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The Aza-ene Reaction of Heterocyclic Ketene Aminals with 4-Phenyl-1,2,4-triazoline-3,5-dione†

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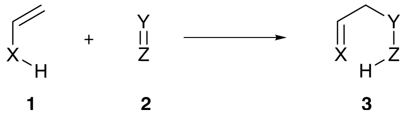
Heterocyclic ketene aminals bearing a secondary enamine moiety underwent an efficient aza-ene reaction with 4-phenyl-1,2,4-triazoline-3,5-dione under very mild conditions, while no reaction was observed with their tertiary enamine analogues.

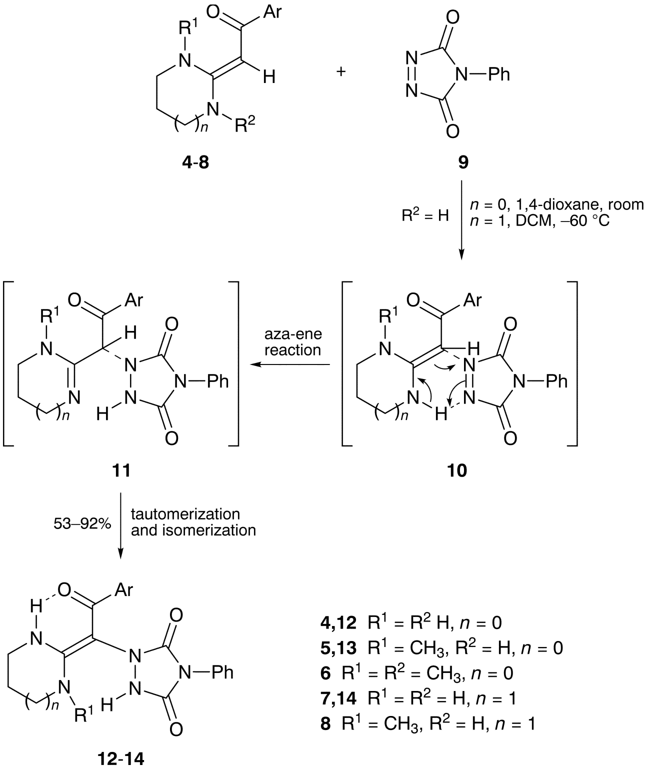
The ene reaction has received much attention for a number of decades because of its synthetic potential and its interesting mechanistic aspects in organic chemistry.[1] While the ene reactions of an olefin bearing an allylic hydrogen atom (the 'carba-ene') with activated alkenes and alkynes (the 'carba-enophiles') and with heteroenophiles, including carbonyl, thiocarbonyl compounds, imines, nitroso and azo compounds, are well documented,[1] little is known of the ene reactions involving hetero-ene components.[2–4] This is particularly true for those of hetero-ene systems containing a heteroatom at the 2-position (X = heteroatom) (Scheme 1).[2,3] Nevertheless, we envisaged that hetero-ene reactions of secondary enamines would provide novel and valuable synthetic routes to imines **3** and to ketones, amines and N-heterocycles, respectively, upon the hydrolysis, reduction and cyclization of **3**.



Scheme 1

Heterocyclic ketene aminals, also known as cyclic 1,1-ene-diamines, are powerful and versatile synthons for various types of compounds that are difficult to obtain by other synthetic methods.[5] Most noticeably, however, heterocyclic ketene aminals bearing a secondary amino group have been shown recently to be a unique aza-ene component, and the aza-ene reaction proceeded readily when ethyl propiolate was used as an enophile.[6] To examine the scope and limitations of this novel aza-ene component in organic synthesis, we have extended the aza-ene reactions of heterocyclic ketene aminals utilizing a range of carba- and heteroenophiles. Herein we report the reaction of aroyl-substituted heterocyclic ketene aminals with 4-phenyl-1,2,4-triazoline-3,5-dione (**9**, PTAD).

