



Synthesis of 3-aryl substituted benzo[1,2,5]triazepin-4-ones via intramolecular imine formation

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ABSTRACT

3-Aryl substituted benzo[1,2,5]triazepin-4-ones and their pyrido counterparts have been synthesized in five steps from commercially available starting materials. The key step involves base-induced cleavage of trifluoroacetyl-protected hydrazine intermediates and in situ intramolecular imine formation.

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The benzodiazepinone scaffold (**A**, Fig. 1) has emerged over the years as an extremely rewarding template for drug discovery.^{1,2} Besides the widely used sedative diazepam, benzodiazepinones have shown promise for treating a variety of conditions, including ventricular arrhythmia,³ rheumatoid arthritis,⁴ obesity,⁵ migraine,⁶ and Alzheimer's disease (AD).⁷ Compounds possessing a benzo [1,2,5]triazepine core (**B**) also display significant activities against an array of molecular targets,⁸ such as the dopamine D-1 and serotonin (5HT) receptors^{9,10} and the reverse transcriptase of HIV-1.¹¹

Although several methods for constructing benzotriazepines can be found in the literature,¹² the related benzotriazepinones (**C**) have only received scant attention.^{13,14} Members of the latter class were first prepared by Rossi and co-workers using cyclization of diazonium salts derived from acyl-*o*-phenylenediamines.¹³ While the yields of benzotriazepinones are generally high, the preparation of diazonium salts is an obvious inconvenience, especially on a large scale. An alternative, more recent approach relies on the dehydrative cyclization of *N*-(*o*-aminoaryl) succinate or malonate hydrazones.^{14a,b} However, this approach is limited with regard to the nature of the C3-substituent due to competing 1,2,4-triazine formation.^{14b,c} Hence there is a need for new methodology that would allow access to a range of custom-designed benzotriazepinones from readily available precursors.

Of particular interest to us were the hitherto unknown 3-aryl-substituted benzo and pyrido[1,2,5]triazepin-4-ones (**1**). Earlier attempts to prepare such compounds by Kodato and co-workers have failed due to competing 6-*endo-trig* cyclization of the hydra-

zone intermediates.¹⁵ Here we report a successful strategy for constructing **1** based on the retrosynthetic analysis outlined in Scheme 1. Assemblage of the triazepinone ring was envisioned by intramolecular imine formation of hydrazine α -ketoamides **2** which would arise from halonitroaromatics **4** by S_NAr substitution (cf. **4**→**3**), reduction of the nitro group, α -ketoamide formation, and removal of the *N*-protecting group (PG).

Initial efforts to probe the feasibility of this pathway established that the trifluoroacetyl group was a good choice for hydrazine protection (vide infra). The preparation of the requisite trifluoroacetylhydrazines (cf. **3a–d**) was readily achieved from commercially available chloro or fluoro nitroaromatics (**4a–d**), by conversion to the corresponding methylhydrazines (**5a–d**)¹⁶ and ensuing reaction with trifluoroacetic anhydride in the presence of Hünig's base (Table 1).

Chemoselective reduction of the nitro group in **3** was achieved with over 90% efficiency by reaction with hydrogen in the presence of Adam's catalyst in toluene (Table 2). Keeping reaction times short, by monitoring amine formation with LC–MS, proved essential due to the instability of the resulting amine products, attributed to their propensity of undergoing cyclization to triazines.^{16b,17} The crude

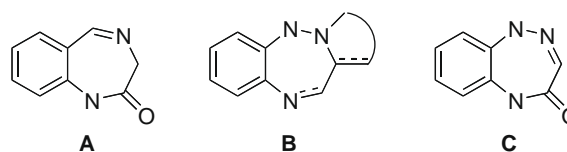
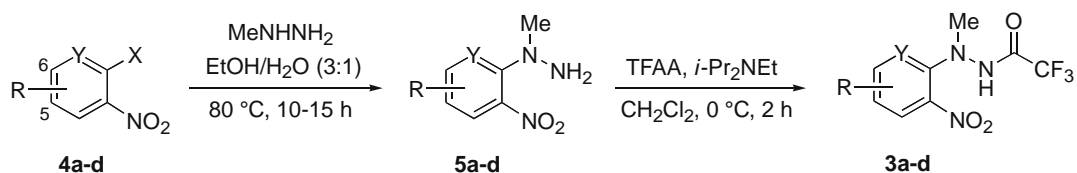


Figure 1. Scaffolds A–C.

