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A novel four-component reaction for the synthesis of functionalised dihydropyrimidines†

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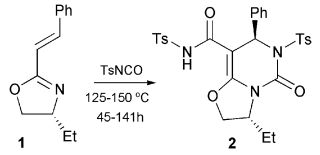
In a multi-component reaction (MCR) of a phosphonate, nitriles, aldehydes and isocyanates, *N*3-functionalised dihydropyrimidines can be synthesised efficiently *via* a Horner–Emmons/aza Diels–Alder pathway.

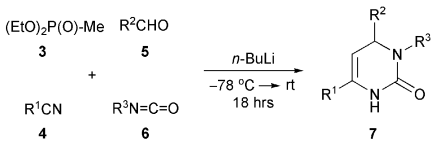
Dihydropyrimidines (DHPMs) are heterocyclic systems of remarkable pharmacological potency. They show antiviral, antitumor, antibacterial and anti-inflammatory activities and are *e.g.*, used as calcium channel modulators, α_{1a} adrenoceptor selective antagonists and antihypertensive agents.[1,2] At present several general methods for the preparation of DHPMs exist. The most well-known approach is the Biginelli three-component reaction, in which aromatic aldehydes, ureas and alkyl acetoacetates are condensed to DHPMs.[3] The classical Biginelli reaction proceeds under relatively harsh conditions (EtOH, HCl, Δ), which are detrimental to sensitive functional groups present in the components used.[3,4] Further, the use of aliphatic and *o*-substituted aromatic aldehydes or thioureas as starting materials affords the desired DHPMs in only moderate yields.[4] However, several improved procedures have been reported, including various solid phase modifications suitable for combinatorial chemistry applications.[4b,5] Unfortunately, these methods all involve additional steps and the simplicity of the original one-pot, one-step synthesis is lost. Recently the use of Lewis acids or polyphosphate esters and also the application of microwave conditions have been reported to successfully promote the Biginelli reaction.[4,6] Another drawback of the above-mentioned (improved) Biginelli protocols as well as other approaches[7] to DHPMs is that only the pharmacologically less important *N*1 substituted and *N*3 unsubstituted DHPMs can be obtained.[1,4b,8] Additional synthetic manipulations are needed to afford the biologically active *N*3 substituted DHPMs.

Interesting in this respect is a condensation reaction of dihydrooxazole derivative **1** with tosylisocyanate (TsNCO) (Scheme 1).[9,10] The resulting DHPM **2** is substituted at both *N*1 and *N*3. Compound **1** could be considered a 1-azadiene analogue. *In situ* generation of such species followed by [4 + 2] cycloaddition with suitable isocyanates can be envisioned, which renders a novel one-pot multicomponent approach to otherwise difficult to access *N*3 substituted and *N*1 unsubstituted DHPMs. Here some of our preliminary results using a four-component reaction based on this approach are presented.



Scheme 1 Synthesis of oxazolopyrimidines.

The 1-azadiene analogue is generated by mixing a phosphonate, a nitrile and an aldehyde with a base (*e.g. n*-BuLi) at −78 °C.[11] The mixture is then allowed to warm to rt and addition of an isocyanate induces a formal Diels–Alder (DA) cycloaddition to give DHPMs (Scheme 2). With this protocol,‡ the synthesis of **7** proceeds in moderate to good yields under remarkably mild conditions. The results using **3** in combination with various nitriles (**4**), aldehydes (**5**) and isocyanates (**6**) as reaction inputs are summarised in Table 1.[12]



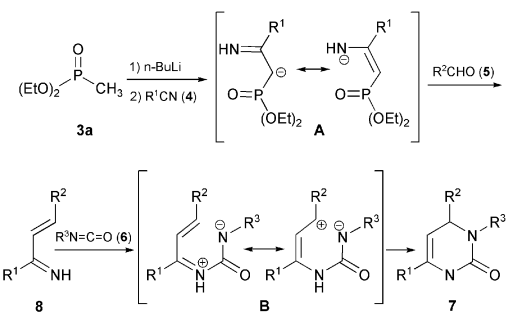
Scheme 2 Four-component reaction to *N*3-substituted DHPMs **7**.