The reaction of imidazolidine-containing heterocyclic ketene aminals **4** and **5** with **9** was rapid and efficient at room temperature and the corresponding adducts (**12**) were obtained immediately and the products **13** were formed within one hour. Significantly, when 1,3-dimethyl-2-aroylmethyleneimidazolidine **6** was employed, no reaction was observed and the starting materials were recovered. It should be noted that the only difference in structure between **4** or **5** and **6** is that the former has at least one secondary amino group, being a secondary enamine species, while the latter is a tertiary enamine compound. These results suggest that the addition of heterocyclic ketene aminals to PTAD does not proceed through a Michael addition mechanism, or through a [2 + 2] cycloaddition followed by rearrangement pathway.[6] In other words, a secondary enamine is a reactive component and therefore the aza-ene reaction is most likely involved (Scheme 2).



4,12 R^1 = R^2 H, $n = 0$
5,13 R^1 = CH$_3$, R^2 = H, $n = 0$
6 R^1 = R^2 = CH$_3$, $n = 0$
7,14 R^1 = R^2 = H, $n = 1$
8 R^1 = CH$_3$, R^2 = H, $n = 1$

4-8, 12-14	a	b	c	d
Ar	Ph	p-CH$_3$C$_6$H$_4$	p-CH$_3$OC$_6$H$_4$	p-ClC$_6$H$_4$

Scheme 2

Surprisingly, the reaction of six-membered heterocyclic ketene aminals **7** with **9** under the same conditions did not yield the desired aza-ene adducts. Instead, benzoylphenylurea (PhCONHCONHPh) **15** was isolated as the sole product. Only when the reaction temperature was lowered to −60 °C, using dichloromethane (DCM) as solvent, was the aza-ene reaction effected efficiently. Aza-ene adduct **14** was found to decompose readily at room temperature when treated with ethanol and other solvents, resulting in the formation of **15**. The instability of aza-ene products from 1-methylpyrimidine-substituted heterocyclic ketene aminals **8** inhibited their successful isolation, though the initial formation of the aza-ene adducts was evident by thin-layer chromatography. The reason for the fragmentation of **14** into **15** is not clear.

From the above findings it can be concluded that heterocyclic ketene aminals are effective aza-ene components. The aza-ene reaction between them and the hetero-enophile

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PTAD takes place easily under very mild thermal conditions.

Experimental

For general experimental details see our previous paper.[6]

General Procedure for the Synthesis of **12** *and* **13**.—To the solution of heterocyclic ketene aminals **4** or **5** (1.0 mmol) in 1,4-dioxane (20 cm^3) was added dropwise a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (**9**)[7] (1.0 mmol) in 1,4-dioxane (5 cm^3) at room temperature. Product **12** precipitated immediately after the addition of **3** while **13** was formed after another 0.5–1 h. Recrystallization from the appropriate solvent gave pure **12** and **13**.

12a. Yield: 75%, mp 203–205 °C (white solid from ethanol); (Found: C, 63.0; H, 4.6; N, 19.2. $C_{19}H_{17}N_5O_3$ requires C, 62.80; H, 4.72; N, 19.28%); ν_{max}/cm^{-1} 3430, 3300, 1740 and 1675; λ_{max}/nm (log ε in ethanol) 226 (4.21) and 292 (4.04). δ_H [200 MHz, $(CD_3)_2SO$] 10.95 (s, 1 H), 9.05 (s, 1 H), 8.00 (s, 1 H), 7.50–7.15 (m, 10 H), 3.75 (t, 2 H) and 3.55 (t, 2 H); δ_C [50 MHz, $(CD_3)_2SO$] 186.4, 163.6, 150.2, 149.6, 141.5, 132.3, 128.4, 128.3, 127.3, 127.1, 126.0, 125.9, 88.1, 44.2 and 41.8; *m*/*z* (FAB) 363 (M^+); *m*/*z* (EI) 303 (4%), 201 (24), 180 (53), 105 (54) and 44 (100).

