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D. Gangaprasad, J. Paul Raj, K. Karthikeyan, R. Rengasamy, M. Kesavan, M. Vajjiravel, J. Elangovan

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## Graphical Abstract

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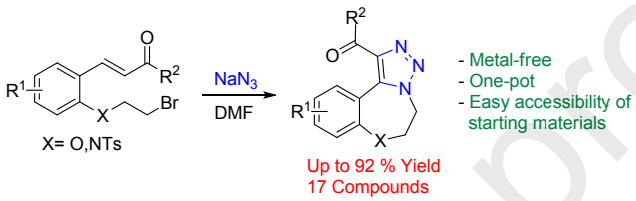

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# A New Route to 1,2,3-Triazole Fused Benzooxazepine and Benzodiazepine Analogues Through Metal-free Intramolecular Azide-Olefin Oxidative Cycloaddition

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[a] *Department of Chemistry, B. S. Abdur Rahman Crescent Institute of Science and Technology, Vandalur, Chennai - 600048, India. E-mail:chemvel@gmail.com*
[b] *Department of Chemistry, Rajah Serfoji Government College, Thanjavore, Tamilnadu - 613005, India.*
*E-mail: elangoorganic@gmail.com*
[c] *Interdisplinary Institute of Indian System of Medicine (IIISM), SRM Institute of Science and Technology, Kattankulathur 603203, India.*

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ABSTRACT

A collection of 1,2,3-Triazole fused benzooxazepine and benzodiazepine analogues was prepared by one pot azide substitution and intramolecular azide-olefin oxidative cycloaddition sequence under metal-free conditions.



Fused oxazepines have sprung into prominence due to their remarkable implications in biology and pharmacy [1] including antipsychotic[2], anti-tumor[3] and anti-inflammatory[4] activities. Similarly fused diazepines also are bestowed with a wide spectrum of applications.[5] Figure 1 gives a glimpse on the paramount importance of these molecules in biology by displaying a few active molecules. Sintamil (**A**) was known to be used as an antidepressant agent.[6] Loxapine (**B**), a piperazine substituted benzooxazepine skeleton is a drug administered for the treatment of schizophrenia.[7] Anthramycin (**C**), which is a pyrrolobenzodiazepine antibiotic, is known for its antitumor

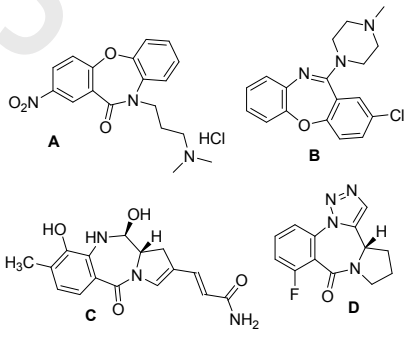


Figure 1. Some biologically important fused oxazepines and diazepines.

activity. [8] Compound (**D**) is a 1,2,3-triazole fused benzodiazepine skeleton and it has emerged as a protease inhibitor.[9]

In continuation of our previous report on synthesis of 1,2,3-triazoles by oxidative azide-olefin cycloadditions (OAOC) and eliminative azide-olefin cycloadditions (EAOC), [10] we were prompted to extend that approach to the synthesis of 1,2,3-triazole fused oxazepines and diazepines. Our literature perusal on these fused heterocycles revealed four precedented strategies to access the triazole fused diazepines. Nevertheless, to the best of our knowledge, no report is found on the synthesis of triazole fused oxazepines. Martin *et al*. have reported the synthesis of triazolefused diazepines by one pot synthesis involving reductive amination, followed by a thermally induced, intramolecular Huisgen cycloaddition (Scheme 1, Equation 1)[11]. Eycken's group has reported a protocol involving Cu-catalyzed azidation followed by intramolecular Huisgen cycloaddition to access the triazole fused benzodiazepines (Scheme 1, Equation 2).[12] Another elegant method was reported by Majumdar and co-workers where tandem Ullmann type coupling and azide-alkyne sequence was employed to prepare this family of molecules (Scheme 1, Equation 3).[13] Finally Sudhapriya *et al* have developed a one-pot sequential diazotization, azidation and cycloaddition reactions to access this family of benzodiazepines (Scheme 1, Equation 4).[14] However, no reports are found in the synthesis of triazole fused benzooxazepines. As an alternative attempt, herein we report a one-pot synthesis of 1,2,3-triazole fused benzooxazepines and diazepines by sequential azidation

