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One step synthesis of highly functionalized thiazolo[3,2b][1,2,4]triazole, triazolo[1,5-a]pyrimidine and triazolo[3,4b][1,3,4]thiadiazine[†]

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sReceived 00th January 20xx, Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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An efficient and straight forward methodology for the preparation of novel functionalized thiazolo[3,2-b]triazole, triazolo[1,5a]pyrimidine and triazolo[3,4-b][1,3,4]thiadiazine has been implemented with excellent yields via one-pot catalyst-free procedure at room temperature by the reaction of dibenzoylacetylene and triazole derivatives . Single crystal X-ray diffraction has been established for structures 21, 24, 25, 27, 34, 36 and 41.

Thiazolo[3,2-b][1,2,4]triazole, triazolo[1,5-a]pyrimidine and triazolo[3,4-b][1,3,4]thiadiazine heterobicycles constitute well established scaffolds that are frequently encountered in highly significant bioactive molecules, pharmaceuticals and agrochemicals¹⁻¹⁷. For instance, thiazolotriazoles **1** and **2** (R³=Ar) act as potent & selective COX-2 inhibitors;^{1,2} 3 has been proved to be an effective anti-cancer agent³ (Fig.1). Similarly, triazolo[1,5-a]pyrimidine sulphonamides constitute the main part of flumetsulam 4 and metosulam 5 which are well known herbicides effective for controlling various broadleaf & grass weed species at low doses in corns & cereals respectively⁴. On the other hand, 7-amino-triazolo[1,5-a]pyrimidines such as BAS600 6 & TTI-237 7 act as fungicides⁵ in plants & as potent anti-cancer agents respectively⁶. As a typical example of triazolo[3,4-b][1,3,4]thiadiazine, 8 has been shown to be effective against various cancer cell lines⁷ while as **9** shows anti-HIV-1 (strain IIIB) and HIV-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells.⁸ A plethora of other medicinally important compounds with thiazolo[3,2-b]triazole, triazolo[1,5-a]pyrimidine and triazolo[3,4-b][1,3,4]thiadiazine as core structure include antihelmintics,⁹ antimicrobial,¹⁰ medicinal fungicides,¹¹ bronchodilators,¹² analgesic,¹³ anti-infl-

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Fig. 1 Thiazolotriazoles, triazolopyrimidines and triazolothiadiazines scaffolds in drug discovery.

ammatory,¹⁴ antipyretic,¹⁴ anticancer,¹⁵ anti-malarial,¹⁶ and vasodilatory drugs.¹⁷

As a class of privileged substructures and with such a range of biological properties, the chemistry and synthesis of polycyclic compounds possessing core scaffold thiazolo[3,2b]triazole, triazolo[1,5-a]pyrimidine and triazolo[3,4b][1,3,4]thiadiazine has attracted enormous attention and hence significant efforts have been devoted to find new synthetic methods in order to access these scaffolds. Hitherto methods for the preparation of heterocyclic core of these substructures involve multistep procedures, high temperature conditions while as some are specific to given substituent pattern^{1,18-20}. The most straightforward synthetic approach to 2, from corresponding triazole-2-thiones and aryl α bromobenzyl derivatives, provides only the aromatic substituents R² and R^{3.1} Other methods for the synthesis of thiazolotriazole skeleton involve cyclisation of triazole-2epoxyphosphonates^{18b} with or utilize thiones 2formamidothiazoles^{18d} or other procedures.^{18a,c} Recently, E. B. Erkhitueva et al. reported highly regioselective heterocyclization reactions of 1,2,4-triazole-3-thiols with chloroacetylenephosphonates to obtain thiazolo[3.2b]triazoles.¹⁹ F. Montel et al. used halogen-metal exchange method for the synthesis of functionalized triazolo[1,5a]pyrimidines.²⁰ Despite the previous accomplishments to obtain the core skeleton,²¹ an economical route is still required for the synthesis of thiazolo[3,2-b]triazole, triazolo[1,5a]pyrimidine and triazolo[3,4-b][1,3,4]thiadiazine derivatives. In continuation of our previous work on synthesis of

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⁺Electronic Supplementary Information (ESI) available: [Detailed experimental procedures, spectral data for all new compounds, and crystallographic data]. See DOI: 10.1039/x0xx00000x

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multichromophoric heterocyclic systems ambient at temperature²², herein we present an efficient one step catalyst-free novel synthesis of a series of thiazolo[3,2b]triazole, triazolo[1,5-a]pyrimidine and triazolo[3,4b][1,3,4]thiadiazine by nucleophilic addition reaction of 3mercapto/amino 1,2,4-triazole and 3-mercapto-4-amino-1,2,4triazole derivatives with dibenzoylacetylene (DBA) at room temperature. The protocol is operationally simple and efficient.

