The reactions of diacetylenic ketones with nitrogen nucleophiles; facile preparation of alkynyl substituted pyrimidines and pyrazoles

PERKIN 1 COMMUNICATION

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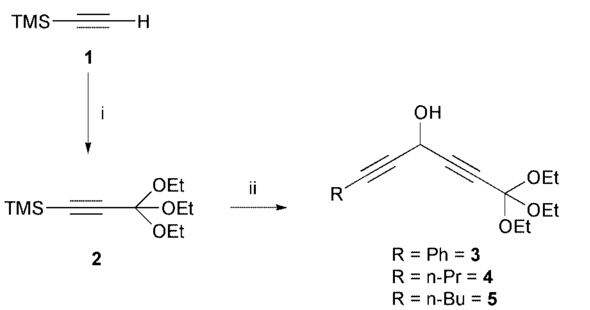
Alkynyl substituted pyrimidines and pyrazoles have been synthesized by cyclocondensations of diacetylenic ketones with amidines and hydrazines.

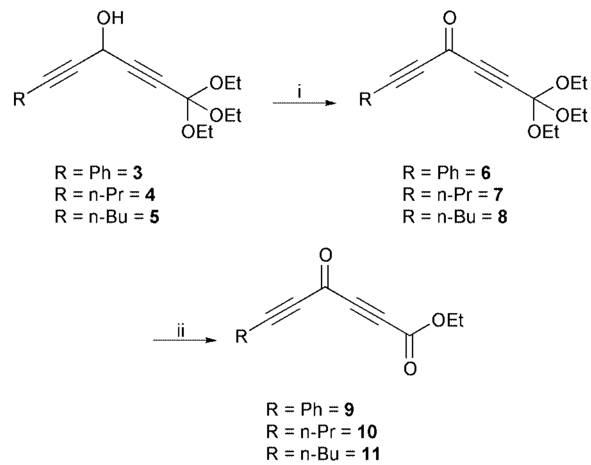
As part of an ongoing program to develop novel routes to various heterocyclic structures, we describe here the facile preparation of alkynyl substituted pyrimidines and pyrazoles. We recently reported a range of reactive electrophiles, which undergo facile reactions with various nucleophiles to form a heterocycle.[1–6] Initial work has been on a novel route to heterocyclic, substituted non-proteinogenic α-amino acids. The route made use of the reaction of α-amino acid substituted alkynyl ketones with a range of nucleophiles to form the heterocyclic ring system.[1,2] We have also reported the use of similar chemistry to generate a range of novel *C*-nucleosides.[3] Other related work makes use of vicinal tricarbonyls as the reactive core permitting the synthesis of novel non-proteinogenic α-amino acids.[4] Two new approaches to novel C-4 heteroaromatic kainoid analogues have also been reported, both routes make use of key reactive precursors to introduce a variety of heteroaromatic rings.[5,6]

We now wish to describe our related studies on diacetylenic ketones **9**–**11**. We have recently reported a route to unsymmetrical diacetylenic ketoesters.[7] The chemistry reported makes use of orthoesters, which can be removed under very mild conditions to give ethyl esters.[8] Our route makes use of chemistry developed by Boche.[9] Thus treatment of (trimethylsilyl)acetylene **1** with *n*-butyllithium in diethyl ether at low temperature and reaction with triethoxycarbenium tetrafluoroborate gave **2** in good yield.[10] Treatment of **2** with *n*-butyllithium, in THF, generates the organolithium which can be reacted with a range of acetylenic aldehydes to give the diynols **3**–**5** in excellent yields (Scheme 1).



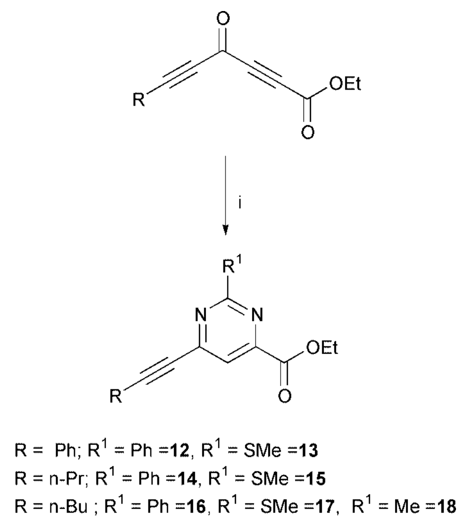
Scheme 1 *Reagents and conditions*: i, n-BuLi, Et_2O, −78 °C; $(EtO)_3$-CBF_4, 80%; ii, n-BuLi, THF, −0 °C; RCCCHO, 74–80%.

With a good route established to alcohols **3**–**5** we now looked at oxidation routes to the ketones. We found, after some experimentation, that freshly prepared manganese dioxide gave the optimum yields and product purity of the ketones **6**–**8** (Scheme 2). The orthoesters could then be converted to the ethyl ester by stirring with Amberlyst resin, to give the required ketones **9**–**11**. The facile deprotection reaction gives material that is essentially homogeneous. Further purification was unnecessary and unreliable due to the highly reactive nature of the products **9**–**11**.



Scheme 2 *Reagents and conditions*: i, MnO_2, benzene, RT, 90 min, 99%; ii, Amberlyst 15, benzene, RT, 98%.

With a range of diacetylenic ketoesters in hand we were now able to examine reactions with a range of nitrogen nucleophiles. Our starting point was to apply the conditions we had developed for the synthesis of heterocyclic substituted non-proteinogenic α-amino acids.[1,2] Thus diacetylenic ketoesters **9**–**11** reacted smoothly with amidines to yield a range of densely functionalised pyrimidines **12**–**18** in excellent yields (Scheme 3 and Table 1).



