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Simple and one-pot synthesis of tri and tetracyclic frameworks containing [1,8]naphthyridin-2-one moiety from the Baylis–Hillman adducts

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ABSTRACT

A facile synthesis of tri and tetracyclic frameworks containing [1,8]naphthyridin-2-one skeleton from the Baylis–Hillman alcohols via the Johnson–Claisen rearrangement, followed by the treatment with Fe/AcOH in simple one-pot multi-step process is described.

1. Introduction

The Baylis–Hillman reaction has been and continues to attract the attention of synthetic chemists as it provides a variety of densely functionalized molecules via the coupling of α-position of activated alkenes with electrophiles under the influence of a catalyst/catalytic system in operationally simple one-pot procedure.[1,2] Applications of these multifunctional molecules, which are normally referred to as the Baylis–Hillman adducts, have been well documented in various organic transformation methodologies.[1,2]

The [1,8]naphthyridine derivatives[3–5] represent an important class of molecules, which are found to possess interesting biological properties, such as antiinflammatory,[4a,b] analgesic,[4a] antiaggressive,[4b] anticancer,[4c] antibacterial,[4d] antitumor,[4e] antihypertensive,[4f] antiallergitic,[4g] antimalarial,[4h] and also they are found to be potential diuretic agents.[4i] Therefore, there has been increasing interest in developing facile methodologies for synthesis of [1,8]naphthyridine framework of medicinal relevance.[5–7] In continuation of our interest in the development of Baylis–Hillman adducts[8] as a valuable source for various interesting methodologies and also for one-pot multi-step synthesis we, herein, report a facile one-pot synthesis of tri and tetracyclic systems containing [1,8]naphthyridin-2-one framework starting from the Baylis–Hillman (B–H) adducts, derived from 2-nitrobenzaldehydes/1-nitro-2-naphthaldehyde and acrylonitrile.

2. Results and discussion

Most of the known methodologies for synthesis of [1,8]naphthyridine framework employ either 2-aminopyridine or 2-halopyridine derivatives[5] as the key starting materials. In the year 1963 Junek reported an interesting synthesis of [1,8]naphthyridine framework via the condensation of 2-nitrobenzaldehydes with appropriate malononitrile derivatives followed by reduction of the nitro group and subsequent cyclization providing the desired [1,8]naphthyridine framework.[6] Batra and co-workers also used similar type of cyclization for the synthesis of fused polycyclic quinolines from the acetates of B-H alcohols, derived from 2-nitrobenzaldehydes.[9] Our research group[10] has, a few years ago, described the Johnson–Claisen rearrangement of Baylis–Hillman alcohols obtained from various aldehydes and acrylonitrile providing 4-cyanoalk-4-enoates with exclusive (*Z*)-selectivity in good yields. Recently we have also developed a convenient methodology for facile transformation of the Baylis–Hillman adducts derived from 2-nitrobenzaldehydes and cyclohex-2-enones into tetrahydroacridine derivatives.[8e] Since the benzo[*b*][1,8]-naphthyridine moiety (**A**) is nothing but aza version of acridine skeleton (**B**) (Fig. 1) we became interested in developing a simple synthetic protocol for obtaining such derivatives from the Baylis–Hillman adducts.

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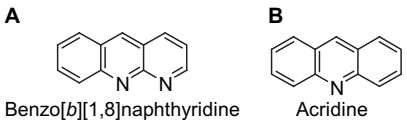
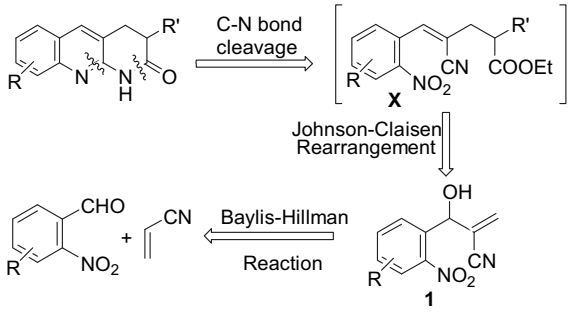


Figure 1. Benzo[*b*][1,8]naphthyridine (**A**) and acridine (**B**) frameworks.