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Table 1
Synthesis of aromatic trifluoroacetylhydrazines

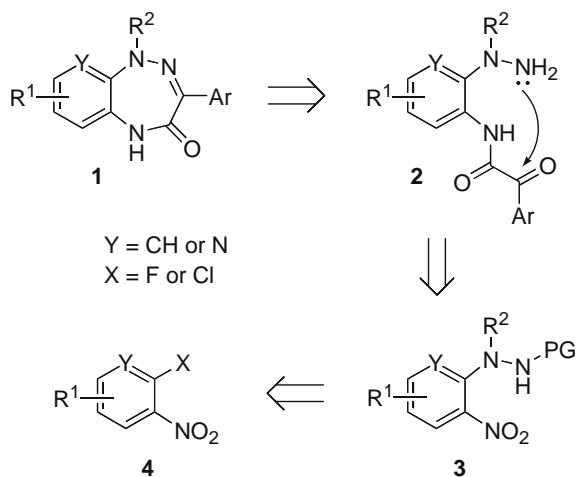


Entry	Substrate	R	X	Y	% Yield ^a of 5	% Yield ^a of 3
1	4a	H	Cl	CH	94 (5a)	77 (3a)
2	4b	5-CF ₃	F	CH	93 (5b)	95 (3b)
3	4c	6-Me	F	CH	82 (5c)	93 (3c)
4	4d	H	Cl	N	75 (5d)	92 (3d)

^a Yields refer to chromatographically isolated products.

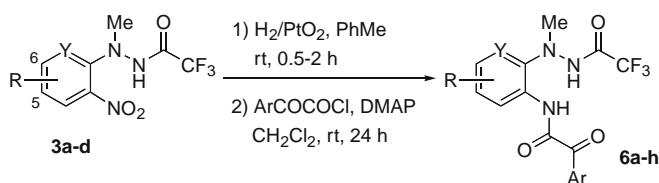
amines were immediately transformed to the desired α -ketoamides by reaction with the appropriate α -ketoacid chloride, prepared in situ from the corresponding α -ketoacid and thionyl chloride. Using this simple procedure,¹⁸ a range of α -ketoamides (**6a–h**) were obtained in good to excellent yields (Table 2).

Exposure of the α -ketoamides to potassium carbonate in MeOH/H₂O at room temperature accomplished both removal of the trifluoroacetyl group and intramolecular imine formation to



Scheme 1. Retrosynthetic analysis of **1**.

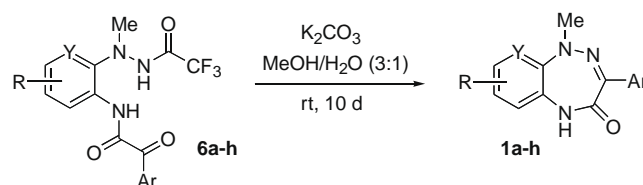
Table 2
Synthesis of α -ketoamides



Entry	Substrate	R	Y	Ar	% Yield ^a of 6
1	3a	H	CH	Ph	84 (6a)
2	3a	H	CH	2-Furyl	75 (6b)
3	3a	H	CH	2-Thienyl	78 (6c)
4	3b	5-CF ₃	CH	Ph	99 (6d)
5	3c	6-Me	CH	Ph	90 (6e)
6	3d	H	N	Ph	95 (6f)
7	3d	H	N	2-Furyl	91 (6g)
8	3d	H	N	2-Thienyl	96 (6h)

^a Overall yields of chromatographically isolated products after two steps.

