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A high yielding route to substituted piperidines via the aza-Diels–Alder reaction

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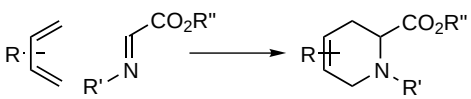
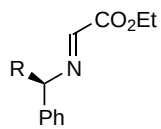
Abstract—The imine $Ph_2CHN{=}CHCO_2Et$, generated from benzhydrylamine and ethyl glyoxylate, is an excellent dienophile in aza-Diels–Alder reactions, giving diastereomerically pure cycloadducts in high yield.

The ubiquitous nature of the piperidine ring system in diverse natural products has ensured that general routes to this sub-structure have remained an important synthetic goal for many years.[1] One particularly powerful approach is the aza-Diels–Alder reaction,[2] especially when an imino–ester is used as the dienophile (Scheme 1).[3–7]

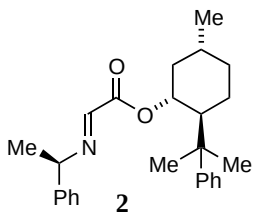
We initially developed an achiral version of this reaction using $PhCH_2N{=}CHCO_2Et$ **1a**, allowing us to establish general conditions that yield piperidines in 50–90% yields in a single step.[3] We have been able to extend this chemistry to an asymmetric procedure by using the 1-phenylethyl auxiliary on nitrogen (**1b**), available in either enantiomeric form;[4,5] this gives moderate asymmetric induction for 2-substituted dienes (typically 6:1 diastereo-control), but the minor isomer must be removed chromatographically, and 1-substituted dienes form cyclo-adducts with poor asymmetric induction. Excellent asymmetric induction can be achieved if a second matched auxiliary is introduced into the ester functionality (**2**),[6] offering a reliable route to enantiopure piperidines; however, the imine requires three steps for its preparation from (–)-pulegone, and only one enantiomeric series is readily accessible. An efficient, diastereospecific aza-Diels–Alder approach would therefore be very attractive, even if it did not provide enantio-control; optically active cyclo-adducts should be readily accessible by resolution because the basic nature of piperidines allows the formation of diastereomeric salts with chiral acids.

Although the aza-Diels–Alder reaction using the achiral benzyl imine **1a** ($PhCH_2N{=}CHCO_2Et$) provides an extremely short and effective route to a range of pipecolic acid derivatives, we had encountered three problems:





1 **a**, R = H
b, R = Me
c, R = Ph



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Scheme 1. Aza-Diels–Alder reaction.

Keywords: alkaloids; Diels–Alder reaction; piperidines.

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(a) Variable yields, which we eventually attributed to inconsistency in the purity of the imine
(b) Modest yields (ca. 50%) with 1-substituted dienes
(c) Incomplete diastereo-control with some dienes (e.g. *cis*/*trans* ratio of 1:12 with penta-1,3-diene).

Concerning the purity of the imine, it is essentially homogeneous and fridge stable for several weeks provided (i) absolutely pure ethyl glyoxylate is used; (ii) the glyoxylate:benzylamine ratio is exactly 1:1; (iii) the resulting imine is stored under dry, solvent-free conditions at 0°C. However, we were often able to identify by-products due to attack of additional nucleophiles on the imine (i.e. $PhCH_2NH–CH(X)–CO_2Et$). We also observed the formation of a further by-product during the aza-Diels–Alder reactions and, by stirring the imine under the cycloaddition conditions in the absence of the diene, we obtained sufficient material for its crystallisation and identification as **4** by X-ray diffraction (see Fig. 1). This was presumably formed from the intermediate betaine **3**, as shown in Scheme 2.

We therefore turned our attention to an alternative achiral imine, and looked at the benzhydryl derivative **1c**. This turned out to be readily obtainable as a white, homogeneous, stable solid by reacting benzhydrylamine with ethyl glyoxylate under dehydrating conditions.

We found the Roberts' conditions for generating ethyl glyoxylate hydrate were very convenient,[8] and the ease with which **1c** could be reprecipitated in homogeneous form overcame all problems of purity. Presumably because it is a solid (cf. **1a**, which is an oil), the benzhydryl imine **1c** is indefinitely stable, being usable after storage for 6–12 months at 0°C. To our delight, it behaved as an excellent and reliable dienophile in aza-Diels–Alder reactions (Scheme 3), and the results are summarised in Table 1.

