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An efficient one-pot synthesis of heterocycle-fused 1,2,3-triazole derivatives as anti-cancer agents

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ABSTRACT

A series of heterocycle-fused 1,2,3-triazoles were easily prepared by the 1,3-dipolar cycloaddition of heterocyclic ketene aminals or *N*,*O*-acetals with sodium azide and polyhalo isophthalonitriles in a one-pot reaction at room temperature without a catalyst and evaluated in vitro against a panel of human tumour cell lines. 1,3-Oxazoheterocycle fused 1,2,3-triazoles were more potent against the tumour cell lines Skov-3, HL-60, A431, A549 and HepG-2 than 1,3-diazoheterocycle fused 1,2,3-triazoles. 4-Methoxyphenyl substituted 1,3-oxazoheterocycle fused 1,2,3-triazole **6j** was found to be the most potent derivative with IC_{50} values lower than 1.9 μg/mL against A431 and K562 human tumour cell lines.

1,2,3-Triazole derivatives possess substantial biological activities, including anti-tumour,[1] anti-HIV,[2] antiallergic,[3] antifungal,[3b] and antimicrobial[4,5] properties. 1,2,3-Triazoles have also been used as building blocks for the synthesis of important bio-conjugations.[6] Due to their broad range of biological activities and their value as synthetic precursors for pharmaceutical compounds, 1,2,3-triazole derivatives have received increasing attention. Many methods for the synthesis of 1,2,3-triazoles have been reported in literature, including 1,3-dipolar cycloaddition or cycloaddition of azides to alkynes,[7] nitroethenes,[8] and sodium phenylacetylide.[9] Among them, the most common method is the azide-alkyne cycloaddition[7h–j] catalyzed by copper. The azides normally used in this reaction are the tosyl azides,[10] trimethylsilyl azide,[8,11] azidobenzene,[12] and sodium azide.[13]

Heterocyclic ketene aminals (HKAs) are versatile intermediates for the synthesis of a wide variety of heterocyclic compounds,[14] especially 1,2,3-triazole derivatives[15] (Fig. 1). For instance, HKAs and glycosyl azide have been used to prepare *N*-glycosyl 1,2,3-triazoles **3**[15a] and **4**.[15b] HKAs have been reacted with 1-azido-4-nitrobenzene at room temperature to synthesize *N*-aryl 1,2,3-triazole **5**,[15c] while other azid-obenzes such as 1-azido-4-chlorobenzene, 1-azido-4-methylbenzene, and 1-azido-4-methoxy benzene, can give both *N*-aryl 1,2,3-triazole **5** as the major product and the heterocycle-fused 1,2,3-triazole **6** as the minor product.[15c] Tosyl azides have been refluxed with HKAs in acetonitrile[15d] or dioxane[15e] to obtain fused 1,2,3-triazole **6** in moderate yields.

However, these methods usually present limitations, such as the need to employ multistep reactions[15a–c] to obtain the dangerous organic azides and the need to heat the reaction mixture,[15c–e] which contain organic azides or 1,2,3-triazoles that are explosive when heated.[16] Among these procedures, only tosyl azides can be used to effectively obtain heterocycle-fused 1,2,3-triazole **6** (Fig. 1). This may be due to the strong electron-withdrawing properties of the tosyl group. It is inferred that increasing the electron-withdrawing ability of substituted azidobenzene can improve its reaction with HKAs to form the heterocycle-fused 1,2,3-triazoles, just as in the case of tosyl azides.

Polyhalo isophthalonitriles have been widely used as synthetic materials in organic synthesis.[17] We envisage the synthesis of

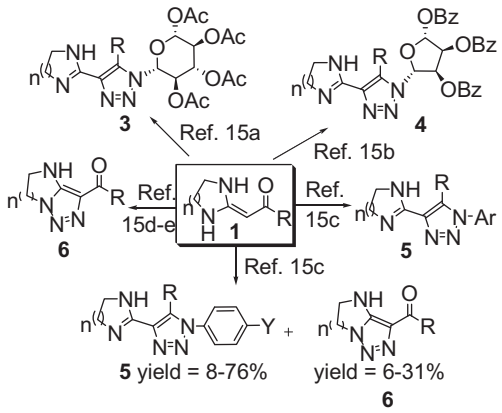

Figure 1. 1,2,3-Triazoles derived from heterocyclic ketene aminals **1**.