Table 1 Yields of the four-component reaction to synthesise DHPMs **7**

Entry	R^1	R^2	R^3	DHPM **7** (%)[a]	Other (%)
1	*i*-Pr	4-ClPh	Ts	65	
2	*i*-Pr	4-MeOPh	Ts	73	
3	*i*-Pr	Ph	Ts	55	
4	*i*-Pr	4-NMe_2Ph	Ts	49	
5	*i*-Pr	3-NO_2Ph	Ts	60	
6	*i*-Pr	4-NO_2Ph	Ts	55	
7	*i*-Pr	*i*-Pr	Ts	40[b]	
8	*i*-Pr	CH_2OCH_2Ph	Ts	21[b]	
9	*i*-Pr	4-MeOPh	4-NO_2Ph	34[b]	
10	Ph	4-ClPh	Ts	80	
11	Ph	4-MeOPh	Ts	65	
12	Ph	Ph	Ts	71	
13	Ph	4-NMe_2Ph	Ts	54	
14	Ph	3-NO_2Ph	Ts	58	
15	Ph	*i*-Pr	Ts	35[b]	
16	Ph	4-MeOPh	4-NO_2Ph	26[b]	
17	Ph	4-MeOPh	Ph	—	**9** (11), **10** (32)[c]
18	*n*-Pr	4-MeOPh	Ts	10[b]	

[a] Isolated yields.[12] [b] The rest of the product mixture could not be identified. [c] Recovery was 75%, based on PhNCO consumption.

The synthesis of **7** most likely starts with abstraction of the α-H of **3** by *n*-BuLi, followed by nucleophilic addition to a nitrile **4** (Scheme 3). The intermediate ketimines **A** are more nucleophilic at carbon than at nitrogen, resulting in a Horner–Emmons reaction with the third component, an aldehyde **5**, to give 1-azadienes **8**. Efficient generation of the resonance stabilised **A** is crucial and strongly depends on the type of nitrile used. The use of nitriles with poorly accessible α-hydrogens as



Scheme 3 Horner–Emmons/aza Diels–Alder pathway to DHPMs **7**.

† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR data for **9** and **10**. See http://www.rsc.org/suppdata/cc/b3/b308243a

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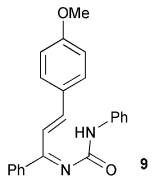
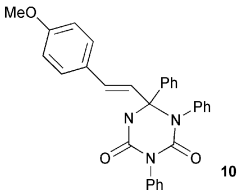
well as aromatic nitriles generally produces the ketimines efficiently,[11b] which is reflected in the yields of DHPMs **7** (entries 1–9 and 10–16, respectively, *versus* entry 18).

Although a nitrogen at the 1-position of **8** creates a π-deficient diene, which usually shows much lower reactivity towards dienophiles, 1-azadienes **8** must undergo a formal DA reaction with the electron-deficient N=C π-bond of isocyanates **6** in order to afford the observed DHPMs **7**. Normal aza DA reactions, where an electron-rich (aza)diene reacts with an electron-deficient (aza)dienophile, are well known using 2-azadienes.[13] Similar DA reactions with 1-azadienes, however, often proceed sluggishly and are of limited synthetic significance.[14] Usually, the thermodynamic driving force for a (concerted) aza DA reaction of 1-azadienes is, compared to butadienes or 2-azadienes, about 20 kcal mol^{-1} lower resulting in a much lower reactivity toward dienophiles.[14,15] On the other hand, cycloaddition reactions involving isocyanates are reported to proceed *via* a polar step-wise mechanism in almost all cases.[16] A stepwise mechanism for the cyclocondensation to generate **7** is supported by isolation of non-cyclised **9** together with triazinane dione **10** in the MCR of benzonitrile, 4-methoxybenzaldehyde and PhNCO (entry 17). No DHPM could be isolated in this case.



