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Catalyst-free chemo-/regio-/stereo-selective amination of alk-3-ynones. Synthesis of 1,5-benzodiazepines and 3-amino-2-alkenones†

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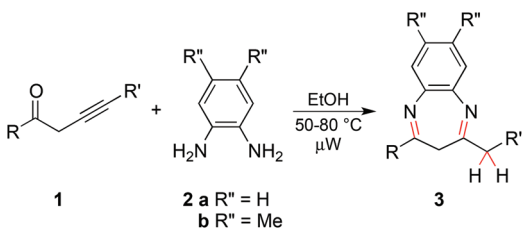
Reaction of alk-3-yn-1-ones with *o*-phenylenediamines provides an effective method with high atom economy for the synthesis of diversely substituted benzodiazepines and conjugated enaminones. This microwave-accelerated reaction proceeds in ethanol in the absence of a catalyst and leads to benzyl-substituted 1,5-benzodiazepines with good yields (70–92%). A room temperature protocol with the same set of reagents (stabilized with triethylamine) leads to enaminones (3-amino-2-alkenones, 70–99%). The tautomer formed and the regio- and stereochemistry of the process are confirmed by the X-ray crystallographic structure determination of 2-(4-methylbenzyl)-4-phenyl-3*H*-benzo[*b*][1,5]-diazepine and (*Z*)-3-[(2-amino-4,5-dimethylphenyl)amino]-4-(4-*tert*-butylphenyl)-1-(4-chlorophenyl)but-2-en-1-one.

Diazepines are known for their pharmaceutical applications and commercial success.[1] Derivatives of this seven-membered ring system exhibit a wide range of biological activities. Among them, the 1,5-benzodiazepines have received less attention than other homologs.[2] An example of active 1,5-benzodiazepines includes the widely prescribed antioxidant and anticonvulsant medication, Clobazam.[3] Due to their potential in pharmaceutical or materials chemistry, new synthetic methods for producing new homologs of benzodiazepines are of considerable interest.[4]

The most commonly used strategies for the synthesis of 1,5-benzodiazepines include cyclocondensation reactions of *o*-phenylenediamines with 1,3-dicarbonyl compounds, 3-haloalk-2-enones, and alk-2-ynones.[5,6] A more straightforward and recent protocol includes *in situ* generation of an alk-2-ynone (from acyl chloride and terminal alkyne *via* a palladium catalyzed cross-coupling). Subsequent addition of the *o*-phenylenediamine occurs in water or in acetic acid/THF, both at 100 °C and involves conjugate addition to an activated alkyne.[4,7] While these methods provide access to benzodiazepines, our interests were directed to improving the sustainability of synthesis of these pharmaceutically important structures. Thus we turned our attention to amination reactions, which are of particular significance.[8] Starting from readily accessible substrates such as alkynes, the hydroamination offers an atom-efficient pathway towards formation of a C–N or C=N bond, but proceeds mostly with the use of a catalyst.[8]

Alk-3-ynones (propargyl ketones, **1**),[9] which could formally be viewed as containing an isolated alkyne function, represent versatile bifunctional materials for the synthesis of heterocycles. Their cycloisomerization or related electrophilic cyclization reactions lead to substituted furans,[10] halofurans,[11] and pyrazoles.[12] Building on the observation of a hydrazination reaction in the latter case, we envisioned the synthesis of 1,5-benzodiazepines as a reaction of alk-3-ynone **1** with *o*-phenylenediamine **2**.

A non-catalytic preparative synthesis for a series of 1,5-benzodiazepines **3** was developed as illustrated in Scheme 1. The reactions were carried out in reagent grade ethanol, usually at 80 °C (1 h), using microwave heating. The process also progresses in the presence of water, but is less selective; water serves as a heat transfer medium due to solubility



Scheme 1 The synthesis of 1,5-diazepines **3** from alk-3-ynones **1** and *o*-phenylenediamines **2**.