From our experience on the synthesis of heterocyclic compounds using the Baylis–Hillman adducts,[8a–j] it occurred to us that the products (**X**) obtained via the Johnson–Claisen rearrangement of Baylis–Hillman alcohols (**1**), derived from 2-nitrobenzaldehydes and acrylonitrile, could serve as appropriate synthons for the synthesis of benzo[*b*][1,8]naphthyridin-2-one framework through reductive cyclization protocol. We also felt that all these steps, in principle, can be performed in one-pot operation as described in retro-synthetic strategy (Scheme 1).



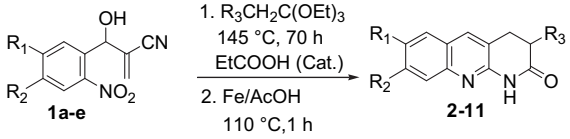
Scheme 1. Retro-synthetic strategy.

Accordingly, we have, first, selected 3-(2-nitrophenyl)-3-hydroxy-2-methylenepropanenitrile (**1a**), Baylis–Hillman (B–H) alcohol, obtained from 2-nitrobenzaldehyde and acrylonitrile under the catalytic influence of DABCO, as a substrate for the multi-step one-pot reaction sequence to obtain the desired benzo[*b*][1,8]naphthyridin-2-one derivative (**2**). In this direction the best result was obtained when 3-(2-nitrophenyl)-3-hydroxy-2-methylenepropanenitrile (**1a**) was treated with triethyl orthopropionate in the presence of a catalytic amount of propanoic acid[11] at 145 °C for 70 h followed by the treatment of the resulting product (obtained after removal of excess triethyl orthopropionate under reduced pressure) with Fe/AcOH at 110 °C for 1 h, thus providing the expected 2,4-diaza-6-methyltricyclo-[8.4.0.0^{3,8}]tetradeca-1(10),2,8,11,13-pentaen-5-one (**2**) in 69% isolated yield (Table 1).

Encouraged by this result, we have successfully transformed the various Baylis–Hillman adducts (Table 1, **1a**–**e**) into benzo[*b*][1,8]naphthyridin-2-ones (**3**–**11**) in 45–63% isolated yields (Table 1).

With a view to understand the generality and also to obtain tetracyclic system having [1,8]naphthyridin-2-one framework we have prepared 3-(1-nitronaphth-2-yl)-3-hydroxy-2-methylenepropanenitrile (**1f**) (from 1-nitro-2-naphthaldehyde and acrylonitrile) and subjected to Johnson–Claisen rearrangement with triethyl orthopropionate and triethyl orthoacetate and subsequent reductive cyclization using Fe/AcOH. The resulting products 3,5-diaza-7-methyltetracyclo[12.4.0.0^{2,11}.0^{4,9}]octadeca-1(14),2(11),3,9,12,15,17-heptaen-6-one (**12**) and 3,5-diazatetracyclo-[12.4.0.0^{2,11}.0^{4,9}]octadeca-1(14),2(11),3,9,12,15,17-heptaene-6-one (**13**) were obtained in 59% and 51% isolated yields, respectively (Table 2). In fact structures of these molecules were further confirmed by single crystal X-ray data (Fig. 2).[12,13] A plausible mechanism for this one-pot interesting transformation is presented in Scheme 2. The first step involves Johnson–Claisen rearrangement of the B–H alcohol to provide trisubstitutued alkene (**X**). The second step proceeds through the reduction of nitro group with Fe/AcOH to generate the amine, in situ, which on subsequent cyclization might provide the desired [1,8]naphthyridin-2-one framework (Scheme 2).