12b. Yield: 65%, mp 205–207 °C (white solid from ethanol); (Found: C, 63.5; H, 5.0; N, 18.9. $C_{20}H_{19}N_5O_3$ requires C, 63.65; H, 5.07; N, 18.56%); ν_{max}/cm^{-1} 3420, 3280, 1740 and 1675; λ_{max}/nm (log ε in ethanol) 228 (4.22) and 296 (4.11); δ_H 10.95 (s, 1 H), 9.10 (s, 1 H), 7.90 (s, 1 H), 7.43 (d, 2 H), 7.12 (d, 2 H), 7.40–7.20 (m, 5 H), 3.65 (t, 2 H), 3.62 (t, 2 H), 2.30 (s, 3 H); δ_C 186.3, 163.7, 150.4, 149.5, 138.7, 138.1, 132.3, 128.6, 128.1, 127.4, 126.1, 126.0, 88.1, 44.3, 41.9 and 20.9; *m*/*z* (EI) 377 (M^+, 2%), 317 (27), 258 (6), 215 (19), 194 (92) and 119 (100).

12c. Yield: 70%, mp 187–189 °C (white solid from ethanol); (Found: C, 60.4; H, 4.97; N, 17.7. $C_{20}H_{19}N_5O_4$ requires C, 61.06; H, 4.87; N, 17.80%); ν_{max}/cm^{-1} 3400, 3300, 1745 and 1670; λ_{max}/nm (log ε in ethanol) 225 (sh) and 302 (4.13); δ_H 10.95 (s, 1 H), 9.10 (s, 1 H), 7.88 (s, 1 H), 7.43 (d, 2 H), 7.40–7.25 (m, 5 H), 6.86 (d, 2 H), 3.75 (s, 3 H), 3.70 (t, 2 H) and 3.55 (t, 2 H); δ_C 185.6, 163.8, 159.7, 150.4, 149.7, 133.7, 132.3, 128.5, 127.9, 127.3, 126.1, 112.8, 87.9, 55.1, 44.3 and 41.9; *m*/*z* (EI) 393 (M^+, 2%), 333 (13), 231 (10), 210 (43) and 135 (100).

12d. Yield: 80.5%, mp 208–210 °C (white solid from ethanol); (Found: C, 57.3; H, 4.3; N, 17.2. $C_{19}H_{16}ClN_5O_3$ requires C, 57.36; H, 4.05; N, 17.61%); ν_{max}/cm^{-1} 3400, 3300, 1745 and 1670; λ_{max}/nm (log ε in ethanol) 228 (4.30) and 296 (4.20); δ_H 10.95 (s, 1 H), 9.02 (s, 1 H), 8.02 (s, 1 H), 7.42 (d, 2 H), 7.40–7.30 (m, 5 H), 7.24 (d, 2 H), 3.75 (t, 2 H), 3.55 (t, 2 H); δ_C 185.0, 163.6, 150.5, 149.8, 140.4, 133.4, 132.3, 128.7, 128.0, 127.7, 127.4, 126.1, 88.2, 44.4 and 41.9; *m*/*z* (FAB) 398 $(M + 1)^+$; *m*/*z* (EI) 337 (6%), 235 (20), 214 (30) and 139 (100).

13a. Yield: 53%, mp 162–164 °C (colourless needles from ethanol); (Found C, 63.8; H, 5.1; N, 18.4. $C_{20}H_{19}N_5O_3$ requires C, 63.65; H, 5.07; N, 18.56%); ν_{max}/cm^{-1} 3410, 3210, 1740 and 1680; λ_{max}/nm (log ε in ethanol) 226 (4.19) and 294 (4.16); δ_H 11.25 (s, 1 H), 9.65 (s, 1 H), 7.45–7.08 (m, 10 H), 3.65 (s, 4 H), 2.95 (s, 3 H); δ_C 188.9, 161.7, 150.2, 149.3, 141.8, 131.8, 128.5, 128.1, 127.5, 127.2, 126.0, 125.6, 88.0, 51.7, 41.5 and 33.2; *m*/*z* (EI) 377 (M^+, 6%), 293 (11), 229 (20), 180 (32) and 119 (100).