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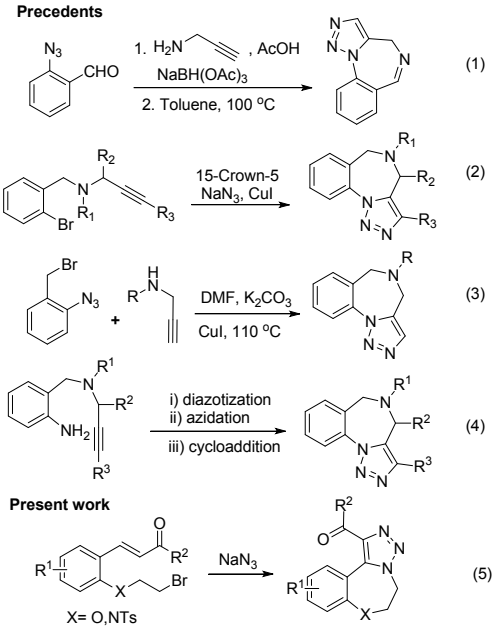
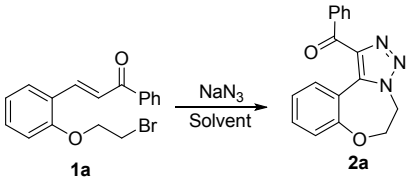
reactions (Scheme 1, Equation 5).




**Scheme 1.** Background of the synthesis of triazole fused benzodiazepines.

At the outset, we started our investigation, fixing the olefin (**1a**) as model substrate for examination and optimization. Fixing the temperature and time invariably as 90°C and 6.0 hours, we carried out the reaction in various solvents. Initial attempt with toluene as solvent resulted in a poor yield of product (Table 1, entry 1). Little enhancement of yield was observed in DMSO (Table 1, entry 2). To our surprise, remarkable enhancement of yield of the fused triazole (**2a**) was obtained when the reaction was carried out in DMF (Table 1, entry 3). Water and tertiary butanol were also found to be ineffective for this transformation as the yield of the product decreased to 53% and 48 % (Table 1, entry 4 and entry 5). Further decrease of the yield of the product was obtained when THF was used as the solvent (Table 1, entry 6). On the other hand, when we moved on to chloroform, the yield plummeted to 32% (Table 1, entry 7). Solvents such as methanol, acetonitrile and dichloroethane also gave a poor yield of 46-49%. (Table 1, entry 8-entry 10). From these above observation, DMF was revealed as the best solvent. Fixing the DMF as the solvent, the role of temperature was also meticulously studied. As we raised the temperature from 60 °C to 80 °C, consistent improvement of yield was noticed (Table 1, entry 11 – entry 12). When the temperature was elevated to 110 °C – 120 °C, no pronounceable improvement was observed (Table 1, entry 13). Hence, we resolved to fix 90°C as the temperature for this transformation. To study the role of time variation, we tested the reaction by prolonging the reaction from 5 hours to 8 hours (Table 1, entries 14 – 16). Reaction for 5 hours, substantially decreased the yield of the product while 7 hours and 8 hours furnished almost equal yield to that of the reaction carried out for 6 hours. Hence we decided to fix 6 hours as the time duration for this protocol.