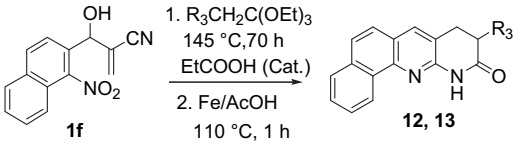
Table 1
Synthesis of benzo[*b*][1,8]naphthyridin-2-one derivatives from the Baylis–Hillman alcohols[a]



B–H Alcohol	R_1	R_2	R_3	Product	Yield[b,c](%)
1a	H	H	Me	**2**	69
1a	H	H	H	**3**	55
1b	Br	H	Me	**4**	56
1b	Br	H	H	**5**	45
1c	Cl	H	Me	**6**	63
1c	Cl	H	H	**7**	58
1d	OMe	OMe	Me	**8**	60
1d	OMe	OMe	H	**9**	48
1e	OMe	OEt	Me	**10**	56
1e	OMe	OEt	H	**11**	49

[a] All reactions were carried out on a 1 mmol scale of B–H alcohols with triethyl orthopropionate (1.25 mL) or triethyl orthoacetate (2.0 mL) at 145 °C in the presence of a catalytic amount of propanoic acid[11] followed by reductive cyclization.
[b] All the compounds were fully characterized (see Experimental section).
[c] Yields were based on B–H alcohols.

Table 2
Synthesis of tetracyclic compounds containing [1,8]naphthyridin-2-one framework[a]



B–H Alcohol	R_3	Product[12,13]	Yield[b,c] (%)
1f	Me	**12**[d]	59
1f	H	**13**[d]	51

[a] All reactions were carried out on a 1 mmol scale of B–H alcohol with triethyl orthopropionate (1.25 mL) or triethyl orthoacetate (2.0 mL) at 145 °C in the presence of a catalytic amount of propanoic acid followed by reductive cyclization.
[b] Compounds **12** and **13** were fully characterized (see Experimental section).
[c] Yields were based on B–H alcohol.
[d] Compounds **12** and **13** were further confirmed by single crystal data.[12,13]

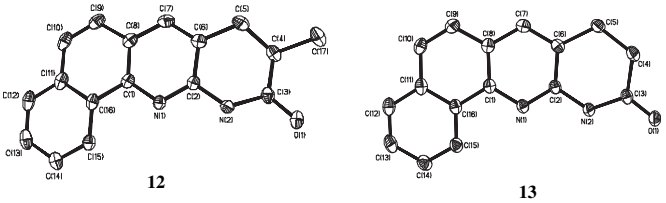
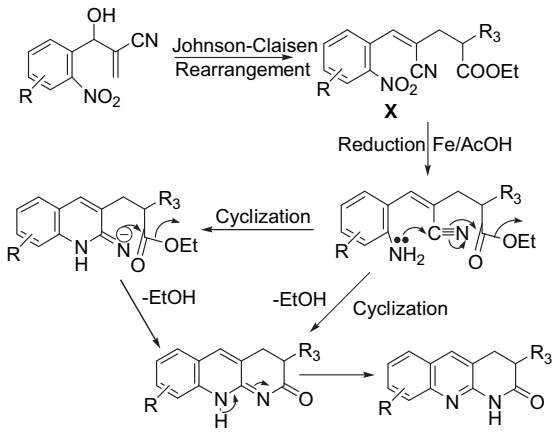


Figure 2. ORTEP diagrams of compounds **12** and **13** (Hydrogen atoms were omitted for clarity).[12,13]

3. Conclusion

In conclusion, we have successfully developed a simple, facile and one-pot procedure for the synthesis of tri and tetracyclic heterocyclic systems containing [1,8]naphthyridin-2-one framework from the Baylis–Hillman alcohols, thus demonstrating the importance of Baylis–Hillman alcohols as valuable synthons in organic chemistry.



Scheme 2. A Plausible mechanism for synthesis of tri and tetracyclic system containing [1,8]naphthyridin-2-one framework.