13b. Yield: 68%, mp 169–171 °C (colourless needles from ethyl acetate/light petroleum, bp 60–90 °C); (Found: C, 64.3; H, 5.4; N, 18.3. $C_{21}H_{21}N_5O_3$ requires C, 64.43; H, 5.41; N, 17.89%); ν_{max}/cm^{-1} 3410, 3200, 1745 and 1690; λ_{max}/nm (log ε in ethanol) 228 (4.17) and 296 (4.16); δ_H 11.30 (s, 1 H), 9.85 (s, 1 H), 7.40 (d, 2 H), 7.38–7.16 (m, 5 H), 7.14 (d, 2 H), 3.63 (t, 2 H) 3.58 (t, 2 H), 2.95 (s, 3 H), 2.35 (s, 3 H); δ_C 190.6, 162.4, 151.1, 151.0, 138.7, 138.1, 131.5, 128.9, 128.4, 127.9, 126.0, 125.8, 89.1, 52.1, 41.5, 33.6 and 21.2; *m*/*z* (EI) 391 (M^+, 2%), 307 (11), 229 (24), 194 (34) and 119 (100).

13c. Yield: 70%, mp 120–122 °C (colourless needles from light petroleum, bp 60–90 °C/1,4-dioxane) (Found: C, 61.7; H, 5.5; N, 17.1. $C_{21}H_{21}N_5O_4$ requires C, 61.90; H, 5.20; N, 17.19%); ν_{max}/cm^{-1} 3400, 3220, 1740 and 1685; λ_{max}/nm (log ε in ethanol) 225 (sh) and 300 (4.20); δ_H 11.15 (s, br, 1 H), 9.75 (s, 1 H), 7.42 (d, 2 H), 7.45–7.10 (m, 5 H), 6.88 (d, 2 H), 3.75 (s, 3 H), 3.60 (s, 4 H), 2.95 (s, 3 H); δ_C 188.3, 161.9, 159.5, 150.3, 149.5, 134.1, 131.9, 128.7, 128.3, 127.5, 126.2, 112.8, 88.0, 55.1, 51.9, 41.6 and 33.4; *m*/*z* (EI) 407 (M^+, 2%), 323 (11), 229 (14), 210 (15) and 135 (100).

13d. Yield: 92%, mp 165–167 °C (colorless white needles from ethanol) (Found: C, 58.4; H, 4.5; N, 16.6. $C_{20}H_{18}ClN_5O_3$ requires C, 58.32; H, 4.40; N, 17.01%); ν_{max}/cm^{-1} 3410, 3200, 1745, 1680; λ_{max}/nm (log ε in ethanol) 228 (4.25) and 296 (4.18); δ_H 11.30 (s, br, 1 H), 9.60 (s, 1 H), 7.40 (d), 7.40–7.30 (m, 5 H), 7.12 (d, 2 H), 3.60 (s, 4 H) and 2.95 (s, 3 H); δ_C 187.6, 161.8, 150.4, 149.5, 140.6, 133.2, 131.8, 128.8, 127.9, 127.8, 127.6, 126.2, 88.2, 51.9, 41.7 and 33.4; *m*/*z* (EI) 411 (M^+, 2%), 327 (4), 292 (4), 273 (4), 214 (6), 139 (45) and 119 (100).

General Procedure for the Preparation of **14**.—A suspension of PTAD (1 mmol) in CH_2Cl_2 (5 cm^3) was added to a stirred solution of heterocyclic ketene aminals **7** (1 mmol) in CH_2Cl_2 (10 cm^3) at −60 °C. The colour of PTAD faded within 0.5 h and white solid products precipitated from the solution. After being filtered off and washed thoroughly with ethanol, pure products **14** were obtained.

14a. Yield: 58%, mp 156–158 °C (white solid from ethanol) (Found: C, 63.4; H, 5.1; N, 18.3. $C_{20}H_{19}N_5O_3$ requires C, 63.65; H, 5.07; N, 18.56%); ν_{max}/cm^{-1} 3420, 3230, 1755 and 1690; λ_{max}/nm (log ε in ethanol) 290 (4.03); δ_H 10.85 (s, 1 H), 10.82 (s, br, 1 H), 7.62 (s, 1 H), 7.62 (s, 1 H), 7.10–7.50 (m, 10 H), 3.38 (t, 4 H), 1.86 (quin, 2 H); δ_C 186.4, 158.4, 151.3, 151.2, 142.5, 132.7, 130.0, 129.5, 129.2, 128.3, 127.0, 126.4, 91.2, 41.1, 38.5 and 20.1; *m*/*z* (FAB) 378 $(M + 1)^+$; *m*/*z* (EI) 359 (29%), 317 (23), 243 (54) and 227 (100).

