The protocol involves heating a solution of 2-aminophenols **36**, aldehydes **37**, benzoic acids **38**, and isocyanates **39** in methanol to 80°C for 20 min in a microwave reactor to furnish intermediates **40**. Compounds **41** (eight examples, 81–94% yields) were prepared by

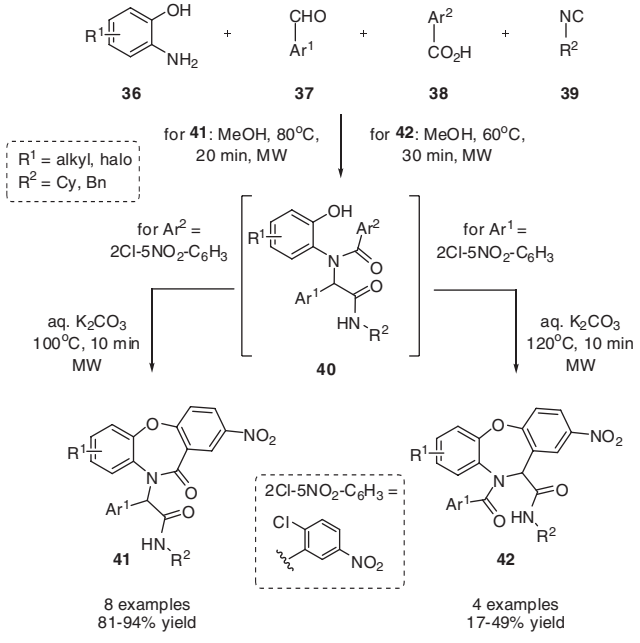


Scheme 7 Synthesis of DBO **35** *via* domino elimination-rearrangement-addition sequence from the *N*-alkoxy(arylmethyl)amines.

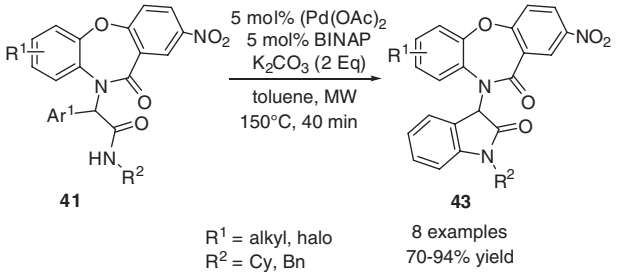
selecting six substituted 2-aminophenols, two isocyanides in combination with 2-bromobenzaldehyde, and 2-chloro-5-nitrobenzoic acid. Synthesis of compounds **42** was not as efficient and was influenced by the pKa of benzoic acids. Four different benzoic acids were used to synthesize four examples of framework **42** (17–49% yields), with increasing acidity of benzoic acids leading to improved yields.

Intramolecular amidation of compounds **41** to assemble novel classical conjugates **43** was accomplished (Scheme 9). These reactions are catalyzed by $Pd(OAc)_2$-BINAP catalyst system.

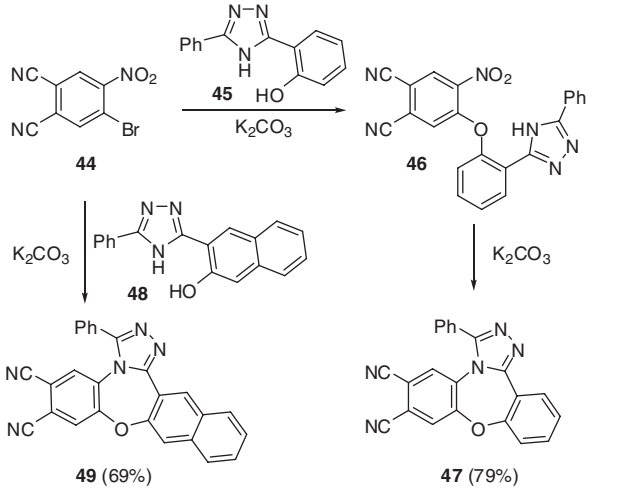
Abramov et al. [16] used known reactions of activated nucleophilic substitution to facilitate novel protocols for synthesis of structurally diverse cyano-substituted DBOs. As shown in Scheme 10, 2-(5-phenyl-4*H*-1,2,4-triazol-3-yl)phenol **45**, in the presence of potassium carbonate, undergoes deprotonation generating the corresponding phenoxide, which undergoes a reaction with 4-bromo-5-nitrophthalonitrile **44** to afford the intermediate product **46**. A potassium carbonate-induced intramolecular substitution of a nitro group in **46** leads to cyclocondensed product **47**. Similarly, **44** undergoes a reaction with



Scheme 8 Synthesis of DBOs **41** and **42** *via* microwave-assisted one-pot U-4CR and intramolecular *O*-arylation.