4. Experimental section

4.1. General remarks

Melting points were recorded on a Superfit (India) capillary melting point apparatus and were uncorrected. IR spectra were recorded on a JASCO-FTIR model 5300 spectrometer using solid samples as KBr plates. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra for all compounds were recorded in deuterochloroform ($CDCl_3$) or in deuterochloroform ($CDCl_3$) containing deuterodimethyl sulfoxide (DMSO-d_6) on a Bruker-AVANCE-400 spectrometer using tetramethylsilane (TMS, δ=0) as an internal standard at room temperature. Elemental analyses were recorded on a Thermo–Finnigan Flash EA 1112 analyzer. Mass spectra were recorded on Shimadzu-LCMS-2010 A mass spectrometer. The X-ray diffraction measurements were carried out at 100 K on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a Mo-Kα fine-focus sealed tube (λ=0.71073 Å).

4.2. Representative procedure

*4.2.1. Synthesis of 2,4-diaza-6-methyltricylo[8.4.0.0^{3,8}]tetradeca-1(10),2,8,11,13-pentaen-5-one (**2**).* To a stirred solution of 3-(2-nitrophenyl)-3-hydroxy-2-methylenepropanenitrile **1a** (1 mmol, 0.204 g) in triethyl orthopropionate (1.25 mL) was added catalytic amount of propanoic acid (four drops), and the reaction mixture was heated at 145 °C for 70 h. The reaction mixture was then allowed to come to room temperature. Excess triethyl orthopropionate was removed under reduced pressure. The residue, thus obtained, was diluted with AcOH (5 mL) and electrolytic Fe powder (6 mmol, 0.336 g), at room temperature, was added. Then the reaction mixture was heated at 110 °C for 1 h and was cooled to room temperature. Acetic acid was removed under reduced pressure and diluted with EtOAc (15 mL). The resulting mixture was filtered to remove any iron impurities. Iron residue was washed twice with EtOAc (15 mL). Filtrate and washings were combined and dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue thus obtained was purified by column chromatography (40% EtOAc in hexanes) to provide the desired product as colorless solid in 69% (0.147 g) isolated yield. R_f (40% EtOAc in hexanes) 0.58; mp: 212–214 °C, IR (KBr): ν 3350–3150 (multiple bands), 1693, 1678, 1626 cm^{-1}; ^{1}H NMR (400 MHz): δ 1.35 (d, 3H, J=6.8 Hz), 2.71–2.97 (m, 2H), 3.18 (dd, 1H, J=5.2 Hz and 15.6 Hz), 7.38–7.48 (m, 1H), 7.60–7.68 (m, 1H), 7.71 (d, 1H, J=8.0 Hz), 7.88–7.95 (m, 2H), 8.55 (s, 1H, D_2O exchangeable); ^{13}C NMR (100 MHz): δ 15.53, 32.73, 35.26, 119.63, 125.08, 125.91, 127.11, 127.49, 129.65, 135.40, 146.20, 150.64, 174.60; LCMS (m/z): 213 (M+H)$^+$; Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.71; H, 5.69; N, 13.28.

Similarly, compounds **4**, **6**, **8**, **10**, **12** were prepared following the above mentioned procedure. The compounds **3**, **5**, **7**, **9**, **11**, **13** were synthesized via Johnson–Claisen rearrangement of corresponding Baylis–Hillman alcohols **1a**, **1b**, **1c**, **1d**, **1e**, **1f**, respectively, with triethyl orthoacetate (2.0 mL), in the presence of catalytic amount of propanoic acid, followed by reductive cyclization using Fe/AcOH.

*4.2.2. 2,4-Diazatricyclo[8.4.0.0^{3,8}]tetradeca-1(10),2,8,11,13-pentaen-5-one (**3**).* Yield: 55%; R_f (40% EtOAc in hexanes) 0.33; reaction time: 71 h (70 h+1 h); mp: 210–211 °C (dec); IR (KBr): ν 3350–3100 (multiple bands), 1695, 1682, 1626 cm^{-1}; ^{1}H NMR (400 MHz): δ 2.76 (t, 2H, J=7.2 Hz), 3.14 (t, 2H, J=7.2 Hz), 7.40–7.47 (m, 1H), 7.61–7.68 (m, 1H), 7.72 (d, 1H, J=8.0 Hz), 7.86 (d, 1H, J=8.4 Hz), 7.92 (s, 1H), 8.28 (s, 1H, D_2O exchangeable); ^{13}C NMR (100 MHz): δ 24.70, 30.80, 119.57, 125.22, 125.97, 127.19, 127.53, 129.73, 135.26, 146.21, 150.54, 171.83; LCMS (m/z): 199 (M+H)$^+$; Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.59; H, 5.12; N, 14.23.