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4-azido-2,5,6-trihalobenz-ene-1,3-dinitriles from a substitution reaction between polyhalo isophthalonitriles and sodium azide in situ. This compound could have considerable reactivity and good electronic properties due to the electron-withdrawing halo and cyano groups. Based on these motivations, we attempted to obtain a series of novel and temporary organic azides.

Furthermore, one-pot reaction at room temperature under catalyst-free conditions, which have become a powerful tool to rapidly construct diverse libraries of organic compounds since the products are formed in a single step and diversity can be achieved by simply varying each component, is highly desirable. Thus, exploring a concise, efficient and safe method for the synthesis of heterocycle-fused 1,2,3-triazole derivatives based on one-pot reactions is very important and necessary.

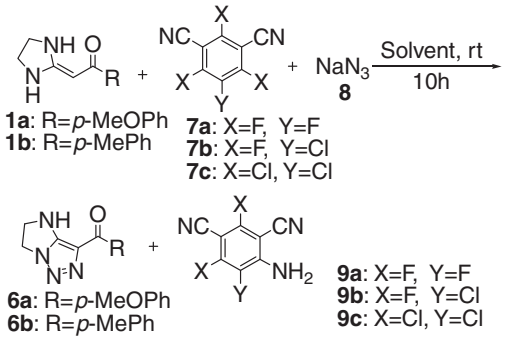
In this Letter, we report a novel one-pot, three-component synthesis of heterocycle-fused 1,2,3-triazole derivatives using a room temperature reaction of sodium azide with polyhalo isophthalonitriles and HKAs or *N*,*O*-acetals. The heterocycle-fused 1,2,3-triazoles **6** (Schemes 1 and 2) were obtained in excellent yields (86–93%).

Initially, the reactions of HKAs **1a** with polyhalo isophthalonitriles **7a** were chosen as models to test this protocol (Scheme 1). As shown in Table 1, different solvents such as acetonitrile, 1,4-dioxane, toluene, and DMF were tested at room temperature (entries 1–6). It demonstrated that DMF was the optimum solvent (entry 6) to afford product **6a**, while toluene was the poorest solvent (entry 1). This is because **1a** and sodium azide are hardly soluble in toluene, which presumably reduced the efficiency of the reaction. The HKAs **1a** reacted with **7a** in DMF at room temperature and proceeded smoothly to form the target product **6a** with 90% yield.

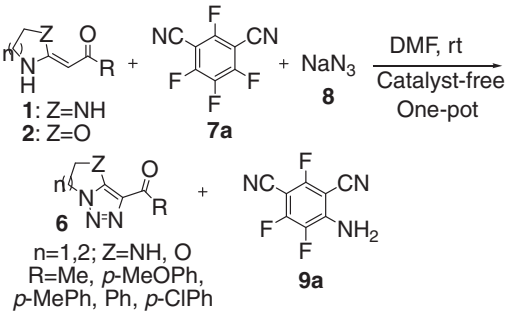
In order to study other organic azides in situ, **7b** and **7c** were used as substrates to react with sodium azide and HKAs **1a** and **1b** under the same conditions. The HKAs **1b** and the polyhalo isophthalonitrile **7a** were reacted in DMF to form the target product **6b** in good yield at room temperature. The results listed in Table 1 demonstrate that polyhalo isophthalonitriles with various substituents **7a–c** were all good substrates for the reaction. The procedure was straightforward and gave very good overall yields (Table 1, entries 6–11). It is also worth mentioning that the structure of the polyhalo isophthalonitrile **7** had a noticeable influence on the reaction.

