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Synthesis of fused triazolo-imidazole derivatives by sequential van Leusen/alkyne–azide cycloaddition reactions

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Abstract—A facile synthesis of fused triazolo imidazole derivatives by a van Leusen/alkyne–azide cycloaddition synthetic sequence is reported. The two-step reaction sequence generates compounds of significant molecular complexity from simple starting materials in an expedient fashion with good overall yields.

The continuing demand for novel lead compounds has led to the emergence of our scaffold-oriented synthesis program that targets functionalized molecular skeletons via multicomponent reactions[1] (MCRs) combined with a post-condensation modification. We have recently reported sequential Ugi/Heck,[2] Ugi/intramolecular nitrile oxide cycloaddition,[3] Ugi/intramolecular alkyne–azide cycloaddition (IAAC)[4] and Ugi/carbonylation intramolecular amidation[5] sequences.

During this endeavor, our group became interested in the synthesis of fused bicylic imidazoles due to their presence in a number of biologically active compounds.[6] It is in this context that we became interested in the van Leusen imidazole synthesis[7] and we have recently reported on sequential van Leusen/ring-closing metathesis strategies to access novel bicyclic imidazoles.[8]

Herein, we report our efforts on post-modifications of the van Leusen reaction using an alkyne–azide cycloaddition as the ultimate step in our reaction sequence (Fig. 1). The use of an azide functionality on the aldehyde and an alkyne functionality on the amine provides bifunctional starting materials for the van Leusen reaction resulting in substrate **1**. Subsequent cyclization via the IAAC will allow access to the fused triazolo imidazole scaffolds **2**. Additionally, the availability of efficient routes to synthesize substituted TosMIC reagents provides another site of diversity in the three-component reaction.[9] This concept has been previously reported by us in the context of Ugi-type MCRs wherein azide–alkyne

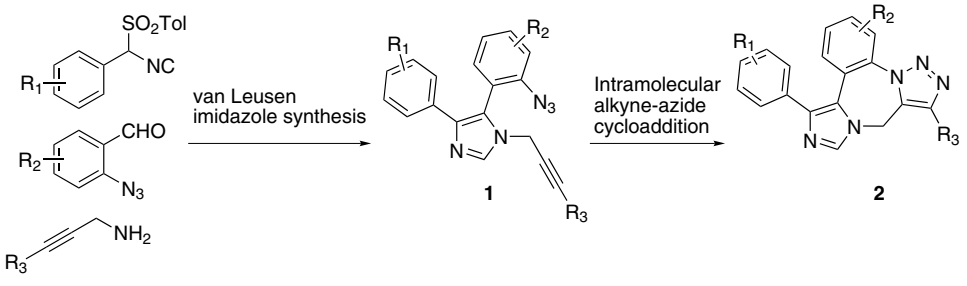

Figure 1. General strategy.

Keywords: Multicomponent reactions; Imidazole; van Leusen; Cycloaddition.
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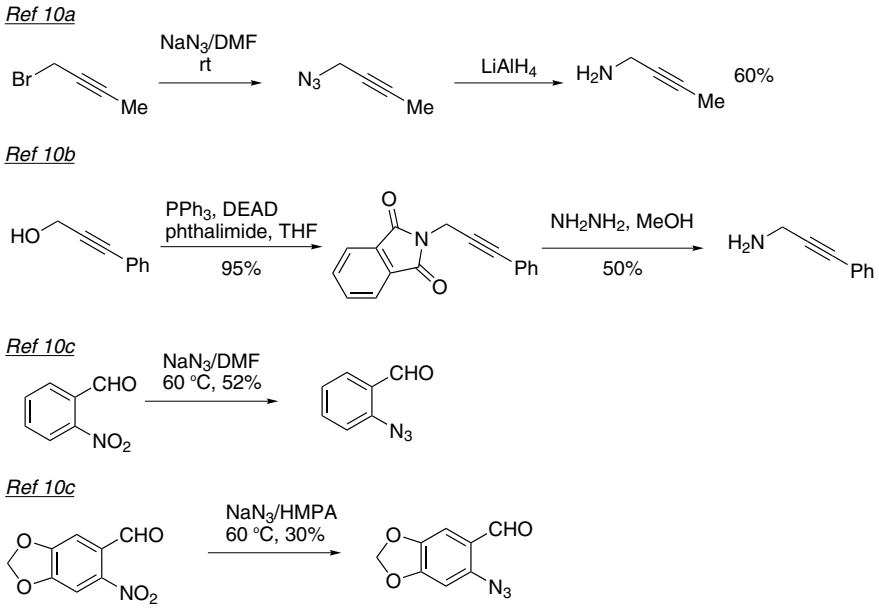

Scheme 1. General synthetic routes for the preparation of the starting materials.