*4.2.3. 12-Bromo-2,4-diaza-6-methyltricyclo[8.4.0.0^{3,8}]tetradeca-1(10),2,8,11,13-pentaen-5-one (**4**).* Yield: 56%; R_f (40% EtOAc in hexanes) 0.59; reaction time: 71 h (70 h+1 h); mp: 215–217 °C; IR (KBr): ν 3350–3160 (multiple bands), 1691, 1624 cm^{-1}; ^{1}H NMR (400 MHz): δ 1.35 (d, 3H, J=6.8 Hz), 2.72–2.96 (m, 2H), 3.18 (dd, 1H, J=5.6 Hz and 15.6 Hz), 7.69 (d, 1H, J=9.2 Hz), 7.78 (d, 1H, J=9.2 Hz), 7.81 (s, 1H), 7.86 (s, 1H), 8.61 (s, 1H, D_2O exchangeable); ^{13}C NMR (100 MHz) (90% $CDCl_3$+10% DMSO-d_6): δ 15.28, 32.46, 34.88, 118.17, 120.66, 126.81, 128.94, 128.99, 132.62, 134.12, 144.58, 150.90, 174.46; LCMS (m/z): 291(M+H)$^+$, 293(M+2+H)$^+$; Anal. Calcd for $C_{13}H_{11}BrN_2O$: C, 53.63; H, 3.81; N, 9.62, Found: C, 53.67; H, 3.71; N, 9.58.

*4.2.4. 12-Bromo-2,4-diazatricyclo[8.4.0.0^{3,8}]tetradeca-1(10),2,8,11,13-pentaen-5-one (**5**).* Yield: 45%; R_f (40% EtOAc in hexanes) 0.38; reaction time: 71 h (70 h +1 h); mp: 248–249 °C (dec); IR (KBr): ν 3250–3000 (multiple bands), 1685, 1626 cm^{-1}; ^{1}H NMR (400 MHz): δ 2.77 (t, 2H, J=7.6 Hz), 3.14 (t, 2H, J=7.6 Hz), 7.69 (dd, 1H, J=2.0 Hz and 8.8 Hz), 7.78 (d, 1H, J=8.8 Hz), 7.82 (s, 1H), 7.86 (d, 1H, J=2.0 Hz), 8.65 (br s, 1H, D_2O exchangeable); ^{13}C NMR (100 MHz): δ 24.69, 30.61, 118.66, 120.66, 127.10, 129.18, 129.23, 133.07, 134.22, 144.81, 150.82, 171.63; LCMS (m/z): 275(M−H)$^+$, 277 (M−H+2)$^+$; Anal. Calcd for $C_{12}H_9BrN_2O$: C, 52.01; H, 3.27; N, 10.11. Found: C, 52.20; H, 3.29; N, 10.04.