The reactivity of **7** varied with the electron-withdrawing properties of groups X and Y, and the reactivities of the polyhalo isophthalonitriles under typical conditions were ranked in the following order: **7a** > **7b** > **7c** (Table 1, entries 6–11).

2,4,5,6-Tetrafluorobenzene-1,3-dinitrile **7a** was found to be the optimum substrate to react with different types of HKAs **1a–i** (Table 2, entries 1–9).[18] The results demonstrated that HKAs with various substituents and different ring-sizes were all good substrates for the 1,3-dipolar cycloaddition reactions (entries 1–9).



Scheme 1. Synthesis of heterocycle-fused 1,2,3-triazole derivatives.



Scheme 2. Synthesis of heterocycle-fused 1,2,3-triazole derivatives **6**.

Table 1
Optimization of reaction conditions[a]

Entry	HKAs	Substrate	Solvent	**6** Yield[b] (%)	**9** Yield[b] (%)
1	**1a**	**7a**	Toluene	56	54
2	**1a**	**7a**	DCM	60	59
3	**1a**	**7a**	THF	67	65
4	**1a**	**7a**	CH_3CN	81	80
5	**1a**	**7a**	Dioxane	84	84
6	**1a**	**7a**	DMF	90	89
7	**1b**	**7a**	DMF	88	88
8	**1a**	**7b**	DMF	89	87
9	**1b**	**7b**	DMF	86	85
10	**1a**	**7c**	DMF	87	86
11	**1b**	**7c**	DMF	83	80

[a] All reactions were done for 10 h at rt.
[b] Isolated yields based on HKAs **1**.

Table 2
Synthesis of heterocycle-fused 1,2,3-triazole **6**

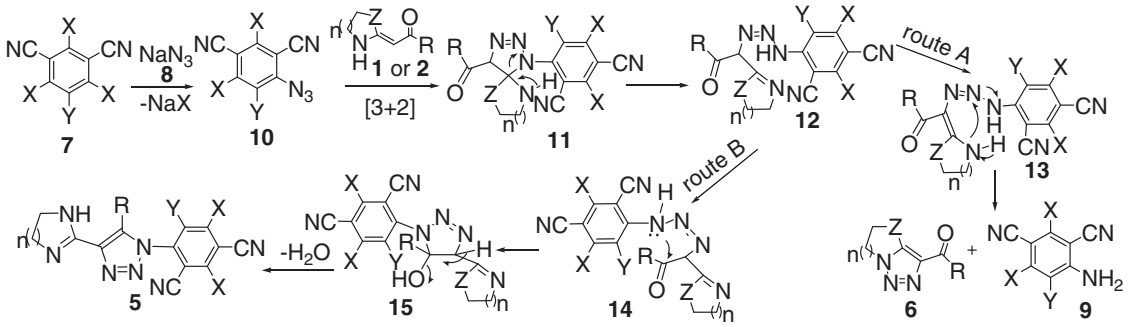
Entry	**1**/**2**	**6**	**9**	*n*	Z	R	**6** Yield[a] (%)	**9a** Yield[a] (%)
1	**1a**	**6a**	**9a**	1	NH	*p*-MeOPh	90	89
2	**1b**	**6b**	**9a**	1	NH	*p*-MePh	88	88
3	**1c**	**6c**	**9a**	1	NH	Ph	91	90
4	**1d**	**6d**	**9a**	1	NH	*p*-ClPh	89	88
5	**1e**	**6e**	**9a**	1	NH	Me	89	87
6	**1f**	**6f**	**9a**	2	NH	*p*-MeOPh	92	90
7	**1g**	**6g**	**9a**	2	NH	*p*-MePh	90	89
8	**1h**	**6h**	**9a**	2	NH	Ph	88	86
9	**1i**	**6i**	**9a**	2	NH	*p*-ClPh	91	89
10	**2a**	**6j**	**9a**	1	O	*p*-MeOPh	93	91
11	**2b**	**6k**	**9a**	1	O	*p*-MePh	86	85
12	**2c**	**6l**	**9a**	1	O	Ph	87	87
13	**2d**	**6m**	**9a**	1	O	*p*-ClPh	89	87

[a] Isolated yields based on HKAs.