Scheme 9 Palladium-catalyzed intramolecular amidation of **41** to afford novel conjugate compound **43**.

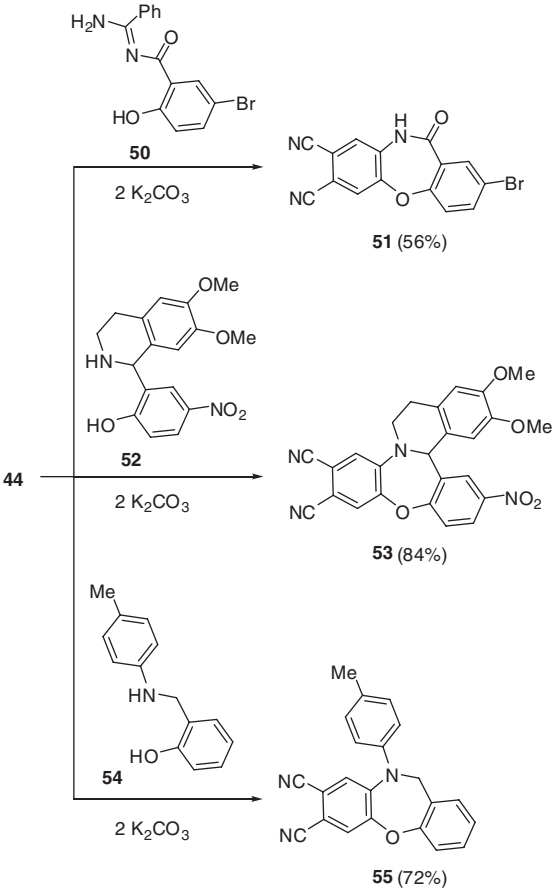


Scheme 10 Synthesis of potassium carbonate-induced formation of DBOs **47** and **49**.

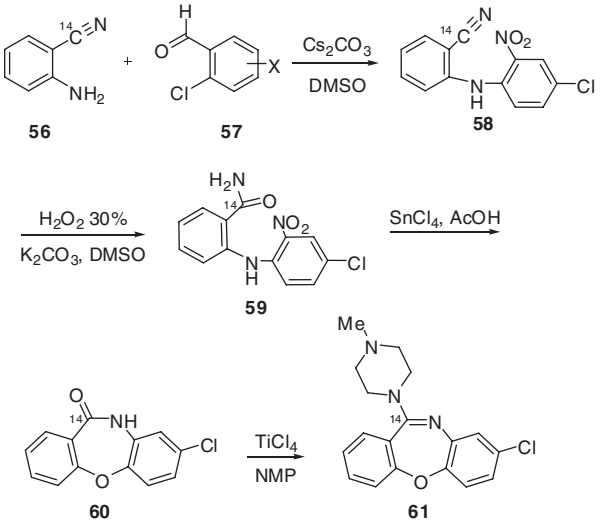
3-(5-phenyl-4*H*-1,2,4-triazol-3-yl)-2-naphtol **48** to afford cyclocondensed product **49**.

Heating equimolar quantities of highly reactive substrate **44** and hydrazonamide of 5-bromo salicylic acid **50** in DMF in the presence of potassium carbonate gave product **51** in 56% yield (Scheme 11). Bifunctional nucleophiles such as **52** and **54** undergo cyclocondensation with **44** in the presence of potassium carbonate to afford corresponding DBOs **53** (84% yield) and **55** (72% yield), respectively.

Matloubi et al. [17] reported a novel synthesis of 11-[C^{14}]-clozapine **61** (Scheme 12) with a marked improvement in yield (6–23%) over a previous report [18]. The synthesis involves coupling 2-aminobenzonitrile **56** with 1,4-dichloro-2-nitrobenzene **57** in the presence of base to afford **58**. The best results were obtained using Cs_2CO_3. The nitrile **58** was then hydrolyzed to amide **59** with basic hydrogen peroxide in 90% yield. Compound **59** was reduced with stannous chloride and acetic acid to afford key diazepine-11-one **60** in 86% yield. Conversion of **60**–**61** was carried out as reported by Fryer et al. [19].



Scheme 11 Synthesis of potassium carbonate-induced formation of DBOs **51**, **53**, and **55**.



Scheme 12 Novel synthesis of 11-[^{14}C]-clozapine **61** from 2-amino benzonitrile **56** and 1,4-dichloronitrobenzene **57**.

Conclusions

We have highlighted recent advances in the preparation of DBO derivatives. Twelve synthetic methods to the DBO ring system have been described. The reported methods include cyclocondensation with two precursors, copper catalysis, 1,3-dipolar cycloaddition, domino elimination-rearrangement-addition sequence, and a U-4CR reaction. The synthetic methods presented in this review are relevant to medicinal and pharmaceutical chemistry and can be used for development of novel DBO derivatives of pharmacological significance.

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