Table 3
Synthesis of benzo and pyridotriazepinones



Product	% Yield ^a
	73 (1a)
	55 (1b)
	46 (1c)
	57 (1d)
	52 (1e)
	76 (1f)
	33 (1g)
	38 (1h)

^a Yields refer to chromatographically isolated products of over 98% purity (HPLC).

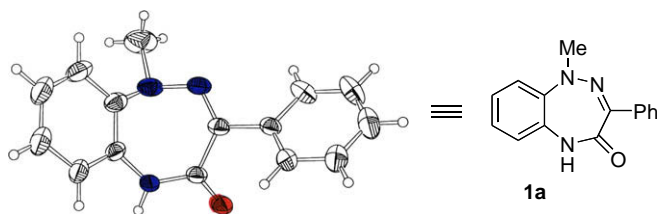


Figure 2. X-ray structure of benzotriazepinone **1a**.

furnish the desired benzotriazepinones in yields of 33–76% after purification by preparative HPLC (Table 3).¹⁹ The products (**1a–h**) were readily identified by the characteristic ¹³C NMR signal of the carbonyl carbon at ca. 163–166 ppm.²⁰ As all of these compounds were crystalline, we were able to secure irrefutable proof for the proposed structures by performing X-ray diffraction analysis of benzotriazepinone **1a** (Fig. 2).²¹

Finally, it is worth mentioning that the choice of trifluoroacetyl group for protecting the hydrazine moiety proved crucial for success of the final step in the synthesis (cf. **6**→**1**). Attempts to transform either the Boc or Fmoc-protected analogues of **6a** to triazepinone **1a** under acidic or basic conditions, respectively, led to complex mixtures in which none of the desired product could be detected by LC–MS.

In summary, a convenient synthesis of the previously unknown 3-aryl-substituted benzo and pyrido[1,2,5]triazepin-4-ones has been developed. The key step involves one-pot deprotection-intramolecular imine formation of trifluoroacetylhydrazines **6**, which are prepared in four straightforward steps from commercial starting materials. Efforts aimed at establishing shorter versions of this pathway are currently underway.