14b. Yield: 72%, mp 158–160 °C (white solid from ethanol) (Found: C, 64.1; H, 5.5; N, 17.7. $C_{21}H_{21}N_5O_3$ requires C, 64.43; H, 5.41; N, 17.89%); ν_{max}/cm^{-1} 3420, 3230, 1755 and 1690; λ_{max}/nm (log ε in ethanol) 292 (4.06); δ_H 10.92 (s, br, 1 H), 10.82 (s, 1 H), 7.60 (s, 1 H), 7.43 (d, 2 H), 7.16 (d, 2 H), 7.06–7.38 (m, 5 H), 3.32 (t, 4 H), 2.26 (s, 3 H) and 1.88 (quin, 2 H); δ_C 185.4, 157.7, 150.5, 150.2, 139.4, 137.5, 132.5, 128.6, 128.0, 127.3, 126.1, 125.9, 89.8, 40.8, 37.7, 21.0 and 19.6; *m*/*z* (EI) 373 (3%), 331 (2), 257 (38), 227 (30) and 119 (100).

14c. Yield: 61%, mp 153–155 °C (white solid from ethanol) (Found: C, 61.7; H, 5.1; N, 17.1. $C_{21}N_{21}N_5O_4$ requires C, 61.90; H, 5.20; N, 17.19%); ν_{max}/cm^{-1} 3420, 3230, 1755 and 1690; λ_{max}/nm (log ε in ethanol) 298 (3.89); δ_H 11.00 (s, 1 H), 10.84 (s, br, 1 H), 7.58 (s, 1 H), 7.40 (d, 2 H), 7.20–7.36 (m, 5 H), 6.82 (d, 2 H), 3.72 (s, 3 H), 3.38 (t, 4 H) and 1.88 (quin, 2 H); δ_C 184.8, 157.7, 150.5, 150.1, 159.4, 134.6, 132.6, 128.6, 127.6, 127.4, 126.2, 112.8, 89.6, 55.1, 37.9, 37.6 and 19.7; *m*/*z* (EI) 389 (4%), 347 (4), 273 (77), 27 (23) and 135 (100).

14d. Yield: 75%, mp 171–173 °C (white solid from ethanol) (Found: C, 58.2; H, 4.8; N, 16.7. $C_{20}H_{18}ClN_5O_3$ requires C, 58.32; H, 4.40; N, 17.01%); ν_{max}/cm^{-1} 3420, 3230, 1760 and 1690; λ_{max}/nm (log ε in ethanol) 292 (4.05); δ_H 10.90 (s, 1 H), 10.76 (s, br, 1 H), 7.70 (s, br, 1 H), 7.40 (d, 2 H), 7.18–7.36 (m, 5 H), 7.17 (d, 2 H), 3.36 (t, 4 H) and 1.86 (quin, 2 H); δ_C 183.9, 157.4, 150.4, 150.1, 140.8, 132.7, 132.3, 128.5, 127.7, 127.4, 127.3, 126.0, 89.7, 37.6, 37.5 and 19.4; *m*/*z* (EI) 393 (19%), 351 (9), 277 (30) and 227 (100).

Reaction of Heterocyclic Ketene Aminal **7a** *with PTAD at Room Temperature*.—This followed the same procedure for the synthesis of **12** and **13**, reaction of **7a** with **9** gave a viscous yellow solution. After the removal of solvent, the residue was recrystallized in ethanol to give benzoylphenylurea as white needles. Yield: 73%, mp 208–210 °C (lit.[8] 208–209 °C); ν_{max}/cm^{-1} 3210 and 1685; δ_H 10.96 (s, 1 H), 9.72 (s, br, 1 H), 7.10–8.10 (m, 10 H); δ_C 168.7, 152.2, 137.2, 133.3, 132.1, 129.0, 128.8, 128.1, 124.4 and 120.5.

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