Table 1. Products obtained from the van Leusen and intramolecular azide–alkyne cycloaddition (IAAC) sequence

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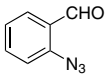
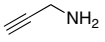
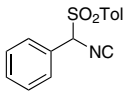
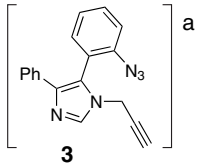
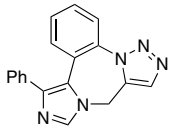
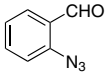
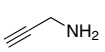
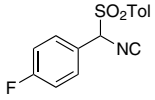
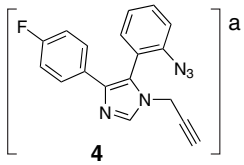
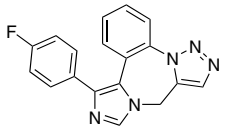
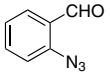
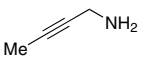
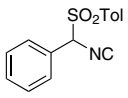
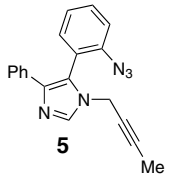
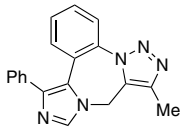
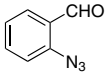
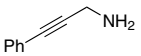
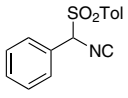
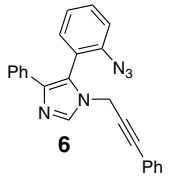
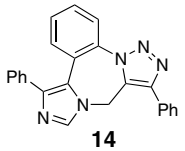
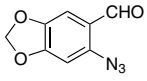
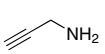
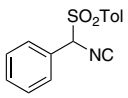
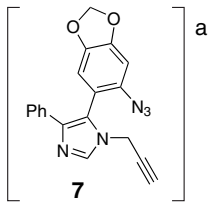
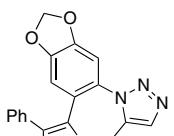
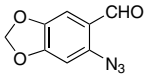
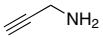
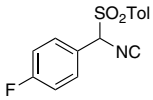
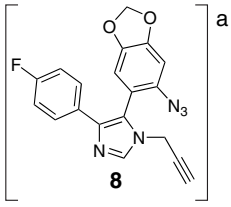
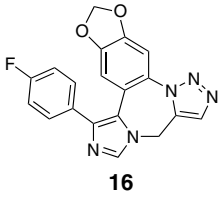
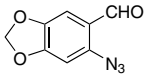
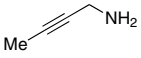
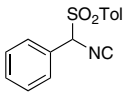
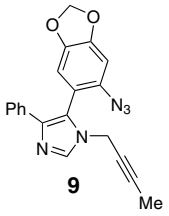
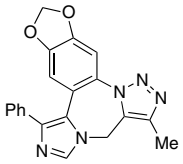
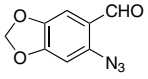
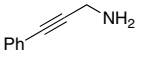
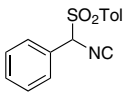
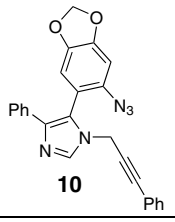
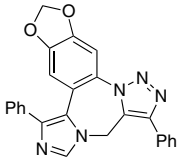
1				 **3**		 **11**	65
2				 **4**		 **12**	72
3				 **5**	53	 **13**	59
4				 **6**	60	 **14**	65
5				 **7**		 **15**	83

Table 1 (*continued*)

Entry	Aldehyde	Amine	TosMIC	van Leusen product	Yield	IAAC product	Yield (%)
6				 **8** [a]		 **16**	93
7				 **9**	43	 **17**	40
8				 **10**	59	 **18**	62

[a]The intermediate van Leusen products were not isolated, 1,3-cycloaddition occurred in situ to afford the triazole products.

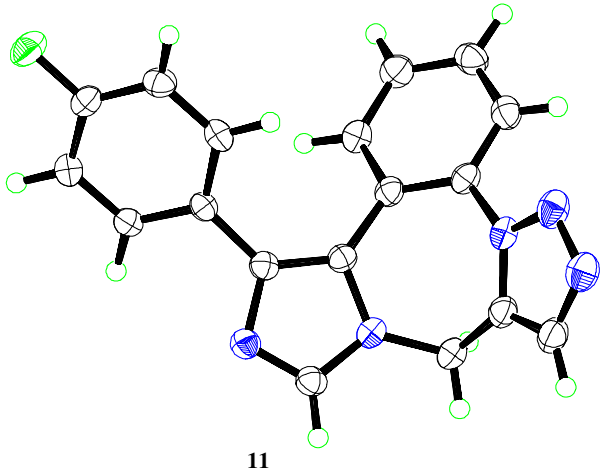
inputs were introduced into the reaction components followed by a post-condensation IAAC reaction to afford fused dihydrotriazolo[1,5-*a*]pyrazinones and triazolobenzodiazepines.[4]

Azides and the propargyl amine building blocks were purchased from commercial sources or prepared according to known procedures as illustrated in Scheme 1.[10] The condensation of the azido aldehyde with propargyl amine in DMF at room temperature generates the imine in situ, which is followed by the addition of phenyl TosMIC and base (K_2CO_3).