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†Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra for diazepines **3**, enaminones **4** and **6**, and cif files for **3aa** and **4cb**. CCDC 929588 and 950049. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3gc41898g

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Table 1 Preparation of 1,5-benzodiazepines **3** from alkynones **1**

Entry	Ynone	R	R′	R″	Product	Yield[a] [%]
1	**1a**	Ph	*p*-MeC_6H_4	H	**3aa**	87
2	**1a**	Ph	*p*-MeC_6H_4	Me	**3ab**	88
3	**1b**	*p*-BrC_6H_4	*p*-MeC_6H_4	H	**3ba**	87
4	**1b**	*p*-BrC_6H_4	*p*-MeC_6H_4	Me	**3bb**	90
5	**1c**	*p*-ClC_6H_4	*p*-*t*-BuC_6H_4	H	**3ca**	92
6	**1c**	*p*-ClC_6H_4	*p*-*t*-BuC_6H_4	Me	**3cb**	80
7	**1d**	Et	Ph	H	**3da**	77[b]
8	**1d**	Et	Ph	Me	**3db**	70[b]

[a] Isolated yield; reactions were carried out in a microwave vial on a 1.0 mmol scale with 1.05 equiv. of diamine, in ethanol, at 80 °C, reaction time 2 h, unless referenced otherwise. [b] At 50 °C, reaction time 12 min.

problems. The products were isolated using silica gel column chromatography (or crystallization). Although we focused on aryl/benzyl-substituted diazepines (entries 1–6), ethyl/benzyl compounds were also introduced (entries 7 and 8). With this substituents the reaction required only 50 °C and 12 min (microwave acceleration). Such an outcome can be attributed to increased reactivity of a carbonyl group in an alkyl-substituted ketone **1d**. In the absence of a catalyst the reaction proceeded in almost quantitative yields, as determined by GC/MS. Results from the reaction of ketones **1** with *o*-phenylenediamine **2a** and its 4,5-dimethyl homolog **2b** are provided in Table 1.[13]

The structure of the new benzodiazepines was confirmed by NMR and MS. The characteristic NMR features for aryl-substituted diazepines **3aa–cb** include the ^{1}H H–3 and CH_2Ar (benzyl) signals (C_6D_6, 2.93–2.72 and 3.66–3.58 ppm) and ^{13}C C=N signals (160.6.3–151.7 ppm). Intense molecular ions and accurate HRMS M + H^+ peaks were observed in the mass spectra for **3**.

As the NMR data indicate, we observed only formation of the commonly predominant diimine (3*H*) tautomeric form.[4,6,14] This observation was confirmed by X-ray crystallography.[15] The structure of *p*-methylbenzyl-1,5-benzodiazepine **3aa** is shown in Fig. 1.

To gain insight into the mechanistic details and to compare the reactivity of the carbonyl and alkyne functions, the reaction was carried out at room temperature (22 °C, EtOH). The reaction of alkynones **1** with monoamines yielding enaminones (3-amino-2-alkenones) **4** has been reported earlier, supported by limited spectroscopic data.[16] When aliphatic diamines have been used, linked bis-enaminones were obtained.

The enaminones represent useful building blocks for the synthesis of a variety of heterocyclic compounds.[17–19] Their therapeutic potential has also been recognized.[20] The available methods for the preparation of enaminones have been elegantly summarized by Katritzky.[17,19g] The majority of methods directed at the construction of the C–N bond lack regioselectivity or show numerous limitations including moderate yields.

Our initial results indicated almost quantitative formation of monoenaminones, as determined by GC/MS (*vide infra*) and NMR. However, further examination of the post-reaction

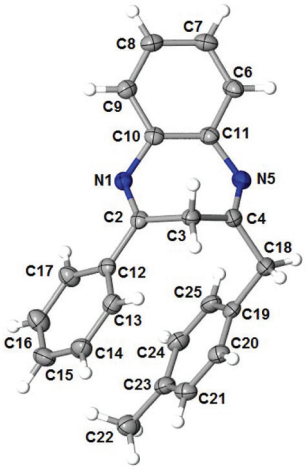
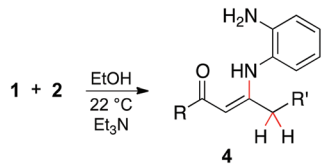


Fig. 1 An ORTEP view of the **3aa** illustrating atom labeling scheme and thermal ellipsoids (50% probability level). Selected interatomic distances (Å): N1–C2 1.288(3), N1–C10 1.412(3), C2–C3 1.520(3), C3–C4 1.505(3), C4–N5 1.283(3), C4–C18, 1.515(3), N5–C11 1.404(3), C10–C11 1.420(3). Key angles (°): C2–N1–C10, 121.95(17), N1–C2–C3 120.21(18), C2–C3–C4 106.32(16), C3–C4–N5 123.08(19), C4–N5–C11 120.25(18), N5–C11–C10 125.55(18), N1–C10–C11 124.86(17).