The reaction of an equimolar mixture of 3-mercapto-5phenyltriazole **12** with DBA **10** in presence of acetonitrile at room temperature led to the formation of a single product with excellent yield (85%), mp 170-171 ⁰C for which IR, ¹H NMR, ¹³C NMR were consistent for 2-(6-hydroxy-2,6diphenylthiazolo[3,2-*b*][1,2-4]triazolo-5(6H)-ylidene)-1-

phenylethanone 21. Theoretically, several other products of such a reaction are possible; hence the structure of product was unambiguously confirmed by single crystal x-ray diffraction (CCDC1410751). The reaction was then employed to other triazole-3-thiol derivatives and to our delight these compounds also led to the formation of thiazolo[3,2b]triazoles in moderate to good yields as shown in table 1. The results exhibited the feasibility to construct biologically important thiazolo[3,2-b]triazoles analogues. The structure of the synthesized products 20-28 was well characterized by IR, ¹H NMR, ¹³C NMR, and mass spectral analysis. IR spectrum of 21 showed strong absorption bands at 1640 cm⁻¹ and 1589 cm⁻¹ ¹ which were assigned respectively to carbonyl group and exocyclic C=C bond in conjugation with carbonyl group and ¹H NMR displayed a characteristic singlet at δ 3.28 ppm which was assigned to proton of OH group. A sharp singlet for olefinic proton resonating slightly down field at δ 6.67 ppm due to adjacent strong electron withdrawing carbonyl group was also observed. A cluster of peaks ranging between δ 7.31-8.7 ppm were assigned to aromatic protons. The ¹³C NMR also showed distinctive peak at δ 187.8 ppm corresponding to carbonyl carbon. Further structural confirmation was provided by ESI-Mass spectrum which showed the molecular ion peak as the base peak at m/z 412.11 [M+H]⁺. The structure of the product **21** was further authenticated by single crystal X-ray analysis (CCDC 1410751).

The reaction pathway for the formation of 21 may be represented by the reaction sequence shown in Scheme 2, involving the attack of lone pair of sulphur on one of the acetylenic carbons of DBA followed by proton transfer to form 29, which may intern undergo cyclisation to give the desired product. When 3-amino-1,2,4-triazole derivatives 14 and 15 were employed, triazolo[1,5-a]pyrimidines 23 and 24 were obtained respectively in good yields. The reaction proceeded possibly by the attack of amino nitrogen of triazole 15 on acetylenic carbon of DBA followed by cyclisation along with loss of water molecule to give 24. The formation of six membered pyrimidine ring as confirmed by single crystal x-ray analysis (CCDC 1410752) could be attributed due the substrate difference; an amino group in case of triazole derivative 15. The presence of vicinal amino and mercapto functions in 4amino-1,2,4-triazole-3-thiol derivates offer nucleophilic loci for



Scheme 1 Schematic Representation for the Synthesis of Thiazolo[3,2-b][1,2,4]triazole, Triazolo[1,5-a]pyrimidine and Triazolo[3,4-b][1,3,4]thiadiazine Analogues.

Table 1 Synthesis of Highly Functionalized Thiazolo[3,2-b][1,2,4]triazole, Triazolo[1,5-a]pyrimidine and Triazolo[3,4-b][1,3,4]thiadiazine Analogues by the Reaction of DBA (**10**) with Triazole/tetrazole Derivatives (**11-19**).



^aReaction conditions: **11** (1 mmol) and **20** (1 mmol) in 10 mL acetonitrile at room temperature. ^bIsolated yield.



Scheme 2 Plausible mechanism for the formation of Thiazolo[3,2-b][1,2,4]triazole (**21**), Triazolo[1,5-a]pyrimidine (**24**) and Triazolo[3,4-b][1,3,4]thiadiazine (**25**).

heterocyclic synthesis involving potential bridging reactings. Hence the reaction of 4-amino-1,2,4-triazole 3- thiol derivative Published on 03 December 2015. Downloaded by University of Liverpool on 03/12/2015 14:15:19.