Notable is that we used a standard set of conditions, so yields are not optimised. Nevertheless, a wide range of

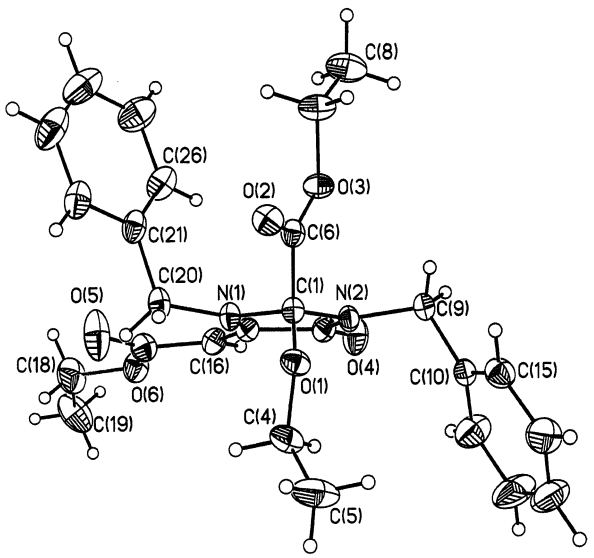
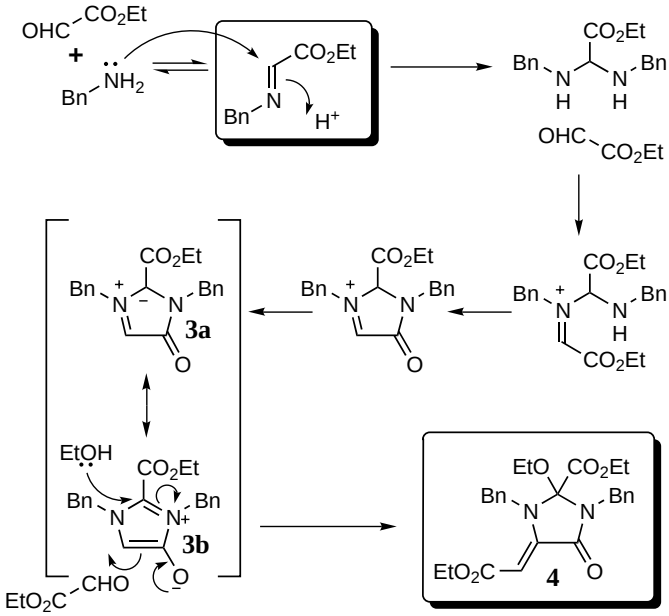
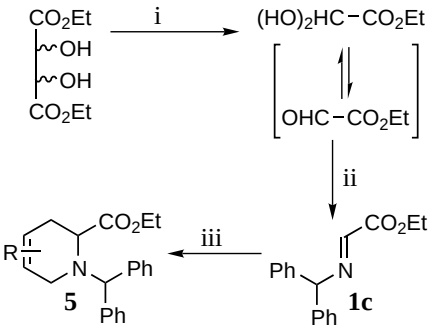


Figure 1. X-Ray crystal structure of **4**.[9]



Scheme 2. Formation of the imidazolone by-product.

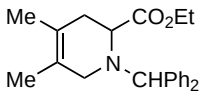
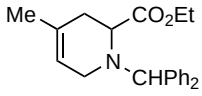
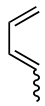
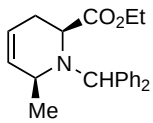
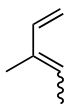
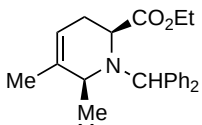
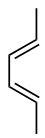
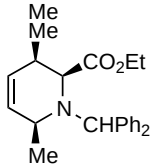


Scheme 3. *Reagents and conditions*: (i) $NaIO_4$, CH_2Cl_2/H_2O 5:1, reflux, 1 h then cool to 0°C and add $MgSO_4$ (94%); (ii) Ph_2CHNH_2 (0.75 equiv.), CH_2Cl_2, 3 Å MS, rt (94%); (iii) diene (2 equiv.), TFA (1 equiv.), TFE, –40°C (see Table 1, and Refs. 13–15 for experimental details and data).

methylated butadienes all gave the Diels–Alder adducts in yields of 42–95%. In all cases, the adduct was relatively easy to purify, as it was usually the highest R_f component. We observed total control of both regiochemistry (*o*/*p* products with respect to nitrogen) and diastereochemistry (the all-*cis* products resulting from pseudo *endo* attack of the imine on the diene). The 1-substituted dienes have in the past given slightly lower yields (and polar by-products that are probably polymeric), and small amounts of the ene products **6** were isolated (Scheme 4) in two cases. However, the key observation is the rapidity and ease with which the piperidine ring can be constructed using this methodology, and with complete regio- and diastereo-control.