Scheme 2 Synthesis of enaminones **4**.

mixtures occasionally revealed the presence of diazepines or decomposition products (as determined by NMR). Due to their limited stability, isolation of enaminones has become problematic. Thus, concluding that traces of acids may accelerate the imination/cyclization reaction as well as product protonation processes, triethylamine (2 equiv.) was added to the reaction mixture (Scheme 2). Such modification resulted in near quantitative formation of enaminones **4**. The use of triethylamine is not required to facilitate the reaction, but is preparatively advantageous, enabling reproducibility and effective isolation.[21] In the most successful case, the reaction of ketone **1a** with diamine **2b** (ethanol, 22 °C, 2 h) proceeded with quantitative yield (Table 2, entry 2). Removal of volatiles from the post-reaction mixture was sufficient to obtain enaminone **4ab** with reasonable purity as indicated by NMR (see ESI†). Other enaminones **4** (entries 1, 3–6) were isolated *via* crystallization.[22]

The characteristic NMR signals for enaminones **4** include the ^{1}H NH and NH_2 (13.08–12.99 and 3.10–2.85 ppm), H–2 (=CH) and H–4 (CH_2Ar) signals (6.04–5.82 and 3.49–3.40 ppm); ^{13}C C–3 (=C–N) and C–4 (CH_2Ar) signals (168.4–166.6 and 39.2–38.3 ppm). Monitoring the reaction using GC/MS may be misleading since elevated injector/column temperature leads to the cyclization reaction and frequently the base peak

Table 2 Preparation of enaminones **4** from alkynones **1**

Entry	Ynone	R	R′	R″	Product	Yield[a] [%]
1	**1a**	Ph	*p*-MeC_6H_4	H	**4aa**	85
2	**1a**	Ph	*p*-MeC_6H_4	Me	**4ab**	>99[b]
3	**1b**	*p*-BrC_6H_4	*p*-MeC_6H_4	H	**4ba**	70
4	**1b**	*p*-BrC_6H_4	*p*-MeC_6H_4	Me	**4bb**	83
5	**1c**	*p*-ClC_6H_4	*p*-*t*-BuC_6H_4	H	**4ca**	70
6	**1c**	*p*-ClC_6H_4	*p*-*t*-BuC_6H_4	Me	**4cb**	93

[a] Isolated yield; reactions were carried out on a 0.18 mmol scale with 1.0 equiv. of diamine, 2 equiv. of triethylamine, in ethanol, at 22 °C, reaction time 2 h. [b] Without recrystallization.

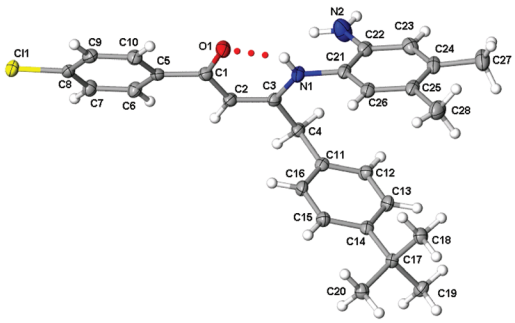


Fig. 2 An ORTEP view of the **4cb** illustrating atom labeling scheme and thermal ellipsoids (50% probability level). Selected interatomic distances (Å): O1–C1 1.2588(19), C1–C2 1.420(2), C2–C3 1.373(2), C3–C4 1.509(2), N1–C3 1.338(2), O1–N1 2.6520(17). Key angles (°): O1–C1–C2 122.31(14), C1–C2–C3 124.15(15), C2–C3–C4 120.96(14), C2–C3–N1 121.62(15), N1–C3–C4 117.37(13), C3–C4–C11 111.38(13), C3–N1–C21 125.65(13).

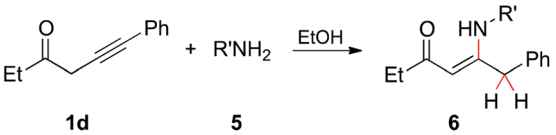
corresponding to $[M - H_2O]^+$ (diazepine) is observed as the highest *m*/*z* ion.

We observed almost exclusive formation of the *Z* isomer presumably due to hydrogen-bond stabilization. Predominance of this stereoisomer has also been observed in other synthetic investigations.[19g,23] Its structure was confirmed with the use of X-ray crystallography (Fig. 2).[15]

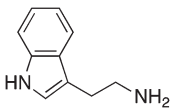
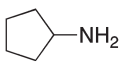
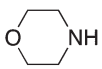
The reaction of alkynone decorated with an ethyl group **1d** proceeds effectively to benzodiazepines **3d**; thus far we have not been able to isolate enaminones **4d** when diamines were used. To monitor the formation of enaminones, and to confirm reactivity of alkyl substituted alkynones, compound **1d** was combined with a variety of monoamines **5**.[16] Such an approach excluded the forthcoming cyclization reaction. Anilines (entries 1 and 2), primary (entries 3–5), and secondary (entries 6 and 7) aliphatic amines gave corresponding enaminones **6a–g** in high yield (Table 3). For aliphatic amines the reaction was completed at 50 °C after 5 min and for aromatic amines at 45 °C after 2–4 h, all using microwave irradiation. The analytically pure products with aliphatic amines **6c–g** were isolated after rinsing with a water etheral solution of the post reaction mixture.