*4.2.5. 12-Chloro-2,4-diaza-6-methyltricyclo[8.4.0.0^{3,8}]tetradeca-1(10),2,8,11,13-pentaen-5-one (**6**).* Yield: 63%; R_f (40% EtOAc in hexanes) 0.57; reaction time: 71 h (70 h+1 h); mp: 210–212 °C (dec); IR (KBr): ν 3350–3150 (multiple bands), 1709, 1685, 1626 cm^{-1}; ^{1}H NMR (400 MHz): δ 1.35 (d, 3H, J=6.8 Hz), 2.72–2.95 (m, 2H), 3.18 (dd, 1H, J=5.2 Hz and 15.6 Hz), 7.57 (dd, 1H, J=2.4 Hz and 8.8 Hz), 7.69 (d, 1H, J=2.4 Hz), 7.82 (s, 1H), 7.89 (d, 1H, J=8.8 Hz), 8.91 (br s, 1H, D_2O exchangeable); ^{13}C NMR (100 MHz): δ 15.51, 32.72, 35.17, 120.78, 125.88, 126.53, 129.01, 130.45, 130.63, 134.45, 144.59, 150.81, 174.37; LCMS (m/z): 247 (M+H)$^+$, 249 (M+H+2)$^+$; Anal. Calcd for $C_{13}H_{11}ClN_2O$: C, 63.29; H, 4.49; N, 11.36. Found: C, 63.13; H, 4.44; N, 11.41.

*4.2.6. 12-Chloro-2,4-diazatricyclo[8.4.0.0^{3,8}]tetradeca-1(10),2,8,11,13-pentaen-5-one (**7**).* Yield: 58%; R_f (40% EtOAc in hexanes) 0.39; reaction time: 71 h (70 h+1 h); mp: 246–248 °C; IR (KBr): ν 3300–3000 (multiple bands), 1700, 1687, 1626 cm^{-1}; ^{1}H NMR (400 MHz): δ 2.77 (t, 2H, J=7.2 Hz), 3.14 (t, 2H, J=7.2 Hz), 7.57 (d, 1H, J=8.8 Hz), 7.68 (s, 1H), 7.83 (s, 1H), 7.92 (d, 1H, J=8.8 Hz), 9.12 (s, 1H, D_2O exchangeable); ^{13}C NMR (100 MHz): δ 24.72, 30.64, 120.68, 125.94, 126.59, 129.09, 130.53, 130.77, 134.31, 144.63, 150.70, 171.52; LCMS

(m/z): 233 $(M+H)^+$, 235 $(M+H+2)^+$; Anal. Calcd for $C_{12}H_9ClN_2O$: C, 61.95; H, 3.90; N, 12.04. Found: C, 61.78; H, 3.95; N, 12.00.

*4.2.7. 2,4-Diaza-12,13-dimethoxy-6-methyltricyclo[8.4.0.0^{3,8}]tetradeca-1(10),2,8,11,13-pentaen-5-one (**8**).* Yield: 60%; R_f (40% EtOAc in hexanes) 0.31; reaction time: 71 h (70 h+1 h); mp: 236–238 °C (dec); IR (KBr): ν 3300–3000 (multiple bands), 1682, 1626 cm^{-1}; ^{1}H NMR (400 MHz): δ 1.33 (d, 3H, J=6.8 Hz), 2.70–2.90 (m, 2H), 3.13 (dd, 1H, J=5.2 Hz and 15.2 Hz), 3.98 (s, 3H), 4.02 (s, 3H), 6.98 (s, 1H), 7.38 (s, 1H), 7.76 (s, 1H), 8.93 (br s, 1H, D_2O exchangeable); ^{13}C NMR (100 MHz): δ 15.58, 32.66, 35.41, 56.07, 56.30, 105.24, 106.99, 117.01, 120.91, 134.00, 142.91, 148.71, 149.07, 152.56, 174.45; LCMS (m/z): 273 $(M+H)^+$; Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29, Found: C, 66.26; H, 5.86; N, 10.43.

*4.2.8. 2,4-Diaza-12,13-dimethoxytricyclo[8.4.0.0^{3,8}]tetradeca-1(10),2,8,11,13-pentaen-5-one (**9**).* Yield: 48%; R_f (40% EtOAc in hexanes) 0.18; reaction time, 71 h (70 h+1 h); mp: 234–236 °C (dec); IR (KBr): ν 3250–3000 (multiple bands), 1685, 1626 cm^{-1}; ^{1}H NMR (400 MHz): δ 2.74 (t, 2H, J=6.8 Hz), 3.09 (t, 2H, J=6.8 Hz), 3.99 (s, 3H), 4.01 (s, 3H), 6.98 (s, 1H), 7.32 (s, 1H), 7.77 (s, 1H), 8.74 (s, 1H, D_2O exchangeable); ^{13}C NMR (100 MHz): δ 24.60, 31.01, 56.09, 56.28, 105.31, 107.00, 117.00, 120.98, 133.83, 142.93, 148.85, 149.04, 152.68, 171.65; LCMS (m/z): 259 $(M+H)^+$; Anal. Calcd'd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.00; H, 5.43; N, 10.83.

