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The azoles: effective catalysts for Baylis–Hillman reaction in basic water solution

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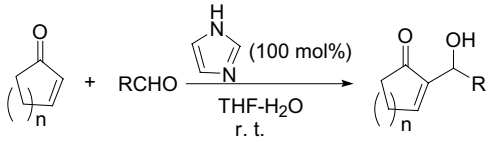
Abstract—The azoles, which were inactive in neutral aqueous media, could be activated in alkaline solution and effectively catalyze the Baylis–Hillman reaction involving cyclic enones.

The Baylis–Hillman reaction, the combination of activated alkene with carbon electrophile under the catalysis of nucleophile, has progressed dramatically during the past decade[1] and now includes several asymmetric versions.[2] However, as a versatile carbon–carbon bond-forming reaction, Baylis–Hillman reaction is generally sluggish and has limited substrate scope, which restricts its further applications in organic synthesis. Due to their low reactivity, cyclic enones are less explored among various activated alkenes. It was previously noted that the reaction was slow or did not work at all in the presence of traditional catalysts such as DABCO.[3] Rezgui and El Gaied reported that DMAP could catalyze the reaction of 2-cyclohexenone with formaldehyde in aqueous media.[4] Later, DMAP was also applied to the reaction of arenecarbaldehydes and *N*-arylidene-4-methylbenzenesulfonamide.[5] Tertiary phosphorus may also catalyze the reaction of cyclic enones. Yamada and Ikegami showed that the addition of a weak Bronsted acid such as phenol could accelerate the Bu_3P-catalyzed reaction of cyclic enones.[6] In addition, the use of Lewis acid and Lewis base pair such as $TiCl_4/Me_2S$ and $TiCl_4$/DBU could also promote the Baylis–Hillman reaction involving cyclic enones, albeit with narrow substrate scope.[5b,7] More recently, Li reported that Lewis acids (such as $TiCl_4$ and Et_2AlI) alone could catalyze the Baylis–Hillman reactions of cyclic enones without the presence of a Lewis base.[8] Although these methods offered good access to the increasingly important α-substituted cyclic α,β-enones,[9] there still remains an active research area concerning the related unsolved aspects such as the applicability of the catalysts, the generality of the reaction and most importantly, the asymmetric version of the reaction.

Previously, we found that imidazole could effectively catalyze the Baylis–Hillman reaction of cyclic enones in neutral aqueous media (Scheme 1).[10] During our further investigations, we found that not all azoles are active in neutral solution, but they can be activated to be an effective catalysts in alkaline solution. Herein we present the primary results.

The reaction of 2-cyclopentenone (**1**) with *p*-nitrobenzaldehyde (**2a**) was chosen as a model for screening purpose. The reaction was conducted in 2 mL of water solution with 0.5 mL of THF added as co-solvent to solubilize the substrates. Various pyrazoles and triazoles were examined and the results were summarized in



Scheme 1.

Keywords: Baylis–Hillman; Azoles; Cyclic enones.
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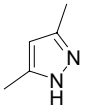
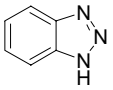
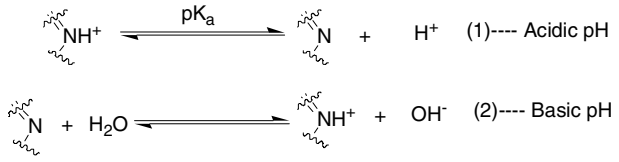
Table 1. Screening of the azoles (100 mol%) in the reaction of *p*-nitrobenzaldehyde (0.5 mmol) and 2-cyclopentenone (0.75 mmol)

Entry	Cat. (100 mol%)	pK_b (as base)[b]	Medium	Time (h)	Yield (%)[a]
1		2.53	THF–H_2O 1 M $NaHCO_3$	24 9	NR[c] 68
2		4.37	THF–H_2O 1 M $NaHCO_3$	24 20	19 80
3		1.17	THF–H_2O 1 M $NaHCO_3$	24 50 min	NR 85
4		—	THF–H_2O 1 M $NaHCO_3$	24 50 min	NR 84
5		2.19	THF–H_2O 1 M $NaHCO_3$	24 50 min	NR 82
6		3.2	THF–H_2O 1 M $NaHCO_3$	24 24	NR 78
7		7.0	THF–H_2O	16	90

[a] Isolated yields.
[b] Cited from Ref. 11.
[c] NR = no reaction.

Table 1. As it shows, in neutral aqueous THF both pyrazoles and triazoles demonstrate low activity or do not catalyze the reaction at all; whereas in weakly basic $NaHCO_3$ solution (pH = 8.6) they are activated and catalyze the reaction effectively (Table 1, entries 1–6). It appears that the catalytic activity of the azoles is related closely to their pK_a (as base) in neutral aqueous media. 3,5-Dimethyl pyrazole, which has higher pK_a than pyrazole, could catalyze the reaction while the latter was inactive in neutral medium. Triazoles generally have low pK_a (<3) and did not catalyze the Baylis–Hillman reaction (Table 1, entries 3–6). In contrast, we found previously that imidazole, with a pK_a value of 7.1, could effectively catalyze the Baylis–Hillman reaction in neutral aqueous THF (Table 1, entry 7),[10] however.

