Microwave-assisted three-component domino reaction: Synthesis of indolodiazepinotriazoles

Rajesh K. Arigela¹, Sudhir K. Sharma¹, Brijesh Kumar² and Bijoy Kundu*¹,²,§

Full Research Paper

Abstract
A microwave-assisted three-component protocol involving N-1 alkylation of 2-alkynylindoles with epichlorohydrin, ring opening of the epoxide with sodium azide, and an intramolecular Huisgen azide–internal alkyne 1,3-dipolar cycloaddition domino sequence has been described. The efficacy of the methodology has been demonstrated by treating various 2-alkynylindoles (aromatic/ali-phatic) with epichlorohydrin and sodium azide furnishing annulated tetracyclic indolodiazepinotriazoles in satisfactory yields.

Introduction
The intermolecular Huisgen azide–alkyne 1,3-dipolar cycloaddition reaction [1-6] for the synthesis of 1,2,3-triazoles in both aqueous [7-10] and organic solvents under either metal-catalyzed [11-13] or metal-free conditions [14-16] has received increasing attention in drug discovery processes [17,18]. The ease of reaction in the intermolecular format has been successfully demonstrated by using both organic/inorganic azides as well as alkynes/diynes [19-21]. In contrast to its employment in an intermolecular format, intramolecular Huisgen azide–internal alkyne 1,3-dipolar cycloaddition domino sequences have also been applied by us and others with the view to synthesize triazole-annulated polyheterocycles. Although these cyclizations have been successfully carried out in either one-pot [22-24] or multistep format [25-28], reports involving their application in a three-component domino format are scarce [29,30]. In our laboratory, we had been employing functionalized indoles for the synthesis of annulated indole-based polyheterocycles either in a multicomponent or in a one-pot format [31-35]. In this continuation, we next directed our efforts to the development of a three-component domino strategy for the synthesis of indole-based polyheterocycles by incorporating the intramolecular azide–alkyne 1,3-dipolar cycloaddition reaction as one of the domino steps. Here
we propose a strategy where N-1 of 2-alkynylindole [36,37] can be first functionalized with epoxide by reacting 2-alkynylindole with epichlorohydrin. This can then be followed by ring opening of the oxirane by azide to furnish a bis-functionalized indole intermediate having azide and alkyne groups in close proximity. Such an intermediate may then undergo annulation following an intramolecular 1,3-dipolar cycloaddition pathway and in turn lead to the sequential formation of 7- or 5-membered diazepine and triazole rings in a single step. In this communication, we report a versatile microwave-assisted three component domino reaction to furnish annulated tetracyclic indolodiazepinotriazoles in good yields.

Results and Discussion

We commenced our studies with the development of a one-pot three-component strategy involving the condensation of the 2-(4-methylphenylethynyl)-1H-indole (1a) with epichlorohydrin (2) and sodium azide (3, Scheme 1, Table 1). Initially, a mixture of 1a, 2 and 3 was allowed to react both in the absence and presence of Cs₂CO₃ in toluene at rt. The reactants under both the conditions remained unchanged even after prolonged stirring for 15 h (Table 1, entries 1–3) and at higher temperature (110 °C).

However, a change in the nature of solvent from toluene to CH₃CN, DMF or DMSO produced a dramatic effect on the outcome of the reaction, resulting in the formation of products comprising intermediates (4a and/or 5a) and/or indole-based polyheterocycle indolodiazepinotriazole 6a. Use of the polar solvent CH₃CN at 90 °C for 15 h furnished a single product in 65% isolated yield, which was characterized as 2-[2-(4-methyl-

