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Anionic [4 + 3] heteroannulation of 2-azidoacrylates: a modular synthesis of 2-benzazepin-1-ones†

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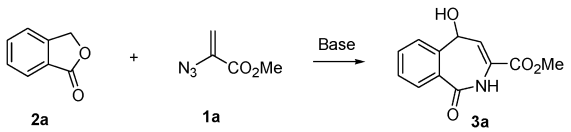
2-Azidoacrylates undergo [4 + 3] annulation with phthalides under anionic conditions at low temperatures to furnish 5-hydroxy-2-benzazepinones, the formation of which represents a new concept for the construction of azepines as well as a new reactivity of 2-azidoacrylates.

Benzazepines are regarded as privileged heterocyclic motifs in that they occur in numerous pharmacologically active synthetic molecules.[1] They are also widespread in bioactive natural products like *Ribasine* alkaloids.[2] Compounds having these motifs exhibit a range of neuroleptic and neurotropic activities.[3] Galanthamine, which features a 2-benzazepine, is now marketed as a hydrobromide salt for the treatment of neurodegenerative disorders like Alzheimer's disease.[4] Consequently, the development of practical and flexible synthetic methods for benzazepines in general is in growing demand. The literature methods for 2-benzazepines include intramolecular Mitsunobu amination,[5] ring closing metathesis,[6] Friedel–Crafts reaction,[7] Pictet–Spengler reaction,[8] Bischler–Napieralski reaction,[9] Pummerer cyclization,[10] 7-*endo*-trig radical cyclization,[11] reductive amination,[12] ring expansion,[13] 1,7-electrocyclization[14] and Heck reaction.[15]

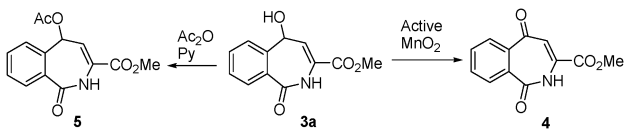
In conjunction with our interest in anionic [4 + 2] benzannulations,[16] we encountered an unprecedented result in the reaction of azidoacrylate **1a** with phthalide **2a**, which resulted in the formation of benzazepinone **3a** (Table 1). The compelling interest in the benzazepinones, the regiochemical integrity of the benzannulation[16] and the chemistry[17] of vinyl azides prompted us to scrutinize the reaction in more detail.

When methyl 2-azidoacrylate[18] (**1a**) was subjected to reaction with phthalide **2a** in the presence of *t*-BuOLi (LTB) in THF at −60 °C to rt, an intractable mixture of products was obtained along with recovered phthalide **2a**. With LDA as the base, the reaction turned deep red at −78 °C and furnished a brown solid after acidic work-up. This was purified and found to be benzazepinone **3a** (45%). There was no indication of the formation of the [4 + 2] annulation[16] product *i.e.*, 2-azido-1-naphthol. The structure of **3a** was established by analysis of the IR, NMR and HRMS data. The resonance of the –OH proton was absent in the ^{1}H NMR spectrum. To confirm its presence, benzazepinone **3a** was oxidized with active MnO_2[19] at rt to afford benzazepinedione **4** (Scheme 1). The signal of C4 hydrogen shifted downfield and appeared at δ 6.89 ppm as a sharp singlet.

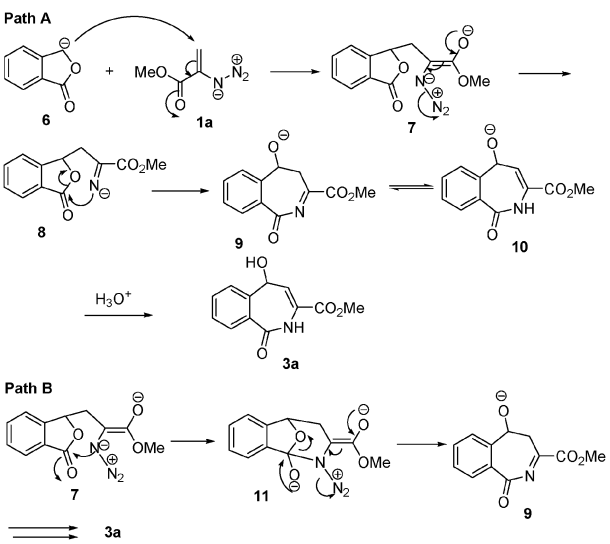
Table 1 Screening of bases for annulation



Entry	Bases	Conditions	Yield %
1	LTB/KHMDS	−60 °C to rt	0
2	LDA	−78 °C to rt	45
3	LHMDS	−78 °C to rt	90
4	NaHMDS	−78 °C to rt	13



Scheme 1 Oxidation and acetylation of azepinone **3a**.