*4.2.9. 2,4-Diaza-13-ethoxy-12-methoxy-6-methyltricylo-[8.4.0.0^{3,8}] tetradeca-1(10),2,8,11,13-pentaen-5-one (**10**).* Yield: 56%; R_f (40% EtOAc in hexanes) 0.34; reaction time; 71 h (70 h+1 h); mp: 227–228 °C (dec); IR (KBr): ν 3250–3050 (multiple bands), 1688, 1626 cm^{-1}; ^{1}H NMR (400 MHz): δ 1.33 (d, 3H, J=6.0 Hz), 1.53 (t, 3H, J=7.2 Hz), 2.68–2.92 (m, 2H), 3.12 (dd, 1H, J=4.4 Hz and 15.2 Hz), 3.97 (s, 3H), 4.24 (q, 2H, J=7.2 Hz), 6.97 (s, 1H), 7.33 (s, 1H), 7.75 (s, 1H), 8.92 (s, 1H, D_2O exchangeable); ^{13}C NMR (100 MHz): δ 14.62, 15.56, 32.62, 35.38, 56.09, 64.52, 105.32, 107.54, 116.87, 120.77, 133.96, 142.86, 148.86, 148.92, 151.86, 174.49; LCMS (m/z): 287$(M+H)^+$; Anal. calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.26; H, 6.36; N, 9.70.

*4.2.10. 2,4-Diaza-13-ethoxy-12-methoxytricyclo[8.4.0.0^{3,8}]-tetradeca-1(10),2,8,11,13-pentaen-5-one (**11**).* Yield: 49%; R_f (40% EtOAc in hexanes) 0.16; reaction time: 71 h (70 h+1 h); mp: 247–248 °C (dec); IR (KBr): ν 3250–3050 (multiple bands), 1687, 1626 cm^{-1}; ^{1}H NMR (400 MHz): δ 1.46 (t, 3H, J=6.8 Hz), 2.66 (t, 2H, J=7.2 Hz), 3.01 (t, 2H, J=7.2 Hz), 3.90 (s, 3H), 4.17 (q, 2H, J=6.8 Hz), 6.89 (s, 1H), 7.27 (s, 1H), 7.68 (s, 1H), 8.99 (br s, 1H, D_2O exchangeable); ^{13}C NMR (100 MHz): δ 14.63, 24.58, 30.99, 56.11, 64.54, 105.35, 107.57, 116.85, 120.84, 133.80, 142.88, 148.90, 148.99, 151.95, 171.71; LCMS (m/z): 273 $(M+H)^+$; Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.03; H, 5.96; N, 10.15.

*4.2.11. 3,5-Diaza-7-methyltetracyclo[12.4.0.0^{2,11}.0^{4,9}]ocatdeca-1(14),2(11),3,9,12,15,17-heptaen-6-one (**12**).* Yield: 59%; R_f (40% EtOAc in hexanes) 0.70; reaction time: 71 h (70 h+1 h); mp: 185–187 °C; IR (KBr): ν 3250–3150 (multiple bands), 1697, 1678, 1616 cm^{-1}; ^{1}H NMR (400 MHz): δ 1.37 (d, 3H, J=6.8 Hz), 2.73–2.98 (m, 2H), 3.20 (dd, 1H, J=5.6 Hz and 15.20 Hz), 7.58–7.78 (m, 4H), 7.84–7.92 (m, 1H), 7.93 (s, 1H), 8.13 (s, 1H, D_2O exchangeable), 9.08 (d, 1H, J=8.8 Hz), ^{13}C NMR (100 MHz): δ 15.51, 32.43, 35.21, 118.77, 123.31, 124.19, 124.72, 125.96, 126.72, 127.79, 128.00, 130.56, 133.75, 135.35, 144.26, 149.25, 174.17; LCMS (m/z): 263 $(M+H)^+$; Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.88; H, 5.37; N, 10.88.

