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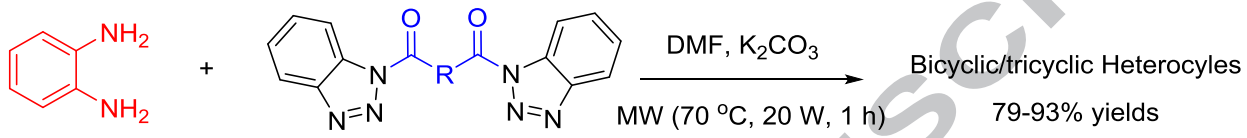

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One-Pot Synthesis of Bi- and Tricyclic Heterocyclic Compounds using Benzotriazole Chemistry

Mohamed Elagawany,[a,b,†] Mohamed A. Ibrahim[c,d,†] and Siva S. Panda[a,*]

[a]*Department of Chemistry & Physics, Augusta University, Augusta, GA 30912, USA*
[b]*Department of Pharmaceutical Chemistry, faculty of pharmacy, Damanhour University, Damanhour, Egypt*
[c]*Department of Pharmaceutical Chemistry, Almaarefa Colleges for Science and Technology, Riyadh 11597, Kingdom of Saudi Arabia*
[d]*Department of Organic Chemistry, College of Pharmacy, Misr University for Science and Technology, 6th of the October, P.O.Box: 77, Egypt*
[†]*These authors contributed equally to this paper*

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ABSTRACT

Microwave-mediated one-step synthesis of several bi- and tricyclic heterocycles via the intermolecular cyclization of *N*-acylbisbenzotriazoles with ortho-phenylenediamine in good yield is reported.

* Corresponding author. Tel.: +1-706-667-4022; fax: +1-706-667-4516; e-mail: sspanda12@gmail.com, sipanda@augusta.edu

1. Introduction

Nitrogen-containing bi- and tricyclic heterocycles bearing diazepine, diazocine, and benzimidazole moieties are of current research interest because of their pharmacological properties.[1–3] They are also found in many potential pharmaceutical compounds (Figure 1).

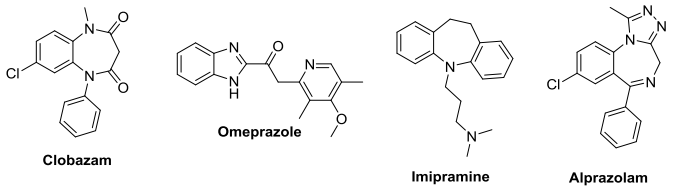


Figure 1. Some potential bicyclic and tricyclic compounds

Several synthetic methodologies were utilized/developed for the synthesis of various bicyclic and tricyclic compounds because of their unique biological properties.[4-8] Benzodiazepines are one of the bicylic heterocyclic class of compounds and are known for various pharmaceutical applications. They are widely used as anticonvulsant, antianxiety, analgesic, sedative, antidepressant, hypnotic, and anti-inflammatory agents.[9-11] 1,5-Benzodiazepines are valuable synthons for the preparation of other fused ring compounds such as triazolobenzodiazepines,[12] oxadiazolobenzodiazepines,[13] oxazinobenzodiazepines,[14] or furanobenzodiazepines.[15] Benzodiazocines and benzimidazoles are known for various biological properties such as amoebicidal, anti-inflammatory, antitumor, anti-inflammatory, antimicrobial, antiviral, antidiabetic, antiparasitic, anthelmintic, anti-HIV, anticonvulsant, antihypertensive, and proton pump inhibitor activities.[16-20] Bicyclic and tricyclic cores are also common in a large number of natural products and pharmacologically active compounds. Research in this field is still very active and is directed towards the synthesis of compounds with enhanced pharmacological activity. Generally, these compounds are synthesized by the condensation of *ortho*-phenylenediamine with α, β-unsaturated carbonyl compounds, β-haloketones, or ketones.[16] Diverse reagents such as BF_3-etherate, $NaBH_4$, polyphosphoric acid, SiO_2, MgO/$POCl_3$, Al_2O_3/P_2O_5, and AcOH under microwave conditions and in ionic liquids have been utilized for the condensation reactions.[21] Most recently, this condensation reaction has also been reported to proceed in the presence of bromodimethylsulfonium bromide, organic acids, and $AgNO_3$.[22] However, all these methods have disadvantages such as drastic reaction conditions, several side reactions and tedious purification process. 1,6-Benzodiazocine has been synthesized by the condensation of *ortho*-phenylenediamine with diethyl succinate for 16 h in 26% yield.[23] 1,6-Benzodiazocine has also been synthesized in three steps by (i) the condensation of anilinic acids with PPA/AcOH, affording 3,4-dihydro-1-benzazepine-2,5(1*H*)diones, (ii) treatment with hydroxylamine hydrochloride, giving the corresponding oxime derivative, and (iii) Beckmann rearrangement of the oxime, furnishing 1,6-benzodiazocine in 76% yield.[24] Nitrogen-containing tricyclic heterocycles bearing a benzimidazole moiety such as 3,4-dihydro-pyrido[1,2-*a*]benzimidazol-1(2*H*)-one has been prepared by the condensation of glutaric anhydride with *ortho*-phenylenediamine catalyzed by dibromotriphenylphosphorane.[25]