The reactions took 10 h at room temperature in DMF, and the yields were generally good. The substituents of the HKAs rings only slightly influenced the reactivity (e.g., entries 1 vs 6, 2 vs 7, 3 vs 8).

In order to expand the scope of the dipolar cycloaddition reaction, HKAs **1a–i** were replaced by *N*,*O*-acetals **2a–d** (entries 1–5 vs 10–13) and subjected to the reaction conditions described above. The reactions provided products in good yields.[18]

According to the observed and reported[15c] findings, the stepwise mechanism employed in this case involved the initial formation of a 4-azido-2,5,6-trihalobenzene-1,3-dinitrile **10** from the reaction of polyhalo isophthalonitrile **7** with sodium azide **8**. Subsequently, the temporary intermediate **10** reacted with HKAs **1** or *N*,*O*-acetals **2** via an intermolecular 1,3-dipolar cycloaddition to form **11**, before the *C*–*N* bond was broken to give **12**, which underwent two competitive reaction pathways. In route A, intermediate **12** afforded **13** through an imine–enamine tautomerization,

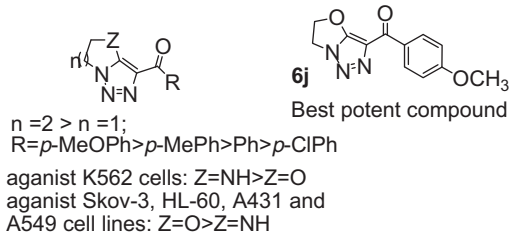


Scheme 3. Proposed mechanism for the formation of 1,2,3-triazoles.

Table 3
Cytotoxic activity of heterocycle-fused 1,2,3-triazoles in vitro[a] (IC_{50}, μg/mL[b])

No.	Compound	K562	Skov-3	HL60	A431	A549	HepG-2
1	**6a**	2.8	159	>200	>200	>200	>200
2	**6b**	9.4	>200	>200	>200	>200	>200
3	**6c**	92	>200	>200	>200	>200	>200
4	**6d**	16.1	>200	>200	57.6	>200	>200
5	**6e**	>200	>200	>200	>200	>200	>200
6	**6f**	3.4	190	>200	64.4	>200	>200
7	**6g**	1.5	124	>200	>200	>200	>200
8	**6h**	28.6	>200	>200	>200	>200	>200
9	**6i**	3.2	>200	>200	>200	>200	>200
10	**6j**	1.0	9.6	21.1	1.9	58	>200
11	**6k**	127	8.5	13.7	12.7	79	198
12	**6l**	>200	66.1	17.2	10.8	78	>200
13	**6m**	>200	8.6	6.5	3.8	42	>200
14	Cisplatin (DDP)	2.2	0.5	1.4	0.6	5.1	8.2

[a] The cytotoxicity (as IC_{50} for each cell line) is the concentration of compound that reduced the optical density of treated cells by 50% with respect to untreated cells using the MTT assay.
[b] Data represent the mean values of three independent determinations.



Scheme 4. Structure–activity relationship of heterocycle-fused 1,2,3-triazole derivatives.

followed by the loss of 4-amino-2,5,6-trihalobenzene-1,3-dinitrile **9** and cyclo-condensation to obtain the target product **6**. In route B, the nitrogen atom of intermediate **12** attacked the carbonyl group to form **15**. After aromatization to eliminate water, *N*-aryl 1,2,3-triazole **5** was produced (Scheme 3). The strongly electron-withdrawing ability of cyano groups and halogen atoms and the larger steric-effects of the highly functionalized aryl ring decreased the nucleophilicity of the nitrogen atom of intermediate **12**. Therefore, the reaction rate in route A was faster than that in route B. As a result, we cannot obtain the *N*-aryl 1,2,3-triazole **5**.