Crystal data for **12**: Empirical formula, $C_{17}H_{14}N_2O$; formula weight, 262.30; crystal color, colorless; habit, plate; crystal dimensions, 0.34×0.22×0.06 mm^3; crystal system, monoclinic; lattice type, primitive; lattice parameters, a=15.2721(9) Å, b=12.3272(8) Å, c=15.1619(9) Å, α=90.00; β=113.1960(10); γ=90.00; V=2623.7(3) Å^3; space group, p 21/c, Z=8; D_{calcd}=1.328 g/cm^3; F_{000}=1104; λ (Mo-Kα)=0.71073 Å; R ($I\geq 2\sigma_1$)=0.0438, wR^2=0.0644, detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK (for compound **12** CCDC # 730557).

*4.2.12. 3,5-Diazatetracyclo[12.4.0.0^{2,11}.0^{4,9}]octadeca-1(14),2(11),3,9,12,15,17-heptaen-6-one (**13**).* Yield: 51%; R_f (40% EtOAc in hexanes) 0.56; Reaction time: 71 h (70 h+1 h); mp:197–198 °C (dec); IR (KBr): ν 3250–3100 (multiple bands), 1676, 1612 cm^{-1}; ^{1}H NMR (400 MHz): δ 2.79 (t, 2H, J=7.2 Hz), 3.17 (t, 2H, J=7.2 Hz), 7.58–7.78 (m, 4H), 7.88 (d, 1H, J=6.8 Hz), 7.94 (s, 1H), 8.17 (s, 1H, D_2O exchangeable), 9.08 (d, 1H, J=8.0 Hz); ^{13}C NMR (100 MHz): δ 24.37, 30.71, 118.70, 123.35, 124.23, 124.71, 126.07, 126.73, 127.78, 128.02, 130.55, 133.76, 135.23, 144.25, 149.26, 171.51; LCMS (m/z): 249 $(M+H)^+$; Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.30; H, 4.85; N, 11.36.

Crystal data for **13**: Empirical formula, $C_{16}H_{12}N_2O$; formula weight, 248.28; crystal color, red color; habit, plate; crystal dimensions, 0.48×0.34×0.20 mm^3; crystal system, monoclinic; lattice type, primitive; lattice parameters, a=6.6279(3) Å, b=7.5251(4) Å, c=23.1973(12) Å, α=90.00; β=96.0860(10); γ=90.00; V=1150.46(10) Å^3; space group, p 21/n; Z=4; D_{calcd}=1.433 g/cm^3; F_{000}=520; λ (Mo-Kα)=0.71073 Å; R ($I\geq 2\sigma_1$)=0.0426, wR^2=0.0453, detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK (for compound **13** CCDC # 730558).

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11. One of the reviewers has suggested to examine the application of other acids (other than propanoic acid) for efficiently performing (faster reaction rate) the Johnson–Claisen rearrangement step. Accordingly, we have carried out the Johnson–Claisen rearrangement of the compound **1a** with triethyl orthopropionate in the presence of other acids such as AcOH, CF_3COOH, $MeSO_3H$, and $BF_3{:}OEt_2$, as catalysts. We noticed that propanoic acid provided better results, both in terms of yield and rate of the reaction, than the other acids.
12. Detailed X-ray crystallographic data are available from the CCDC, 12 union road, Cambridge CB2 1EZ, UK; for compound **12** (CCDC # 730557) and for compound **13** (CCDC # 730558).
13. The single crystal X-ray structure revealed the presence of two molecules in the asymmetric unit in the case of compound **12**. For clarity we have shown one molecule in the ORTEP diagram (Fig. 2).