Presumably the reaction mechanism includes the initial formation of allene **7** corresponding to alk-3-ynone **1**, which would subsequently undergo conjugate addition and isomerization to a conjugated enaminone **4** (Scheme 3). Comparable sequence

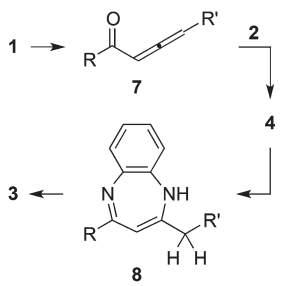
Table 3 Preparation of enaminones **6** from alkynones **1d** and monoamines **5**



1d **5** **6**

Entry	Monoamine **5**	Product	Temp [°C]	Time	Yield[a] [%]
1	$C_6H_5NH_2$	**6a**	45	2.5 h	93
2	*p*-$ClC_6H_4NH_2$	**6b**	45	4 h	92
3	$C_6H_5CH_2NH_2$	**6c**	50	5 min	85
4		**6d**	50	5 min	97
5		**6e**	50	5 min	85
6		**6f**	50	5 min	93
7		**6g**	50	5 min	97

[a] Isolated yield; reactions were carried out on a 1.0 mmol scale with 1.05 equiv. of amine, in ethanol.



Scheme 3 Mechanistic outline for the synthesis of diazepines **3**.

via initial isomerization of **1** to alk-2-ynone (not illustrated) can also be considered. Consecutive formation of an imine in an intramolecular cyclization reaction and isomerization of vinamidine form **8**, driven by higher stability of the C=N bond, lead to the final product **3** (Scheme 3). Alkyne reaction and accompanying hydrogen migrations proceed at room temperature, while reaction of the carbonyl group requires an elevated temperature thus allowing for chemoselectivity. Although a sequence involving anti-Markovnikov direct hydroamination of alkyne **1** (not illustrated) cannot be excluded, such a pathway is less likely since the formation of the C–N bond proceeds under very mild and non-catalytic conditions. Solvent-free intramolecular cyclization of the pure isolated enaminone **4aa** proceeded to benzodiazepine **3aa** at the melting point temperature indicating that the reaction is thermal.

In summary, we have demonstrated that the combination of an amination reaction with subsequent condensation

provides an effective access to diverse 2,4-disubstituted 1,5-benzodiazepines. The methodology allows introduction of benzyl-type substituents at the C-2 position of benzodiazepine that is not easily carried out by currently available methods. The catalyst-free conditions provide an appealing protocol that includes formation of two C=N bonds and does not require the isolation of the enaminone. The overall formal amination reaction proceeds with anti-Markovnikov regiochemistry relative to the initial alkyne bond. With a high degree of rearrangement, this reaction provides a convenient and temperature-controlled synthetic method for the synthesis of benzodiazepines and enaminones. En route, enaminones with the stereoselective positioning of *o*-phenylenediamine across the double bond can be manufactured with no need to protect the second amino function. Determination of scope of the reaction with alkyl-only substituted ketones **1** is the subject of further investigation in our laboratory. The major advantages of the reported protocol as a sustainable process are as follows: (i) the reaction does not require the presence of any catalyst; (ii) it proceeds with high (over 90%) atom economy; (iii) no organic or inorganic waste is produced; the only by-product, water, is easily miscible with the solvent applied; thus its removal does not require an extra separation step; (iv) ethanol is the greenest solvent possible for the reaction due to the solubility of aromatic starting materials and products. The use of reagent grade ethanol, which is an easily recoverable and recyclable solvent, ensures that no moisture-free reaction conditions are necessary; (v) the reaction occurs with high yields and selectivity; (vi) the reaction is a low energy consumption process; it either occurs at ambient temperature (enaminones) or with a moderate temperature microwave irradiation (benzodiazepines). In fact, with the appropriate selection of the activation method, the formation of the desired product can be easily achieved; (vii) finally, the reaction occurs *via* a step-by-step mechanism that allows an easy and selective preparation of diverse compounds from the same starting materials.