16 and **17** with DBA gave triazolo[3,4-b][1,3,4]thiadiazine analogues **25**, **26** in excellent yields (more than 90%) with shorter reaction time as depicted in table 1. The structure of product **25** was unambiguously confirmed by single crystal x-ray analysis (CCDC 1410753). Plausible mechanistic rationale is presented in scheme 2. When 18 was treated with DBA, adduct formed showed the presence of two carbonyls both in IR (1661, 1638 cm⁻¹) and ¹³C (δ 191,188 ppm), thereby confirming that reaction proceeded with simple Michael type addition of thiol group on acetylenic carbon, devoid of any cyclisation. Further structural authentication for **27** came from single crystal x-ray analysis (CCDC 1410754).



Fig. 2 Single crystal x-ray structure of **21** (a, CCDC 1410751), **24** (b, CCDC 1410752), **25** (c, CCDC 1410753), and **27** (d, CCDC 1410754).

To explore the scope of the reactivity of triazole derivatives further, the reaction was extended to other activated acetylenes viz, dimethyl acetylenedicarboxylate (DMAD) 30, methyl propiolate (MP) 31 and ethyl phenylpropiolate (EPP) 32. The reaction of 30 with triazole derivatives 11, 12 and 15 in acetonitrile gave corresponding triazolothiazinone 33-35 at room temperature (table 2). Single crystal x-ray structure has been established for 34. When 31 was refluxed with triazole derivatives (11, 12, 14, 16 and 17) in acetonitrile for 3-4 hours, corresponding acrylic adducts 36-40 were obtained. These adducts adopt cis configuration with olefinic protons displaying coupling constants of J=8-10 Hz, hence reflecting a trans-addition to the acetylenic linkage. Further authenticity came from the single crystal X-ray structure of 36 that displayed two olefinic protons in cis-configuration (Fig. 3b). In contrast, 32 when refluxed with triazole 3-thiol derivatives (11, 12) for 3-4 hrs in methanol elicited different reactivity pattern as that of methylpropiolate. The reaction proceeded with loss of ethoxy group, thus leading to the formation of corresponding triazolothiazinone derivatives 41 and 42. With 16 and 17, corresponding Michael adducts were obtained as depicted in scheme 4. Single crystals of 34, 36 and 41 were obtained successfully and their structures were unambiguously confirmed by X-ray crystallographic analysis (Fig.3.).

In summary, an efficient and catalyst-free one pot synthesis of Thiazolo[3,2-b][1,2,4]triazole, triazolo[1,5-a]pyrimidine and triazolo[3,4-b][1,3,4]thiadiazine heterobicycles has been developed. The procedure was applied to a series of triazole/tetrazole and activated acetylenes to examine the extension and limitation of the methodology. The shorter reac-

DOI: 10.1039/C5RA21270G

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^{*a*}Reaction conditions: **30** (1 mmol) and **11** (1 mmol) in 10 mL acetonitrile at room temperature. ^{*b*}**31** (1 mmol) and **11** in 10 mL acetonitrile at reflux. ^{*c*}**32** (1 mmol) and **11** (1 mmol) in 10 mL methanol at reflux. ^{*d*}Isolated yield.



Fig. 3 Single crystal x-ray structure of **34** (a, CCDC1410755), **36** (b, CCDC 1410756) and **41** (c, CCDC 1410757).

ction time, enhanced reaction rates, substantial yield negligible by-product, fairly mild conditions and easy work-up procedure in this approach can be applied in the synthesis of biological and pharmaceutical molecules with Thiazolo[3,2-b][1,2,4]triazole, triazolo[1,5-a]pyrimidine and triazolo[3,4-b]][1,3,4]thiadiazine skeleton.

Acknowledgement

Financial support from CSIR and UGC New Delhi for the research grant to M. Muneer and funding from the National Science Foundation, USA (MRI, CHE-0420497) for the purchase of the Apex-II diffractometer for the research group of N. P. Rath are gratefully acknowledged. The authors are highly thankful to Prof. Gautam R. Desiraju (IISC Bangalore) for providing single crystal diffraction facility. Tariq A. Shah thanks University Grants Commission New Delhi for providing UGC-BSR (JRF) Fellowship.

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