Acknowledgments

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- Typical procedure:** Preparation of α -ketoamide **6d**. To a solution of trifluoroacetylhydrazide **3b** (1.050 g, 3.02 mmol) in toluene (20 mL), Adam's catalyst (PtO₂, 99.92 mg, 0.44 mmol) was added and the mixture was shaken under hydrogen (50 psi) for 2 h. The reaction mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The resulting crude aniline product was used in the next step without purification. In a separate flask, thionyl chloride (0.20 mL, 2.72 mmol) was added to a stirred solution of DMAP (0.332 g, 2.72 mmol) in CH₂Cl₂ (10 mL) at –20 °C under nitrogen. To this mixture, a solution of 2-oxo-2-phenylacetic acid (0.353 g, 2.35 mmol) in CH₂Cl₂ (10 mL) was added and the mixture was slowly warmed to rt and stirred for a further 3 h. Then DMAP (0.332 g, 2.72 mmol) and a solution of crude aniline (0.545 g, 1.81 mmol) in CH₂Cl₂ (3 mL) were successively added and the resulting mixture was stirred at rt for 24 h. After quenching with water, the aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic layers were washed with brine, dried (Na₂SO₄), and the volatiles were removed under reduced pressure. Purification of the residue by reverse phase preparative HPLC (gradient 30–50% CH₃CN in H₂O containing 10 mM NH₄HCO₃ and 0.375% NH₄OH v/v) afforded α -ketoamide **6d** (0.783 g, 99%) as a light yellow solid (mp 168–170 °C); ¹H NMR (400 MHz, CDCl₃) δ 3.16 (s, 3H), 7.39–7.55 (m, 4H), 7.64 (t, *J* = 7.42 Hz, 1H), 8.01 (s, 1H), 8.34 (d, *J* = 7.42 Hz, 2H), 8.82 (d, *J* = 1.95 Hz, 1H), 10.13 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 43.9, 105.0, 118.6 (q, *J* = 2 Hz), 119.5, 122.2 (q, *J* = 2 Hz), 128.8, 129.5 (q, *J* = 227 Hz), 131.5, 133.3 (q, *J* = 134 Hz), 135.0, 135.4, 139.1, 141.3, 154.6, 160.3, 186.9. HRMS (ESI, MH⁺) *m/z* 434.0938 (calcd for C₁₈H₁₄F₆N₃O₃: 434.0934).
- Typical procedure:** Preparation of benzotriazepinone **1a**. A mixture of α -ketoamide **6a** (20.9 mg, 0.55 mmol) and potassium carbonate (38.0 mg, 0.275 mmol) in MeOH (1 mL) and water (0.3 mL) was stirred at rt for 10 days. The volatiles were evaporated under reduced pressure and water (5 mL) was added. The aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL) and the combined organic layers were washed with brine, dried (MgSO₄), filtered, and the solvent was evaporated under reduced pressure. The residue was purified by reverse phase preparative HPLC (10–30% MeCN/water containing 0.05% TFA) giving **1a** (10.1 mg, 73%) as yellow crystals, mp 181–183 °C; ¹H NMR (400 MHz, CD₃OD) δ ppm 3.25 (s, 3H), 7.06–7.22 (m, 3H), 7.28–7.43 (m, 4H), 7.67–7.73 (m, 2H); ¹³C NMR (100 MHz, CD₃OD) δ ppm 41.1, 117.8, 121.4, 125.2, 125.3, 127.6, 128.1, 130.1, 132.4, 133.4, 145.8, 157.3, 166.2; HRMS (ESI, MH⁺) *m/z* 252.1130 (calcd for C₁₅H₁₄N₃O: 252.1131).
- Data for three other benzotriazepinones: Compound 1d:** yellow crystals, mp 180–181 °C; ¹H NMR (400 MHz, CDCl₃) δ 3.32 (s, 3H), 7.16–7.47 (m, 6H), 7.71–7.92 (m, 2H), 9.71 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 42.2, 118.5, 118.8 (q, *J* = 4 Hz), 122.8 (q, *J* = 4 Hz), 126.1 (q, *J* = 270 Hz), 127.9, 128.1, 128.6, 130.8, 132.4, 132.8, 148.2, 157.1, 166.3; HRMS (ESI, MH⁺) *m/z* 320.1010 (calcd for C₁₆H₁₃F₃N₃O 320.1005). **Compound 1f:** yellow crystals, mp 140–142 °C; ¹H NMR (400 MHz, CD₃OD) δ 3.33 (s, 3H), 7.11 (dd, *J* = 7.81, 1.95 Hz, 1H), 7.30–7.40 (m, 3H), 7.43 (dd, *J* = 7.81, 1.95 Hz, 1H), 7.65–7.72 (m, 2H), 8.06 (dd, *J* = 4.88, 1.95 Hz, 1H), 8.52 (s, 1H); ¹³C NMR (100 MHz, CD₃OD) δ 40.0, 120.7, 127.2, 127.6, 128.1, 129.4, 130.1, 133.4, 143.0, 155.2, 156.4, 165.6; HRMS (ESI, MH⁺) *m/z* 253.1084 (calcd for C₁₄H₁₃N₃O 253.1084). **Compound 1h:** orange crystals; ¹H NMR (400 MHz, CDCl₃) δ 3.39 (s, 3H), 6.95–7.05 (m, 2H), 7.26–7.35 (m, 2H), 7.57 (d, *J* = 2.73 Hz, 1H), 8.11 (dd, *J* = 4.69, 1.56 Hz, 1H), 8.52 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 41.1, 120.6, 126.0, 127.7, 129.1, 129.2, 130.1, 137.1, 143.9, 149.9, 155.1, 164.1; HRMS (ESI, MH⁺) *m/z* 259.0646 (calcd for C₁₂H₁₁N₄O 259.0648).
- CCDC 677004 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk/deposit>.