Acknowledgements

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13 Representative procedure. Synthesis of benzodiazepine **3bb**. A 10 mL round bottom microwave vial equipped with a stir bar was charged with alkynone **1b** (0.222 g, 0.709 mmol), 4,5-dimethyl-1,2-phenylenediamine **2b** (0.101 g, 0.745 mmol), and ethanol (2 mL). The vial was sealed and the reaction was irradiated in the microwave reactor at 80 °C for 1 h. The solvent was removed by rotary evaporation. Crystallization (methanol) gave **3bb** as a white solid (0.246 g, 0.571 mmol, 81%). Silica gel column chromatography of the filtrate (20 × 2.5 cm; hexanes–ethyl acetate 80 : 20) gave a yellowish fraction. The solvent was removed by rotary evaporation and the residue was dried by oil pump vacuum to give **3bb** as a colorless solid (second crop 0.028 g, 0.064 mmol; total 0.274 g, 0.635 mmol, 90%): mp 174–175 °C. MS (EI, *m*/*z*): 430 (M^+, 100%), 415 ($M - CH_3^+$, 58%), 275 ($M - C_6H_4Br^+$, 40%), 246 ($M - C_8H_7 - Br^+$, 24%), 105 ($C_8H_9^+$, 24%). HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{25}H_{24}BrN_2$ 431.1123, found 431.1122. IR (cm^{-1}, solid): 1630 m, 1613 m, 1484 s, 1308 s, 1098 m, 1087 s, 1007 s, 884 s, 809 s. NMR (C_6D_6, δ): ^1H: 7.60 (s, 1H), 7.55 (s, 1H), 7.34 (AA′XX′, 2H, J = 8.6 Hz), 7.14 (AA′XX′, 2H, J = 8.7 Hz), 6.80 (AA′XX′, 2H, J = 7.9 Hz), 6.68 (AA′XX′, 2H, J = 7.8 Hz), 3.62 (s, 2H), 2.78 (br s, 2H), 2.10 (s, 6H), 2.05 (s, 3H); ^{13}C: 158.2, 151.9, 139.6, 139.1, 136.7, 136.3, 134.6, 134.3, 133.2, 131.4 (2C), 130.1(2C), 129.8, 129.8(2C), 129.5(2C), 129.4, 124.6, 47.0, 36.0, 21.0, 19.5, 19.4.

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15 Crystals of **3aa** and **4cb** were grown from the ethyl acetate–hexanes by layering. CCDC 929588 and 950049 contain the supplementary crystallographic data for this paper.

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22 Representative procedure. Synthesis of enaminone **4ab**. A 50 mL round bottom flask equipped with a stir bar was charged with **1a** (0.0464 g, 0.198 mmol), 4,5-dimethyl-1,2–phenylenediamine **2b** (0.062 g, 0.20 mmol), triethylamine (0.06 mL, 0.43 mmol), and ethanol (8 mL). The reaction mixture was stirred for 2 h at rt. The solvent was removed by rotary evaporation and the residue was dried by oil pump vacuum for 2 h to give a yellow solid (0.0733 g, 0.198 mmol, >99%), mp 111–112 °C. MS (EI, *m*/*z*): 352 ($[M - H_2O]^+$, 100%), 337 ($[M - H_2O - CH_3]^+$, 35%). HRMS (ESI-TOF) $[M + H]^+$ calcd for $C_{25}H_{27}N_2O$ 371.2123, found 371.2123. IR (cm^{-1}, solid) 3420 w, 3400 w, 1637 w, 1591 m, 1571 s, 1532 s, 1502 m, 1481 m, 734 s, 508 s. NMR (C_6D_6, δ): ^1H: 13.07 (s, 1H), 8.17–8.14 (m, 2H), 7.14–7.12 (m, 3H), 6.94 (d, 2H, J = 8.2 Hz), 6.90 (d, 2H, J = 8.1 Hz), 6.46 (s, 1H), 6.09 (s, 1H), 6.04 (s, 1H), 3.49 (s, 2H), 3.02 (br s, 2H), 2.08 (s, 3H), 1.97 (s, 3H), 1.89 (s, 3H); ^{13}C: 188.8, 167.1, 140.9, 140.6, 136.0, 135.8, 134.1, 130.6, 129.2, 129.1(2C), 129.0(2C), 128.2(2C), 127.4(2C), 125.6, 121.8, 117.0, 93.6, 38.3, 20.7, 19.1, 18.3.

23 See for example: A. Jezierska, L. B. Jerzykiewicz, J. Kołodziejczak and J. M. Sobczak, *J. Mol. Struct.*, 2007, **839**, 33–40.