The synthesized heterocycle-fused 1,2,3-triazoles **6** were evaluated for in vitro anti-cancer activity against human cells according to procedures described in the literature.[19] The tumour cells included myeloid leukaemia (K562 and HL-60), ovarian carcinoma (Skov-3), epidermoid carcinoma (A431), lung adenocarcinoma (A549) and laryngeal carcinoma (Hep-2) cells. Cisplatin (DDP) was used as the reference drug. The results of the cytotoxicity studies are summarized in Table 3 (IC_{50} value, defined as the concentration corresponding to 50% growth inhibition). As shown in Table 3, some of the compounds showed good activity against the cells.

The data indicate that 1,3-diazoheterocycle fused 1,2,3-triazoles **6a–i** have good activity towards K562 tumour cell line (Table 3, entries 1–9 vs 14). The structures of the 1,3-diazoheterocycle fused 1,2,3-triazoles **6** have an obvious influence on the cytotoxicity against K562 cells. The different substituents and same ring-sizes ($n = 1$ or $n = 2$) of 1,2,3-triazoles all contribute to their bioactivity. For example, the activity of five-membered 1,3-diazoheterocycle fused 1,2,3-triazoles **6** against human K562 cells was increased by the electron-rich properties of the R group (Table 3, entries 1–4). The activity of the six-membered 1,3-diazoheterocycle fused 1,2,3-triazole **6** against K562 cells followed the same pattern (Table 3, entries 5–9). On the whole, the activity of six-membered 1,3-diazoheterocycle fused 1,2,3-triazoles against K562 cells more active than that of five-member 1,3-diazoheterocycle fused 1,2,3-triazoles (Table 3, entries 1–4 vs 6–9). As a result, **6g** more active than cisplatin against K562 cells (Table 3, entry 7). On the other hand, **6a–i** have lower activity to Skov-3, HL-60, A431, A549 and Hep-2 cell lines (Table 3, entries 1–9).

However, the 1,3-oxazoheterocycle fused 1,2,3-triazoles **6j–m** exhibited lower cytotoxic activity against K562 cells (except **6j**), comparing with DDP (entries 10–13 vs 14). These four compounds exhibited moderate cytotoxic activity against Skov-3, HL-60, A431 and A549 tumour cell lines (entries 10–13). **6j–m** almost not exhibited any cytotoxic activity against HepG-2 cells. These results suggest that the isostere of N and O (Z = NH, O) play a vital role in the modulation of cytotoxic activity to different tumour cell lines (Table 3, entries 1–9 vs 10–13).

All in all, compounds **6a–m** were more potent against the K562, Skov-3 and A431 tumour cells. Of these, compound **6j**, bearing 4-methoxy-phenyl substituents, was the most potent derivative with IC_{50} values lower than 1.9 μg/mL against A431 and K562 human tumour cells (entry 10 and Scheme 4).

In conclusion, we have developed a simple one-pot synthesis of biologically significant heterocycle-fused 1,2,3-triazole derivatives in good yields at room temperature under catalyst-free conditions. The protocol is applicable to a wide range of HKAs and polyhalo isophthalonitrile compounds and allows the assembly of a diverse set of heterocycle-fused 1,2,3-triazole derivatives. Compounds **6j–m** proved to have moderate to good cellular cytotoxicity. The electron-rich properties of the R group and 1,3-oxazohetero-cycle played a vital role in the modulation of the cytotoxic activity, and **6j** proved to be the most promising lead for further structural modifications guided by the valuable information provided by the detailed SARs described here.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.06.141.