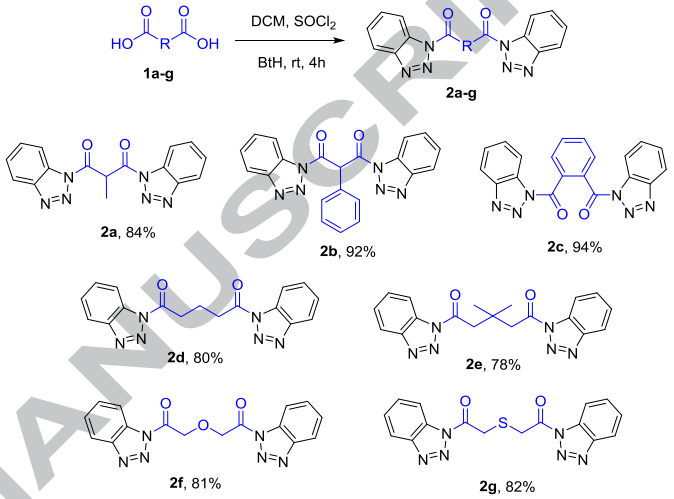
To the best of our knowledge, all the current methods for the synthesis of bi- and tricyclic heterocycles which are biologically important class of compounds involve multiple steps synthesis, column chromatography or tedious purification process and moderate to high yields. Therefore, alternative an efficient and high-yielding methods for these class compounds are in demand.

Benzotriazole chemistry has been practiced extensively in our group in various types of reactions like acylation, aroylation, heteroaroylation, cyclization, alkylation etc. and has often been found to be superior to conventional routes.[26,27] In this communication we report an efficient synthetic route to bicyclic and tricyclic heterocyclic compounds through *N*-acylated benzotriazoles. The reaction gives excellent yields and runs either under microwave or conventional heating. The best results are achieved under microwave irradiation.

2. Results and Discussion

*2.1. Preparation of N-acylbisbenzotriazoles **2a–g***

N-acylbisbenzotriazoles **2a–f** were prepared in 78–94% yields using our standard procedure by the reaction of the corresponding dicarboxylic acids **1a–g** with 8 equiv of 1*H*-benzotriazole and 2.2 equiv of $SOCl_2$ in DCM at 20 °C for 4 h (Scheme 1).[28]



Scheme 1. Synthesis of *N*-acylbisbenzotriazoles **2a-g**.