| Entry | Base | Solvent | Temp (°C) | Time  | Yield (%) of 4a/5a/6a |
|-------|------|---------|-----------|-------|----------------------|
| 1     | –    | toluene | rt        | 15 h  | NR                   |
| 2     | Cs₂CO₃ | toluene | rt        | 15 h  | NR                   |
| 3     | Cs₂CO₃ | toluene | 110       | 15 h  | NR                   |
| 4     | Cs₂CO₃ | CH₃CN  | 90        | 15 h  | 65/-/-               |
| 5     | Cs₂CO₃ | DMF     | rt        | 15 h  | NR                   |
| 6     | Cs₂CO₃ | DMF     | 120       | 1 h   | 77/-/-               |
| 7     | Cs₂CO₃ | DMF     | 120       | 4 h   | 40/30/-              |
| 8     | Cs₂CO₃ | DMF     | 120       | 15 h  | 15/50                |
| 9     | Cs₂CO₃ | DMF     | 120       | 18 h  | 1/-60                |
| 10    | Cs₂CO₃| DMSO    | 120       | 1 h   | 82/-/-               |
| 11    | Cs₂CO₃| DMSO    | 120       | 4 h   | 42/40/-              |
| 12    | Cs₂CO₃| DMSO    | 120       | 10 h  | 30/20/52             |
| 13    | Cs₂CO₃| DMSO    | 120       | 15 h  | 1/-64                |
| 14    | Cs₂CO₃| DMSO    | 120       | 10 min| 80/-/-               |
| 15    | Cs₂CO₃| DMSO    | 120       | 30 min| 20/45/10⁶³          |
| 16    | Cs₂CO₃| DMSO    | 120       | 1 h   | 18/42                |
| 17    | Cs₂CO₃| DMSO    | 120       | 1 h   | 1/-71                |
| 18    | Cs₂CO₃| DMF     | 120       | 1.5 h | 7/-/64               |
| 19    | Cs₂CO₃| CH₃CN  | 90        | 1.5 h | 80/-/-               |
| 20    | Cs₂CO₃| CH₃OH  | 90        | 1.5 h | NR                   |
| 21    | K₂CO₃ | DMSO    | 120       | 1.5 h | 10/54⁶³              |
| 22    | Na₂CO₃| DMSO    | 120       | 1.5 h | 12/65²⁶³             |
| 23    | K₂PO₄ | DMSO    | 120       | 1.5 h | 1/-62                |
| 24    | t-BuOK| DMSO    | 120       | 1.5 h | 1/-65                |
| 25    | DBU   | DMSO    | 120       | 1.5 h | 15/48⁶³             |
| 26    | TEA   | DMSO    | 120       | 1.5 h | 20/45⁶³             |

Isolated yields. ²⁶³ Yields based on HPLC (C18 reversed-phase column, 150 × 4.8 mm, 5 µm). NR = no reaction.

![Scheme 1](image-url)
phenyl)ethynyl]-1-(oxiran-2-ylmethyl)-1H-indole (4a, Table 1, entry 4). In contrast, use of the polar aprotic solvent DMF with high dielectric constant produced both intermediates 4a/5a as well as the annulated product 6a. Interestingly, a significant increase in the yield of the title compound 6a was observed by prolonging the reaction. Carrying out the reaction in DMF at rt also failed to promote annulation even after 15 h of prolonged stirring (Table 1, entry 5). Increasing the temperature to 120 °C furnished the intermediate 4a as a single product in 77% isolated yield within 1 h (Table 1, entry 6). Further stirring up to 4 h at 120 °C led to the partial conversion of 4a (by ring opening of the epoxide with NaN₃) into yet another intermediate 1-azido-3-[[2-[2-(4-methylphenyl)ethynyl]-1H-indol-1-yl]propan-2-ol (5a, Table 1, entry 7) in 30% isolated yield. Nonetheless, extending the reaction times up to 15 h, led to the complete disappearance of 4a and furnished a mixture of the intermediate 5a in 15% isolated yield and the title compound 6a characterized as 1-(4-methylphenyl)-6,7-dihydro-5H-indol-1-yl propan-2-ol (Table 1, entry 8). The findings clearly suggest that the formation of indole-based annulated product 6a in the three-component domino format occurs via 4a and 5a intermediacy and requires higher temperature and prolonged stirring. This was again evident from the fact that a prolonged stirring up to 18 h led to the complete disappearance of the intermediates 4a and 5a and afforded 6a as a single product in 60% isolated yield (Table 1, entry 9). The role of intermediates 4a and 5a in the formation of 6a was further substantiated by treating 4a with NaN₃ in DMF at 120 °C and by heating 5a in DMF at 120 °C. As envisaged, both reactions furnished 6a as a single product in 87% and 90% isolated yield, respectively (Scheme 2).