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18. *General procedure for the 1,3-dipolar cycloaddition reaction*: a 25 mL round-bottom flask was charged with polyhalo isophthalonitrile **7** (2 mmol), DMF (10 mL), and sodium azide (156 mg, 2.4 mmol). Then, HKAs **1** or *N*,*O*-acetals **2** (2 mmol) were added. The mixture was stirred for 10 h at room temperature until **1** or **2** was completely consumed. The reaction was quenched with subsequent additions of water (30 mL) and EtOAc (30 mL). The organic phase was washed with water (10 mL × 2), dried over Na_2SO_4, concentrated, and purified by flash column chromatography to acquire the heterocycle-fused 1,2,3-triazole **6** in 86–93% yield and compound **9** in 85–91% yield. *Compound* **6e**: light yellow solid, mp = 169–169.5 °C. IR (KBr): 3266, 2955, 1637, 1584 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 2.41 (s, 3H, CH_3), 4.21 (t, J = 8.5, 2H, NCH_2), 4.41 (t, J = 8.2 Hz, 2H, NCH_2), 7.26 (br, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 26.2, 44.6, 52.8, 126.0, 152.9, 190.3. HRMS (TOF ES$^+$): m/z calcd for $C_6H_8N_4NaO$ [(M+Na)$^+$], 175.0590; found, 175.0597. *Compound* **6j**: white solid, mp = 148.5–149 °C. IR (KBr): 3265, 2966, 2924, 2846, 1590, 1506, 1428, 1253, 1169 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 3.85 (s, 3H, CH_3O), 4.66 (t, J = 8.3 Hz, 2H, NCH_2), 5.53 (t, J = 8.3 Hz, 2H, OCH_2), 7.08 (d, J = 8.8 Hz, 2H, ArH), 8.29 (d, J = 8.8 Hz, 2H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 44.6, 55.8, 82.6, 114.0, 123.2, 129.6, 132.4, 160.8, 163.4, 182.0. HRMS (TOF ES$^+$): m/z calcd for $C_{12}H_{11}N_3NaO_3$ [(M+Na)$^+$], 268.0693; found, 268.0697. *Compound* **6k**: white solid, mp = 142–143.5 °C. IR (KBr): 3432, 2920, 1637, 1570, 1164 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 1.94 (s, 3H, CH_3), 4.20 (t, J = 8.3 Hz, 2H, NCH_2), 5.07 (t, J = 8.4 Hz, 2H, OCH_2), 6.91 (d, J = 7.9 Hz, 2H, ArH), 7.69 (d, J = 8.0 Hz, 2H, ArH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 21.1, 44.2, 82.3, 122.6, 128.9, 129.7, 133.9, 143.2, 160.4, 182.8. HRMS (TOF ES$^+$): m/z calcd for $C_{12}H_{11}N_3NaO_2$ [(M+Na)$^+$], 252.0743; found, 252.0748. *Compound* **6l**: white solid, mp = 135–137 °C. IR (KBr): 3436, 3072, 2985, 1542, 1572, 1168 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 4.67 (t, J = 8.3 Hz, 2H, NCH_2), 5.54 (t, J = 8.3 Hz, 2H, OCH_2), 7.49–7.57 (m, 2H, PhH), 7.63–7.66 (m, 2H, PhH), 8.20–8.27 (m, 1H, PhH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 44.6, 82.9, 123.0, 128.7, 129.9, 133.2, 137.0, 161.0, 183.7. HRMS (TOF ES$^+$): m/z calcd for $C_{11}H_9N_3NaO_2$ [(M+Na)$^+$], 238.0587; found, 238.0590. *Compound* **6m**: white solid; mp = 145–147 °C. IR (KBr): 3433, 2971, 1641, 1583, 1162, 1088 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 4.67 (t, J = 8.5 Hz, 2H, NCH_2), 5.55 (t, J = 8.4 Hz, 2H, OCH_2), 7.65 (d, J = 8.5 Hz, 2H, Ph), 8.26 (d, J = 8.3 Hz, 2H, Ph). ^{13}C NMR (125 MHz, DMSO-d_6): δ 44.7, 83.0, 129.0, 131.9, 135.5, 138.3, 161.1, 182.3. HRMS (TOF ES$^+$): m/z calcd for $C_{11}H_8ClN_3NaO_2$ [(M+Na)$^+$], 272.0197; found, 272.0204.
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