In summary, we have shown that the benzhydryl imine **1c** ($Ph_2CHN{=}CHCO_2Et$) is a readily prepared, storable dienophile that reacts with acyclic dienes in high yield (typically ca. 70%), and with complete regio- and

Table 1. Cycloadducts **5** from the aza-Diels–Alder reactions, which were single regio- and diastereo-isomers, as shown

entry	diene	cycloadduct **5**	yield[a]
1			95%
2			87%
3			62% (5%)
4			42% (6%)
5			60%

[a] Isolated yield of **5**; yield of acyclic by-product **6** shown in brackets, see Scheme 4.

diastereo-control. It therefore provides a particularly short and attractive route to substituted piperidines and, because of the double bond within the ring, is also amenable to further functionalisation. The application of this approach to natural product synthesis, and the indirect stereochemical control conferred by the benzhydryl group, is discussed in the following paper.

Acknowledgements

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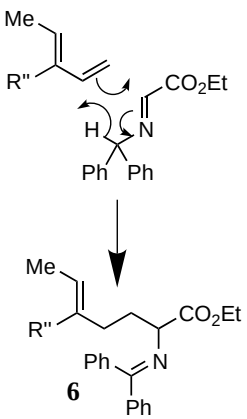

Scheme 4. Formation of ene by-product **6** from Table 1, entries 3/4 (R″ = H/Me).

References

1. Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633.
2. (a) Boger, D. L.; Weinreb, S. M. *Hetero-Diels–Alder Methodology in Organic Synthesis*; Academic Press: Orlando, 1987; (b) Waldmann, H. *Synthesis* **1994**, 535; (c) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099.
3. Bailey, P. D.; Wilson, R. D.; Brown, G. R. *Tetrahedron Lett.* **1989**, *30*, 6781.
4. Bailey, P. D.; Wilson, R. D.; Brown, G. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1337.
5. Bailey, P. D.; Brown, G. R.; Korber, F.; Reid, A.; Wilson, R. D. *Tetrahedron: Asymmetry* **1991**, *2*, 1263.
6. Bailey, P. D.; Londesbrough, D. J.; Hancock, T. C.; Heffernan, J. D.; Holmes, A. B. *Chem. Commun.* **1994**, 2543.
7. Abraham, H.; Stella, L. *Tetrahedron* **1992**, *48*, 9707.
8. Hursthouse, M. B.; Malik, K. M. A.; Hibbs, D. E.; Roberts, S. M.; Seago, A. J. H.; Sik, V.; Storer, R. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2419.
9. *X-Ray data for* ***4***. A small single crystal of **4** was mounted on a glass wool fibre in perfluoropolyether oil. The intensity data were collected at 160 K on a specially adapted Siemens SMART CCD area detector diffrac-

tometer located at Station 9.8 on the Daresbury Laboratory Synchrotron Radiation Source.[10] Crystal data for **4**, $C_{26}H_{30}N_2O_6$, $M_w=466.52$, monoclinic, space group $P2_1lc$, $a=13.162(3)$, $b=8.8710(10)$, $c=21.643(3)$ Å, $\beta=102.980(13)°$, $V=2462.4(7)$ Å^3, $Z=4$, $D_c=1.258$ mg m^{-3}, $\mu=0.090$ mm^{-1}, $T=160(2)$ K. Crystal size $=0.020\times0.015\times0.010$ mm^3, independent reflections 5247 [$R_{(int)}=0.0367$], $R_1=0.0528$, $wR_2=0.1515$ for [$I>2\sigma(I)$]. Data collection and reduction used XSCANS,[11] and structure determination and refinement used SHELXTL.[12]