**Table 1**. Optimization of one-pot azidation, intramolecular OAOC.[a]

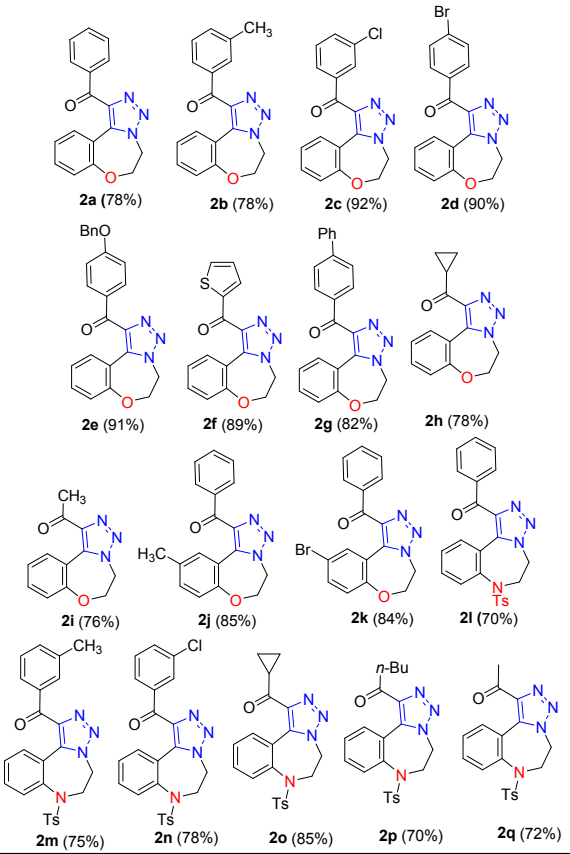



| | | | | [b] |
|---|---|---|---|---|
| 1 | Toluene | 90°C | 6 h | 45 |
| 2 | DMSO | 90°C | 6 h | 56 |
| **3** | **DMF** | **90°C** | **6 h** | **78** |
| 4 | $H_2O$ | 90°C | 6 h | 53 |
| 5 | t-BuOH | 90°C | 6 h | 48 |
| 6 | THF | 90°C | 6 h | 42 |
| 7 | $CHCl_3$ | 90°C | 6 h | 32 |
| 8 | MeOH | 90°C | 6 h | 49 |
| 9 | ACN | 90°C | 6 h | 47 |
| 10 | DCE | 90°C | 6 h | 46 |
| 11 | DMF | 60°C | 6h | 52 |
| 12 | DMF | 80°C | 6h | 67 |
| 13 | DMF | 110-120°C | 6h | 79 |
| 14 | DMF | 90°C | 5h | 60 |
| 15 | DMF | 90°C | 7h | 77 |
| 16 | DMF | 90°C | 8h | 79 |

[a]Olefin (1.0 mmol), sodium azide (2.0 mmol), were dissolved in (1.0 ml) solvent, heated into 90°C at 6h under open atmosphere. [b] Isolated yield.

Having established the optimized conditions (Table 1, entry 3) for metal-free synthesis of 1,2,3-triazole fused benzooxazepines and benzodiazepines, we extended that condition to various substrates (Table 2).Various changes in the substitution on the ketone side and the alkene side of the starting material were meticulously examined. As shown in the optimization table, ketone with an unsubstituted aryl group furnished the benzooxazepine (**2a**) with 78% yield. While introducing substitution in the *meta* position of the aryl ring, methyl substitution has shown almost similar efficacy while chloro substitution has displayed a remarkable enhancement as stated

**Table 2 .** Metal-free synthesis of triazole fused benzooxazepines and benzodiazepines




[a]Olefin (1.0 mmol), sodium azide (2.0 mmol), were dissolved in (1.0 ml) DMF, heated into 90°C at 6h under open atmosphere. [b] Isolated yield.

from while considering the *para* substitutions, bromo and benzyloxy substitutuions excelled to ensure excellent yield of the benzooxazepines **2d** and **2e**. A thiophene ring on the ketone side exhibited a similar effect as evident from the yield of the product **2f**. On the other hand, significant retardation in the efficiency of this protocol was observed when biphenyl system is present in the ketone side as evident from the decrease of yield of **2g**. Furthermore, when aliphatic substitution was on the ketone side as reflected from the lower of yields of the products **2h** and 2**i**. Substitution on the aryl ring on the olefin side of the starting material also was carefully examined. Methyl and bromo substitutions were examined and it was perceived that both were equally forwarded this transformation as reflected from the similar yields of the products **2j** and **2k**. Similarly, benzodiazepines also were synthesized in this approach. Benzodiazepine (**2l**) was prepared in 70% yield which is slightly less than the yield of its oxygen analogue **2a**. Unlike **2b** and **2c**, the methyl and chloro substitutions on the phenyl ring of the ketone part of the starting material, exhibit almost similar effect as testified from the yields of **2m** and **2n**. In the case of aliphatic substitution on the ketone part, cyclopropyl group was perceived to be more effective than *n*-butyl and methyl groups since the yield of **2o** is greater than **2p** and **2q**.

A new protocol to access 1,2,3-triazole fused benzooxazepine and benzodiazepine analogues was developed by intramolecular azide-olefin oxidative cycloaddition. This method differs from its predecessors owing to the following attributes. 1. This method involves azide-olefin cycloaddition to construct the 1,2,3-triazole moiety while the other methods use azide-alkyne cycloaddition approach. It is worth mentioning that the alkenes are commercially and synthetically more viable than alkynes. 2. This method becomes versatile because this can be used to access both triazole fused benzooxazepine and benzodiazepine moieties while other methods can be used to achieve only triazole fused benzodiazepines. 3. This method also holds the advantage of copper-free condition owing to the cytotoxicity of copper catalysts.[15] 4. The azide substitution and oxidative azide-olefin cycloaddition steps take place consecutively in one-pot. Hence this method can prove to be a promising alternative to the existing methods to access this family of 1,2,3-triazole fused benzooxazepines and benzodiazepines

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## Highlights

- A collection of 1,2,3-triazole fused benzooxazepine and benzodiazepine analogues was prepared
- Using one pot azide substitution and intramolecular azide-olefin oxidative cycloaddition sequence under metal-free conditions.
- Conditions are grabs the advantage of copper-free condition owing to the cytotoxicity of copper catalysts.