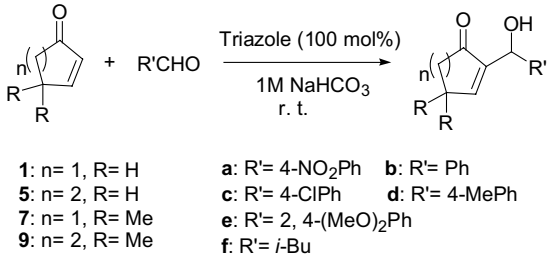
The dramatic pH effect on the catalytic activity may be attributed to the protonation of the azoles in aqueous media (Scheme 2). Azoles generally have low pK_a (<5), so consequently, they mainly exist in the protonated state that is the azolium, at neutral or acidic solution according to equilibrium (1). The azolium is deactivated and cannot participate in the Baylis–Hillman reaction as nucleophile. While in an alkaline solution, as shown in equilibrium (2), the proton exchange between water and the azoles is depressed, leaving more unprotonated azoles to take roles in Baylis–Hillman reaction as nucleophiles. This kind of proton transfer in water has been well studied for azoles, especially for imidazole,[12] which may account for the activation of the azoles in alkaline solution for Baylis–Hillman catalysis.



Scheme 2.

The reaction was then tried at various pH values and the optimal condition was found to be with the reaction in 1 M $NaHCO_3$ solution (pH = 8.6). At higher pH, the reaction led to poor results due to various by-pathways. As shown in Table 1, triazoles are superior catalysts compared to pyrazoles. In the presence of triazoles, the reactions conducted in 1 M $NaHCO_3$ solution proceeded smoothly to afford the desired Baylis–Hillman products with good yields in 50 min (Table 1, entries 3–5). *N*-Substituted triazoles such as 1-butyl-1,2,4-triazole could also promote the reaction, albeit much slower (Table 1, entry 6).

To examine the applicability of the present reaction, 1,2,3-triazole (**3**) and 1,2,4-trizaole (**4**) were selected as catalysts and tested in the reaction of various cyclic enones and aldehydes in 1 M $NaHCO_3$ solution (Scheme



Scheme 3.

3, Table 2).[13] As revealed in Table 2, the current reaction showed good scopes for both cyclic enones and aldehydes. For aldehydes, both aromatic and aliphatic aldehydes showed similar effectiveness when treating with 2-cyclopentenone (Table 1, entries 1–7). It is noteworthy that even the strong electron-rich 2,4-dimethoxybenzaldehyde can give 47% yield after 60 h. In addition, the reactions of 2-cyclohexenone and 4,4-dimethyl cyclic enones also gave very good yields (up to 89%, Table 2, entries 8–12). On the other hand, the substituted cyclic enones **7** and **9** demonstrated lower reactivity than the unsubstituted counterparts **1** and **5**, probably due to steric hindrance. Both 1,2,3-triazole and 1,2,4-triazole promoted Baylis–Hillman reaction smoothly, and in most cases, the former showed a superior catalytic activity than the latter.

In summary, we have found that the azoles could be activated in alkaline solution and effectively catalyze the Baylis–Hillman reaction involving cyclic enones. The present reaction condition is suitable for a range of cyclic enones and aldehydes. And notably, it facilitated the coupling of unreactive aldehyde with cyclic enones. Further improvement and asymmetric version using chiral azoles are currently underway in our laboratory.

Acknowledgements

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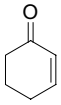
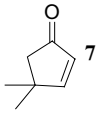
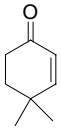
References and notes

1. (a) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049–3052; (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–892.
2. (a) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 4317–4318, Chemtracts; commentary by

Table 2. Baylis–Hillman reaction of cyclic enones and aldehydes catalyzed by triazoles in 1 M $NaHCO_3$ solution

Entry	Cylic enones	Aldehyde (R′)	Cat.	Products	Time (h)	Yield (%)[a]
1	 **1**	Ph (**2b**)	 **3**	**5b**	12	98
2	**1**	4-ClPh (**2c**)	**3**	**5c**	11	90
3	**1**	4-ClPh (**2c**)	 **4**	**5c**	18	90
4	**1**	4-MePh (**2d**)	**3**	**5d**	36	86
5	**1**	4-MePh (**2d**)	**4**	**5d**	40	67
6	**1**	2,4-$(MeO)_2$Ph (**2e**)	**3**	**5e**	60	47
7	**1**	*i*-Bu (**2f**)	**3**	**5f**	18	69
8	 **5**	4-NO_2Ph (**2a**)	**3**	**6a**	3	74
9	**5**	4-NO_2Ph (**2a**)	**4**	**6a**	3	51
10	 **7**	4-NO_2Ph (**2a**)	**3**	**8a**	12	89
11	**7**	4-NO_2Ph (**2a**)	**4**	**8a**	12	61
12	 **9**	4-NO_2Ph (**2a**)	**3**	**10a**	46	50

[a] Isolated yields.