Scheme 2 Proposed mechanism for the annulation.

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Acetylation of **3a** with acetic anhydride-pyridine accordingly afforded *O*-acetylated product **5**.

To improve the yield of the annulation reaction, KHMDS, LDA, LHMDS and NaHMDS (Table 1, entries 1–4) were examined in THF. LHMDS was found to be the most effective base with respect to the yields of the annulation.

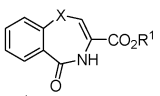
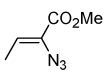
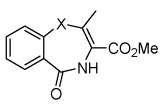
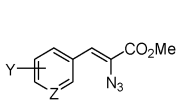
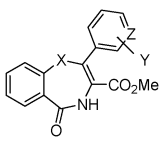
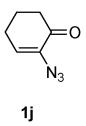
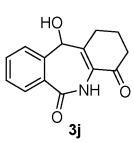
Mechanism. The formation of azepinone **3a** can be explained by the speculative mechanism shown in Scheme 2. At low temperature, the incipient phthalide anion **6** adds to azidoacrylate **1a** in Michael mode to form new anion **7**. The enolate ion **7** then expels N_2 to form imine anion **8** in a manner similar to that of 2-azido esters.[20] This, in turn, intramolecularly attacks the lactone carbonyl, resulting in the formation of 7-membered lactam **9** (Path A). Finally, protonation followed by tautomerization leads to the azepinone **3a** *via* intermediate **10**. Alternatively, the azido anion **7** can attack the lactone carbonyl to give intermediate **11**(Path B), which undergoes ring cleavage and N_2 expulsion to form **3a** *via* **9**.

Scope. In order to establish the scope of this unprecedented reaction, we examined the reactivity of ethyl-2-azidoacrylate[20] (**1b**) (Table 2, entry 1) which produced benzazepinone **3b** in 85% yield. The patterns of the spectral data of **3b** were in consonance with those of **3a**, confirming the initially proposed structure. Our next motivation was to generalize the reaction with various azidoacrylates keeping the donor phthalide invariant (Table 2). First, we considered examining methyl 2-azidocrotonate (**1c**) to increase the number of substituents in the product. Reaction of **1c** with phthalide **2a** in the presence of LHMDS produced 4-methylbenzazepinone **3c** (entry 2) as a white solid. Although its ^{1}H NMR spectrum was in accordance with the proposed structure, the ^{13}C NMR spectrum did not reveal all the expected signals. This is perhaps due to rapid equilibration with its tropylium-like cation. To further support the structure, oxidation of a sample of **3c** with MnO_2 in chloroform at rt was carried out to furnish benzazepinedione **12** (structure was confirmed by single crystal X-ray analysis, see ESI†), spectral data including ^{13}C NMR data of which conformed to the structure. To validate the structure of benzazepinone **3c** by correlation with a known compound, we attempted to reduce the olefinic bond of the azepinone ring in **12** to obtain methyl 4-methyl-1,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine-3-carboxylate.[21] But, the reduction of benzazepinone **12** with H_2/Pd–C (10%) in methanol (Scheme 3) at rt produced triply reduced benzazepinone **13** in 75% yield. Similar was the result when benzazepinone **3c** was subjected to hydrogenation. In this case, benzazepinone **13** was obtained in 85% yield.

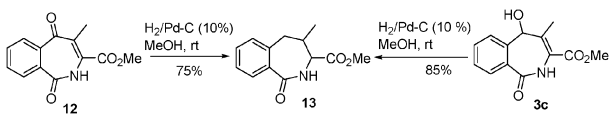
Next, we turned to the 3-arylazidoacrylates to test their applicability in the annulation. 3-Phenylazidoacrylate **1d** (Table 2, entry 3) produced the benzazepinone **3d** in 65% yield on annulation with phthalide **2a**. The structure of benzazepinone **3d** was confirmed by analysis of X-ray data.

Entries 4–7 exemplify the types of substituted aryl groups that can be placed in the azide acceptors. In all cases, the annulation products were obtained in good yields. For substituted arylazidoacrylates **1e–1h** (entries 4–7), the reactions proceeded

Table 2 [4 + 3] Heteroannulation of 2-azidoacrylates with phthalide **2a** to 2-benzazepinones