It was observed that with unsubstituted alkynes the intermediate van Leusen imidazoles were not isolated, but the IAAC reaction proceeded in situ at room temperature to afford the cycloaddition products (Table 1, entries 1, 2, 5 and 6).[11] This was confirmed by IR analysis (absence of the $-N_3$ functionality in the products), and ^1H NMR data (absence of the alkyne –CH, appearance of the $-CH_2$ of the azepine ring and –CH of the triazole ring). Additionally, a single-crystal X-ray for **11** was obtained (Fig. 2).

With the substituted alkynes, the intermediate van Leusen imidazoles were isolated (Table 1, entries 3, 4, 7 and 8). The IAAC reaction was then effected by treating the intermediate imidazole products with copper(II) sulfate pentahydrate.[12] Using this procedure, a diverse set of fused triazolo imidazoles have been synthesized by varying the aldehyde, alkyne and TosMIC inputs.

In conclusion, we have demonstrated that by introducing azide and alkyne functionality via the van Leusen reaction, followed by an intramolecular 1,3-cycloaddition reaction, a variety of fused triazolo imidazoles can be readily generated under mild conditions from easily accessible starting materials. These compounds represent useful scaffolds for lead generation. Other van Leusen post-modification reactions are currently in progress and will be reported in due course.



11

Figure 2. Crystal structure of **11**.

Acknowledgements

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11. A representative procedure for reactions with unsubstituted alkynes is demonstrated by the preparation of **11**. To the azido aldehyde (221 mg, 1.5 mmol) in DMF (2 mL) was added propargyl amine (110 mg, 2.0 mmol) and the reaction mixture was stirred at rt for 2.5 h. This was followed by the addition of phenyl TosMIC (271 mg, 1.0 mmol) and K_2CO_3 (138 mg, 2.0 mmol) and the reaction mixture was allowed to stir for an additional 17 h at rt. The reaction was quenched by the addition of water. The aqueous layer was extracted with EtOAc, dried (anhyd $MgSO_4$), concentrated and purified by flash chromatography (97:2.5:0.5, CH_2Cl_2–CH_3OH–NH_3) to afford 185 mg (62%) of **11** as a clear oil. ^1H NMR (300 MHz, $CDCl_3$): δ 5.01 (br s, 1H), 5.66 (br s, 1H), 7.30–7.39 (m, 4H), 7.50–7.60 (m, 4H), 7.85 (s, 1H), 8.10 (m, 1H), 8.16 (s, 1H); MS (ESI): *m/z* 300 (M+H).
12. (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599; (b) A representative procedure for reactions with substituted alkynes is demonstrated by the preparation of **13**. To the azido aldehyde (221 mg, 1.5 mmol) in DMF (2 mL) was added but-2-yn-1-amine (138 mg, 2.0 mmol) and the reaction mixture was stirred at rt for 2.5 h. This was followed by the addition of phenyl TosMIC (271 mg, 1.0 mmol) and K_2CO_3 (138 mg, 1.0 mmol) and the reaction mixture was allowed to stir for an additional 17 h at rt. The reaction was quenched by the addition of water. The aqueous layer was extracted with EtOAc, dried (anhyd $MgSO_4$) concentrated and purified by flash chromatography (97:2.5:0.5, CH_2Cl_2–CH_3OH–NH_3) to afford 145 mg (53%) of **5** as a clear oil. ^1H NMR (300 MHz, $CDCl_3$): δ 1.81 (t, $J = 3.0$ Hz, 3H), 4.32 (d, $J = 12.0$ Hz, 1H), 4.50 (d, $J = 12.0$ Hz, 1H), 7.12–7.33 (m, 6H), 7.44–7.54 (m, 3H), 7.88 (s, 1H); MS (ESI): *m/z* 314 (M+H); To **5** in *t*-BuOH–H_2O (1:1, 2 mL), sodium ascorbate (8.3 mg, 0.042 mmol), copper(II) sulfate pentahydrate (1 mg, 0.0042 mmol) were added and the reaction mixture was heated at 60 °C for 17 h. The reaction was cooled to rt, quenched with H_2O. The aqueous layer was extracted with EtOAc, dried (anhyd $MgSO_4$), concentrated and purified by flash chromatography (97:2.5:0.5, CH_2Cl_2–CH_3OH-NH_3) to afford 78 mg (59%) of **13** as a white solid. ^1H NMR (300 MHz, $CDCl_3$): δ 2.48 (s, 3H), 4.97 (br s, 1H), 5.29 (br s, 1H), 7.26–7.32 (m, 4H), 7.47–7.53 (m, 4H), 7.76 (s, 1H), 8.04 (d, $J = 6.0$ Hz, 1H); MS (ESI): *m/z* 314 (M+H).