Replacing DMF with yet another polar aprotic solvent, i.e., DMSO, produced similar results except for a marginal increase in the isolated yield of 6a to 64% in 15 h (Table 1, entries 10–13).

Next, in order to reduce the reaction times and to enhance the isolated yield of the annulated product 6a, we applied microwave conditions instead of conventional heating and monitored the progress of the reaction at different time intervals. A significant increase in the yield of 6a resulting from the increase in the reaction times under microwave conditions was observed. Initially, a 10 min irradiation of the reaction mixture furnished the intermediate 4a as the only product in 80% isolated yield (Table 1, entry 14), whereas a 30 min irradiation resulted in a mixture of 4a/5a/6a in 20/45/10% yields as evident from HPLC (Table 1, entry 15). Extending exposure to microwave conditions for 1 h produced a mixture of 5a and 6a (Table 1, entry 16); however, a further exposure up to 1.5 h furnished the desired compound 6a as the only product in 71% isolated yield (Table 1, entry 17). Thus, under microwave irradiation conditions, not only the isolated yield of 6a increased from 60% under conventional heating to 71%, but the duration of reaction was also reduced from 15 h to 1.5 h. Switching the solvent from DMSO to DMF under microwave conditions furnished 6a in slightly reduced yield (Table 1, entry 18) while the use of CH₃CN and CH₃OH failed to produce the desired product (Table 1, entry 19 and 20). Replacing Cs₂CO₃ with other bases such as K₂CO₃, Na₂CO₃, KH₂PO₄, t-BuOK, DBU and TEA either produced a mixture of 5a/6a or furnished 6a in reduced yields (Table 1, entries 21–26). The observations clearly suggest that the formation of 6a in the three-component format involved intermolecular N-1 alkylation of the 2-alkynylindole 1a with epichlorohydrin to form 4a, ring opening of 4a with sodium azide to form 5a, and finally an intramolecular Huisgen azide–internal alkyne 1,3-dipolar cycloaddition reaction.

Once the reaction conditions for the three-component format had been optimized, several 2-alkynylindoles bearing different functional groups were treated with epichlorohydrin and sodium azide in order to establish the scope and limitation of the strategy. In total 22 compounds 6a–v (Scheme 3) were synthesized, with their isolated yields varying from 54–73%. The findings suggest that although the electronic properties of the substituent (R¹) on the phenyl ring of the indole had no effect on the outcome of the isolated yield of the final products, the nature of R² had a profound effect on the yields. When the aromatic group was used as R², the final products 6a–c and 6e–q were obtained in isolated yields ranging from 66–73%, whereas substituting R² with aliphatic/triethylsilyl moieties furnished the cyclized products (6d and 6r–v) in diminished (54–65%) isolated yields.

**Conclusion**

In conclusion, we have developed a simple and efficient three-component domino reaction for the synthesis of highly substituted indolodiazepinotriazoles in good yields under microwave conditions. The domino sequence comprising N-1 alkylation, ring opening of the epoxide, and intramolecular Huisgen azide–internal alkyne 1,3-dipolar cycloaddition reaction, led to the generation of the diazepine and triazole rings annulated to the indole through the formation of four new sigma bonds in a single step.
Scheme 3: Three-component domino reaction for the synthesis of tetracyclic indolodiazepinotriazole compounds based on 6a. Reaction conditions: 1a (1.0 mmol), 2 (1.1 mmol), 3 (1.5 mmol) and Cs₂CO₃ (1.5 mmol) in DMSO (2.5 mL) at 120 °C, MW under N₂ atmosphere.
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