Venkatesan, H.; Liotta, D. C. **1998**, 29; (b) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219–10220; (c) Shi, M.; Xu, Y.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4507–4510; (d) Yang, K. S.; Lee, W. D.; Pan, J. F.; Chen, K. M. *J. Org. Chem.* **2003**, *68*, 915–919; (e) Shi, M.; Chen, L.-H. *Chem. Commun.* **2003**, 1310–1311; (f) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094–12095.

3. Ciganek, E. *Org. React.* **1997**, *51*, 201; For catalysis with 3-HQD, see: Aggarwal, V. K.; Dean, D. K.; Mereu, A.; Williams, R. *J. Org. Chem.* **2002**, *67*, 510–514.
4. Rezgui, F.; El Gaied, M. M. *Tetrahedron Lett.* **1998**, *39*, 5965–5966.
5. (a) Lee, K. Y.; Gong, J. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 659–660; (b) Shi, M.; Xu, Y.-M.; Zhao, G.-L.; Wu, X.-F. *Eur. J. Org. Chem.* **2002**, 3666–3679; (c) Shi, M.; Huang, J. M. *Adv. Synth. Catal.* **2003**, *345*, 953–958.
6. Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Lett.* **2000**, *41*, 2165–2169.
7. Kataoka, T.; Iwama, T.; Tsujiyama, S.; Iwamura, T.; Watanabe, S. *Tetrahedron* **1998**, *54*, 11813–11824.
8. (a) Li, G. G.; Wei, H. X.; Gao, J. J.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1–5; (b) Pei, W.; Wei, H.-X.; Li, G. G. *Chem. Commun.* **2002**, 2412–2413.
9. Rezgui, F.; Amri, H.; El Gaied, M. M. *Tetrahedron* **2003**, *59*, 1369–1380.
10. (a) Luo, S. Z.; Zhang, B.; He, J.; Janczuk, A.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2002**, *43*, 7369–7371; (b) Catri, R.; El Gaied, M. M. *Tetrahedron Lett.* **2002**, *43*, 7835–7836.
11. Schofield, K.; Grimmett, M. R.; Keene, B. R. T. *Heteroaromatic Nitrogen Compounds: The Azoles*; Cambridge University: Cambridge, 1976, p 281.
12. Schneider, F. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 583–592, and references cited therein.
13. General procedure: To a stirred mixture of aldehyde (0.5 mmol) and triazole (0.5 mmol) in 1 M $NaHCO_3$ (2 mL) and THF (0.5 mL) was added the respective cyclic enones (0.75 mmol). The mixture was stirred at ambient temperature and monitored by TLC. Upon completion or after the indicated reaction time, the reaction mixture was quenched with 1 N HCl and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatograph on silica gel to give the desired product. Spectra data for representative compounds: **5e**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.44–2.47 (2H, m), 2.58–2.59 (2H, m), 3.75–3.77 (1H, m), 3.80 (6H, s), 5.75–5.76 (1H, m), 6.46–6.50 (2H, m), 7.24–7.31 (2H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.6, 35.3, 55.4, 65.1, 98.6, 104.2, 122.0, 128.1, 147.0, 157.5, 159.3, 160.5, 209.8. HRMS calcd for $C_{14}H_{15}O_3$ (M^++1−H_2O) 231.1021, found 231.1017. Compound **8a**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.09 (3H, s), 1.22 (3H, s), 2.25 (2H, s), 3.45 (1H, br s), 5.53 (1H, s), 6.96 (1H, s), 7.47 (2H, d, $J = 8.7$ Hz), 8.11 (2H, d, $J = 8.7$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.7, 39.3, 50.7, 68.5, 123.6, 127.0, 143.4, 147.3, 148.4, 168.6, 208.8. $C_{14}H_{15}NO_4$: calcd C 64.36, H 5.79, N 5.36; found: C 64.20, H 5.72, N 5.24. Compound **10a**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18 (3H, s), 1.20 (3H, s), 1.87 (2H, t, $J = 6.9$ Hz), 2.50 (2H, t, $J = 6.9$ Hz), 3.60 (1H, br s), 5.56 (1H, s), 6.56 (1H, s), 7.54 (2H, d, $J = 8.7$ Hz), 8.21 (2H, d, $J = 8.7$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.6, 27.8, 33.1, 34.8, 35.5, 72.2, 123.6, 127.2, 136.9, 147.3, 149.5, 157.1, 200.0. MS (FAB): 258 (100) [M^++1−H_2O], 276 [M^++1], 298 [M^++Na].