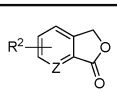
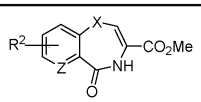
Entry	Azido acrylate	Benzazepinone	Yield %
1	 **1a** R^1 = Me, **1b** R^1 = Et	 **3a** R^1 = Me, X = CHOH; **4** R^1 = Me, X = C=O; **3b** R^1 = Et, X = CHOH	90[a], 60[b], 85[a,e]
2	 **1c**	 **3c** X = CHOH; **12**[f] X = C=O	75[a], 80[b]
3	 **1d** Y = H, Z = CH	 **3d**[f] X = CHOH; **14** X = C=O	65[a], 80[b]
4	**1e** Y = *ρ*-OMe, Z = CH	**3e** X = CHOH; **15** X = C=O	65[a], 72[b]
5	**1f** Y = *ρ*-Me, Z = CH	**3f** X = CHOH; **16** X = C=O	75[a], 78[b]
6	**1g** Y = *ρ*-Cl, Z = CH	**3g**[f] X = CHOH; **17** X = C=O	75[a], 75[b]
7	**1h** Y = *m*-NO_2, Z = CH	**3h** X = CHOH; **18** X = C=O	72[a], 80[b]
8	**1i** Y = 6-OMe, Z = N	**3i** X = CHOH; **19** X = C=O	70[d]
9	 **1j**	 **3j**	65[a]

[a] Yields of benzazepinones. [b] Yields of oxidized products. [c] MnO_2, $CHCl_3$, rt. [d] Overall yield for two steps *i.e.* annulation followed by oxidation. [e] Yield of compound **3b**. [f] X-Ray crystal data are available in ESI.



Scheme 3 Reduction of benzazepinones **3c** and **12**.

Table 3 [4 + 3] Heteroannulation of substituted phthalides with methyl 2-azidoacrylate (**1a**) to 2-benzazepinones

Entry	Phthalide	Benzazepinone	Yield %
1	 **2b** R^2 = 6-OMe, Z = CH	 **3k** X = CHOH; **20** X = C=O	68[b]
2	**2c** R^2 = 5,6-dimethoxy, Z = CH	**3l** X = CHOH	70[a]
3	**2d** R^2 = 5,6-O–CH_2–O, Z = CH	**3m** X = CHOH; **21** X = C=O	70[b]
4	**2e** R^2 = H, Z = N	**3n** X = CHOH; **22** X = C=O	57[b]

[a] Yield of benzazepinone. [b] Overall yield for two steps *i.e.* annulation followed by oxidation. [c] MnO_2, $CHCl_3$, rt.

smoothly to provide the corresponding azepinones **3e–3h** in 65, 75, 75 and 72% yields respectively. Benzazepinones **3d–3h** (entries 3–7) were fully characterized after oxidation to benzazepinediones **14–18** respectively. It appears that the substituents in the benzene ring of azidoacrylates have little effects on the outcome of the reaction. We were interested in the reactivity of 3-heteroarylazidoacrylate **1i** (entry 8) to discern whether *ortho* lithiation or nucleophilic substitution interferes the annulation. The annulation of **1i** gave regioselectively benzazepinone **3i** with intact pyridine nucleus. The hydroxy product **3i** was fully characterized after oxidation to benzazepinedione **19**. For the annulations of entries 3–8, the temperature of the reactions was maintained at −78 °C for 1.5 h after adding the azido acrylates to avoid their hydrolysis and the yields significantly increased. The annulation is also compatible with the azido cyclic ketone **1j** (entry 9). The reaction of phthalide **2a** with **1j** resulted in the formation of tricyclicazepinone **3j**, which may serve as the precursor for dibenzoazepinones.

Next we examined the reactivity of methoxy substituted phthalides with azidoacrylate **1a** (Table 3) in view of the occurrence of methoxy substitutions in natural aromatic polyketides. We were also interested in ruling out the possibility of nuclear lithiation of methoxyphthalides (**2b** and **2c**) (entries 1 and 2) under the annulation conditions. The reaction of these phthalides with **1a** afforded azepinones **3k** and **3l** respectively. The azepinone **3k** was fully characterized as its oxidized derivative **20**. The study was further extended to the reaction of phthalide **2d** with **1a** (entry 3). This annulation led to the formation of azepinone **3m**. It was oxidized to benzazepinedione **21** and then fully characterized. Since heteronuclear systems are susceptible towards nucleophilic addition, we inquisitively treated azaphthalide **2e** with azidoacrylate **1a** (entry 4). Interestingly, the reaction led to the formation of benzazepinones **3n** which were subjected to oxidation and then characterized. This method can be useful for the synthesis of pyridinoazepinones as antagonists of the nociceptin receptor, which is implicated in a plethora of diseases.[22]

In conclusion, the studies above have led to the development of a modular and regiospecific method for the synthesis of 2-benzazepinones. It relies upon a previously unreported reaction of vinyl azides. Full scope of the reaction is under further study.

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