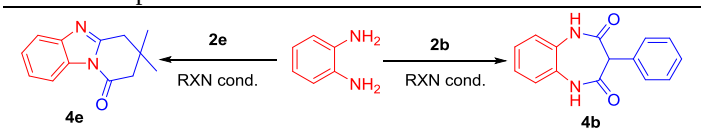
*2.2. Preparation of bi- and tricyclic compounds **4a-g***

The nucleophilic attack of *ortho*-phenylenediamine **3** (1 equiv) with *N*-acylbisbenzotriazoles **2a-g** (1.2 equiv) in the presence of K_2CO_3 (1.5 equiv) in DMF under microwave irradiation at 70 °C for 1 h afforded bicyclic and tricyclic compounds **4a-g** in excellent yields. The nucleophilic attack of *ortho*-phenylenediamine **3** (1 equiv) with compound **2a-c** (1.2 equiv) resulted in the formation of bicyclic compounds **4a-c** however compound **2d-g** leads to tricyclic compounds **4d-g** under same reaction condition in excellent yields. All the synthesized compounds were fully characterized with NMR and mass spectroscopy. The structure of the compounds were also confirmed by 2D NMR studies.

Most of the compounds are synthesized earlier by different methods which are more tedious and less efficient. Compound **4a** and **4b** were synthesized form *ortho*-phenylenediamine in two step synthesis with moderate yields.[29,30] Compound **4c** was prepared from *ortho*-phenylenediamine and diethyl ester of phthalic acid in presence of NaH in THF with less yield.[31] Compound **4d** was synthesized in various methods with multistep synthesis and less yield. The synthesis of compound **4d** was reported in 39% yield.[25] Compound **4e-g** are new to the literature.

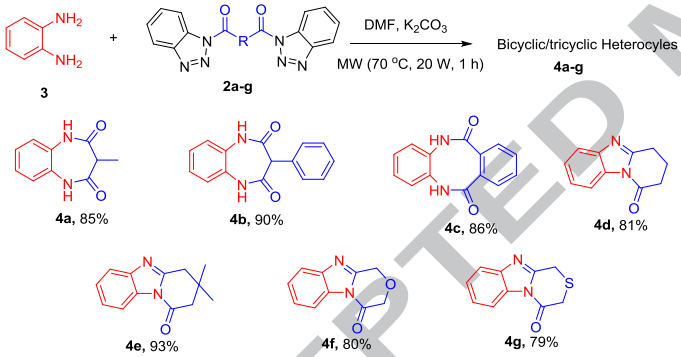
Optimization of reaction conditions (Table 1) revealed the best results for the preparation of both bicyclic and tricyclic compounds was under microwave heating at 70 °C for 1 h in DMF. However the formation of bicyclic compounds with some impurities was also observed in THF. In conventional heating method in DMF we have observed the formation of both the products as well with some other byproducts which needs column chromatography for purification.

Table 1. Optimization of reaction conditions



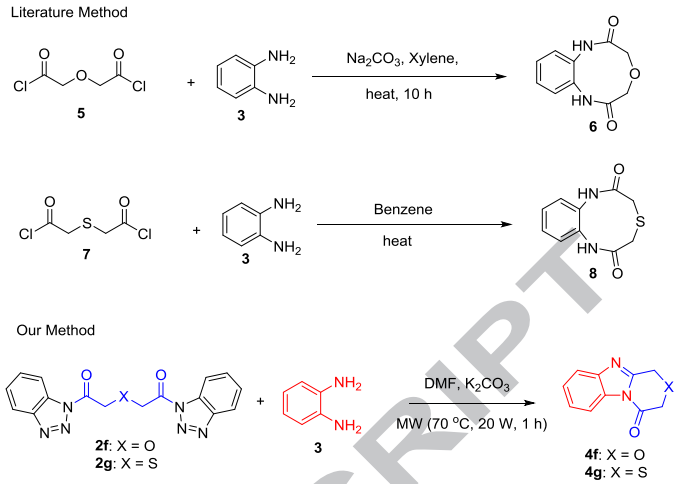
Entry	Solvent	Base	Temp. (°C)	Time (h)	**4b** (%)[a]	**4e** (%)[a]
1	THF	TEA	20	12	42	-
2	THF	K_2CO_3	20	12	60	-
3	THF	K_2CO_3	70 (Conv.)	6	74	-
4	THF	K_2CO_3	70 (MW)	2	78	-
5	CH_3CN	TEA	20	12	40	-
6	CH_3CN	K_2CO_3	20	12	63	-
7	CH_3CN	K_2CO_3	70 (Conv.)	6	70	-
8	CH_3CN	K_2CO_3	70 (MW)	2	76	-
9	DMF	TEA	20	12	55	-
10	DMF	K_2CO_3	20	12	66	-
11	DMF	K_2CO_3	70 (Conv.)	6	80	58
12	DMF	K_2CO_3	70 (MW)	1	93	90

[a]crude isolated yield after treating with Na_2CO_3 solution



Scheme 2. Synthesis of bi- and tricyclic heterocyclic compounds **4a-g** using *N*-acylbisbenzotriazoles **2a-g**.