9



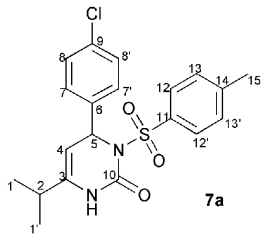
10

These observations suggest that the final cyclocondensation proceeds through stabilised dipolar intermediates **B** although a concerted DA cyclisation for the MCRs using the more electron-deficient TsNCO cannot be excluded.[17a] Thus, non-cyclised **9** can be formed from **B** *via* a 1,3-H shift. Formation of triazinane dione **10** can be rationalised by addition of a second molecule of PhNCO to **B** followed by ring closure to the thermodynamically favoured six-membered heterocycle. In line with what may be expected, (functionalised) aromatic R^2 groups promote the reaction compared to aliphatic R^2 groups (entries 1–6 *versus* entries 7 and 8, or entries 10–14 *versus* entry 15). An aromatic R^2 substituent stabilises more efficiently the intermediate carbocation in **B**. On the other hand the electronic characteristics of R^1 are less important. Besides aromatic nitriles also aliphatic nitriles can be used and the corresponding DHPMs are obtained in moderate to good yields (entries 1–6 and 10–14, respectively). The substituents R^3 on the isocyanates **6** prove particularly important. Strongly electron-withdrawing groups R^3 (Ts- or 4-NO_2Ph-, entries 1–16) favour formation of DHPMs **7**, while with a phenyl (entry 17) substituent R^3 the formation of **7** is hampered. Again this is easily accounted for by assuming that the last step proceeds *via* intermediates **B**, where the negative charge is more localised on the nitrogen with strong withdrawing R^3 groups.[17b] In conclusion, aromatic substituents R^2 on the *in situ* generated intermediate 1-azadienes **8**, but especially electron-withdrawing substituents R^3 on the isocyanates **6**, result in a most efficient final aza cyclocondensation towards **7**.

In general, the four-component procedure described here produces DHPMs **7** in an efficient and highly flexible manner. The approach can easily be adapted to a parallel synthesis set-up in order to generate small, dedicated, libraries of pharmacologically relevant *N*3-functionalised DHPMs **7**. Future research will focus on the mechanistic aspects of this reaction in order to establish rational control over the generated stereocenter and more relevant substituents R^3, like amide and ester functions, will be examined.

Notes and references

‡ *Typical procedure*: diethylmethylphosphonate **3** (1 mmol, 0.146 mL) was dissolved in 5 mL dry THF and cooled to −78 °C. One equiv. *n*-BuLi (0.63 mL, 1.6 M in hexane) was added dropwise and the resulting solution was stirred for 1 h. Subsequently, isobutyronitrile (1 mmol, 0.069 g) was added and the reaction was warmed to −5 °C in 1.5 h. Then 4-chlorobenzaldehyde (1 mmol, 0.140 g) was added and the reaction was kept at −5 °C for 0.5 h. The reaction mixture was allowed to warm to rt and after stirring for an additional 1.5 h TsNCO (1 mmol, 0.197 g) was added dropwise in 10 min. The resulting solution was stirred overnight. The solvent was removed under reduced pressure and the resulting light yellow solid was crystalised from THF/pentane (8/1) to afford 0.263 g (0.65 mmol) DHPM **7a** as white crystals in 65 % yield.



7a

m.p. 185.5–187.0 °C; ^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.08 (d, *H*-1/1′, J = 6.8 Hz, 6H), 2.25 (sept, J = 6.8 Hz, *H*-2, 1H), 2.33 (s, *H*-15, 3H), 4.87 (d, *H*-4, J = 5.3 Hz, 1H), 5.9 (d, *H*-5, J = 5.3 Hz, 1H), 7.05 (d, J = 8.3 Hz, *H*-13/13′, 2H), 7.24 (m, *H*-7/7′ & *H*-8/8′, 4H), 7.34 (d, J = 8.3 Hz, *H*-12/12′, 2H), 7.9 (s, N*H*, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$): δ 20.11 (*C*-1/1′), 21.52 (*C*-15), 30.62 (*C*-2), 58.83 (*C*-5), 97.90 (*C*-4), 128.69 (*C*-7/7′, *C*-13/13′), 128.88 (*C*-12/12′), 128.97 (*C*-8/8′), 134.15 (*C*-9), 136.30 (*C*-11), 140.16 (*C*-6), 140.74 (*C*-3), 144.26 (*C*-14), 155.01 (*C*-15); IR (KBr): 3225 (m), 3117 (m), 2962 (m), 1705 (s), 1676 (s), 1344 (s), 1169 (s); HRMS (EI): *m*/*z* 404.0961 $[M]^+$, calc. for $C_{20}H_{21}N_2SO_3Cl$: 404.0961.

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17 (*a*) PM3 semi-empirical calculations suggest that the $\Delta E_{HOMO-LUMO}$ of 1-azadiene **8** (R^1 = Ph; R^2 = 4-MeOPh) and TsNCO is considerably lower compared to $\Delta E_{HOMO-LUMO}$ of the same 1-azadiene and PhNCO (*b*) the calculations[17a] confirm that for intermediates **B** with R^3 = Ts much more negative charge is localised on *N*3 compared to intermediates **B** with R^3 = Ph.