10. (a) Cernik, R. J.; Clegg, W.; Catlow, C. R. A.; Bushnell-Wye, G.; Flaherty, J. V.; Greaves, G. N.; Burrows, I.; Taylor, D. J.; Teat, S. J.; Hamichi, M. *J. Synchrotron Rad.* **1997**, *4*, 279; (b) Clegg, W.; Elsegood, M. R. J.; Teat, S. J.; Redshaw, C.; Gibson, V. C. *J. Chem. Soc., Dalton Trans.* **1998**, 3037.
11. XSCANS *Data collection and reduction program*, 1994, Version 2.2, Bruker AXS, Madison, Wisconsin, USA.
12. Sheldrick, G. M. *SHELXTL, Structure determination and refinement programs*, 1999, Version 5.1 Bruker AXS, Madison, Wisconsin, USA.
13. **Ethyl glyoxylate hydrate**.[8] A solution of diethyl-L-tartrate (20.9 g, 101.5 mM) in CH_2Cl_2 (200 ml) was rapidly stirred (motorised stirrer) at room temperature in a flask equipped with a reflux condenser. To this was added solid sodium periodate (43.4 g, 203 mM, 2 equiv.) then H_2O (40 ml, approx. 20% by volume). The biphasic mixture was heated to reflux with rapid stirring for ~1 h, whereupon a thick white precipitate had formed. Over the course of a further hour, the solution became ever more cloudy, with the white precipitate had to be manually broken up on several occasions. TLC analysis (ammonium molybdate/Δ visualisation) indicated complete consumption of the tartrate, at which point the solution was cooled to 0°C. At this point $MgSO_4$ (approximately 80 g) was added in portions to the stirred mixture (CAUTION: exotherm), and the, by now, very thick white reaction mixture was stirred for 15 min before all solids were removed by filtration. The solids were washed with a further portion of CH_2Cl_2 (200 ml), before the filtrate solution was evaporated under reduced pressure to reveal the **ethyl glyoxylate hydrate**, in the form of an opaque oil (22.8 g, 94%). Data: δ_H (200 MHz, $CDCl_3$), δ: 1.31 (3H, t, J 7.1 Hz), 4.24 (2H, m), 4.60–5.40 (3H, m, broad); δ_C (50 MHz, $CDCl_3$), δ: 13.76 (CH_3), 62.32 (CH_2), 88.32 (CH), 168.87 (C=O).
14. **Ethyl *N*-benzhydryliminoethanoate**. To a solution of ethyl glyoxylate hydrate (12.3 g, 120 mM) in dry CH_2Cl_2 (150 ml) was added activated 3 Å molecular sieves (~4 g). The solution was then stirred at 0°C under Ar atmosphere for about 5 min before addition of benzhydrylamine (16.5 g, 90 mM, 0.75 equiv.) via syringe as a solution in dry CH_2Cl_2 (10 ml). The cloudy solution was left to stir for 16 h at 4°C. Filtration to remove molecular sieves followed by removal of solvent under reduced pressure (30°C) gave a yellow oil which started to crystallise. This was triturated with 40/60 pet. ether to provide, after filtration, white crystalline **product** (22.6 g, 94%), mp 55–56°C. Data δ_H (200 MHz, $CDCl_3$), δ: 1.34 (3H, t, J 7.1 Hz), 4.34 (2H, q, J 7.1 Hz), 5.68 (1H, s), 7.19–7.39 (10H, m), 7.77 (1H, s); δ_C (50 MHz, $CDCl_3$), δ: 14.07 (CH_3), 61.75 (CH_2), 77.39 (CH), 127.44 (CH), 127.75 (CH), 128.54 (CH), 141.46 (C), 153.68 (CH), 163.08 (C=O); ν (Nujol, cm^{-1}): 2940.2, 2925.5, 2854.6, 1740.9, 1493.6, 1454.8, 1211.4, 1015.8, 737.3, 697.0; m/z (EI) 535.6 (0.19%, 2M+1), 268.3 (5.2%, M+1), 167.1 (100%); HRMS, calcd for $C_{17}H_{17}NO_2$: 267.126, found: 267.121.
15. **General procedure for the aza-Diels–Alder reaction using ethyl *N*-benzhydryl-iminoethanoate**. A solution of ethyl *N*-benzhydryliminoethanoate in trifluoroethanol (10 ml/g) is cooled to −40°C under Ar. To this solution is added, via syringe, trifluoroacetic acid (1 equiv.), immediately followed by slower syringe addition of the required diene (2 equiv. or more). The solution is then left to stir at −40°C until reaction is deemed complete (as indicated by TLC monitoring, usually ~20 min), whereupon the reaction is warmed to room temperature. After evaporation of the solvent under reduced pressure, the reaction mixture is taken up in Et_2O. Successive washings with satd $NaHCO_3$ solution (3×), then H_2O (1×), then brine (1×) and drying over $MgSO_4$ followed by removal of solvent under reduced pressure gives the crude product. Further purification by column chromatography (SiO_2) may be carried out if necessary.