Synthesis of tricyclic compounds **4f** and **4g** were achieved by treating *ortho*-phenylenediamine with corresponding *N*-acylbisbenzotriazoles **2f** and **2g** in presence of K_2CO_3 in DMF under microwave irradiation. However in the literature when *ortho*-phenylenediamine was treated with 2,2'-oxydiacetyl chloride **5** and 2,2'-thiodiacetyl chloride **7** under basic condition yields the corresponding bicyclic compounds **6** and **8**.[32,33] In our case we did not observed the formation of compound **6** or **8**. The structure of the compounds **4f** and **4g** clearly identified in NMR (Figure 2) since these compounds are not symmetric as **6** or **8**. The structure of compounds **4f** and **4g** further confirm from the 2D NMR. In case of compounds **4d-g** the formation of tricyclic compounds is more favorable than the bicyclic structures probably because of stability of five member ring over nine member ring. . The plausible mechanisms for the formation of bicyclic and tricyclic compounds are described in Scheme 4a & 4b.



Scheme 3. Literature method *vs* our method

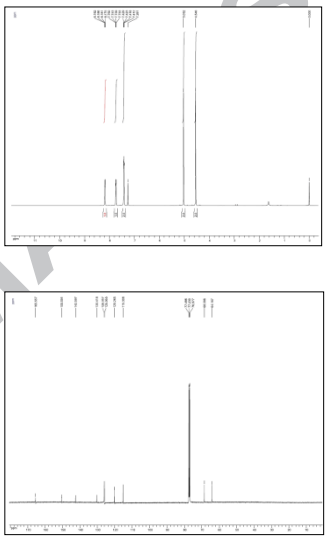
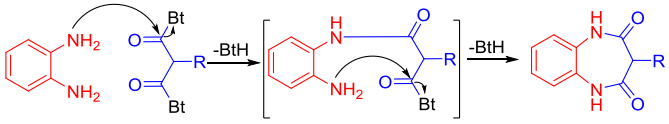
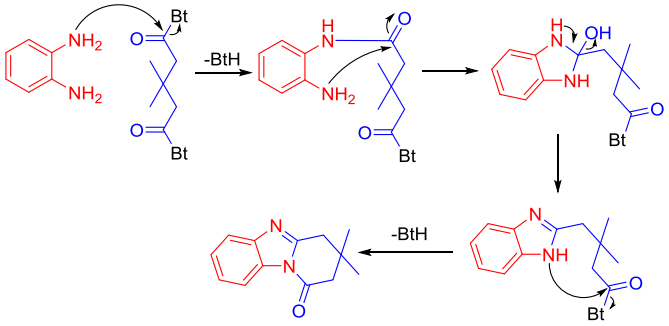


Figure 2. ^{1}H and ^{13}C NMR spectra of compound **4f**.



Scheme 4a. Plausible mechanism for bicyclic compounds.



Scheme 4b. Plausible mechanism for tricyclic compounds.

3. Conclusion

N-acylbisbenzotriazoles were used as the precursors for the efficient synthesis of bicyclic and tricyclic heterocycles. The intermolecular cyclization of N-acylbisbenzotriazoles with ortho-phenylenediamine under microwave conditions afforded several bi- and tricyclic heterocycles in one step in good yields.

Acknowledgments

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Supplementary Material

Supplementary data (synthetic procedures, NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/

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Highlights:

- Efficient synthesis of bicyclic and tricyclic heterocycles
- Utilized benzotriazole chemistry for the efficient synthesis
- High yield and mild reaction condition compared to literature methods
- Characterized and confirmed the compounds by 1D and 2D NMR studies