Scheme 3 *Reagents and conditions*: i, $R^1C(NH)NH_2$, MeCN–H_2O, 55–90%.

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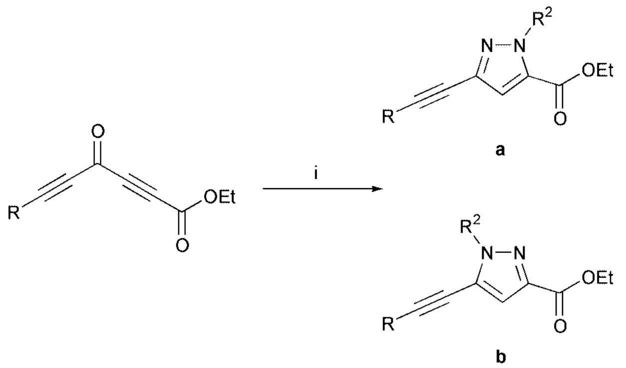
Compounds **12**–**18** were formed as single regioisomers, attributed to the acetylenic carbon bearing the ester group being the most electron deficient, making this the initial site for nucleophilic attack of the amidine. Miller has reported that on symmetrical ketones after initial attack of simple nitrogen nucleophiles the second acetylene moiety becomes deactivated towards further nucleophilic attack, resulting in only mono-addition of the nucleophile.[11]

We have also observed that diacetylenic ketoesters **9**–**11** react well with both substituted and unsubstituted hydrazines to give the corresponding pyrazoles **19**–**24** in good yield (Scheme 4 and Table 2). When phenylhydrazine was used a mixture of regioisomers **a/b** was generated in approximately 3 : 2 ratio. When hydrazine hydrate was used as the nucleophile only regioisomer **a** was isolated, presumably due to hydrogen bonding to the ethyl ester group.



R = Ph; R^2 = Ph = **19a/b**, R^2 = H = **20a**
R = n-Pr; R^2 = Ph = **21a/b**, R^2 = H = **22a**
R = n-Bu ; R^2 = Ph = **23a/b**, R^2 = H = **24a**

Scheme 4 *Reagents and conditions*: i, R^2NHNH_2, EtOH, RT, 55–90%.

In summary we have shown that it is possible to prepare a range of functionalised pyrimidines **12**–**18** and pyrazoles **19**–**24** in good yield by reaction of highly reactive diacetylenic ketones with nitrogen nucleophiles. Both ethyl ester and alkyne are versatile groups for further synthetic steps and manipulation.

Table 1 Preparation of functionalised pyrimidines

Substrate	Compound	R	R^1	Yield[a]
9	**12**	Ph	Ph	90
9	**13**	Ph	SMe	85
10	**14**	C_3H_7	Ph	92
10	**15**	C_3H_7	SMe	90
11	**16**	C_4H_9	Ph	87
11	**17**	C_4H_9	SMe	90
11	**18**	C_4H_9	Me	55

[a] Isolated yields after chromatography.

Experimental

General experimental details are as previously published.[1]

General procedure for the preparation of pyrimidines

A solution of freshly prepared ketone (1.0 eq.) in $MeCN–H_2O$ [10 : 1] (3 cm^3/50 mg) was added to a stirred solution of the amidine (1.5 eq.) and K_2CO_3 (3.0 eq.) in $MeCN–H_2O$ [10 : 1] (10 cm^3/100 mg). The resultant deep red solutions were stirred at room temperature for 30 min before being absorbed onto silica gel and purified by flash chromatography.

2-Phenyl-6-phenylpropargyl pyrimidine-4-carboxylic acid ethyl ester 12.† ν_{max} (Film)/cm^{-1} 2981 (CH), 2930 (CH), 2217 (C≡C), 1749 (CO_2Et); δ_H (200 MHz, $CDCl_3$) 8.59–8.54 (2H, m, Ar), 7.56 (1H, s, C*H*), 7.70–7.66 (3H, m, Ar), 7.46–7.41 (6H, m, Ar), 4.41 (2H, q, *J* = 7 Hz, O-C*H*$_2$CH$_3$), 1.49 (3H, t, *J* = 7 Hz, O-CH$_2$-C*H*$_3$); δ_C (50.3 MHz, $CDCl_3$) 165.59, 164.15, 155.72, 153.13, 136.48, 132.45, 131.35, 130.02, 128.75, 128.58, 120.66, 97.77, 87.09, 62.55, 14.18 (Found: MH^+ 329.1222, $C_{21}H_{16}N_2O_2$ requires *M*, 328.1211); *m*/*z* 329 (100%, MH^+).

General procedure for the preparation of pyrazoles

Phenylhydrazine or hydrazine (1.5 eq.) was added to a stirred solution of the respective freshly prepared ketone (1.0 eq.) in EtOH (10 cm^3/50 mg). The resultant deep red solutions were stirred at room temperature for 90 min before being absorbed onto silica gel and purified by flash chromatography.

2-Phenyl-5-phenylpropargyl-2*H*-pyrazole-3-carboxylic acid ethyl ester 19a. R_f = 0.4 [light petroleum–EtOAc (10 : 1)]; ν_{max} (Film)/cm^{-1} 2985 (CH), 2932 (CH), 2244 (C≡C), 1732 (CO_2Et); δ_H (200 MHz, $CDCl_3$) 7.59–7.34 (11H, m, Ar and CH), 4.48 (2H, q, *J* = 7 Hz, O-C*H*$_2$CH$_3$), 1.43 (3H, t, *J* = 7 Hz, O-CH$_2$-C*H*$_3$); δ_C (50.3 MHz, $CDCl_3$) 165.49 (C), 140.92 (C), 139.18 (C), 134.87 (C), 132.70 (CH), 129.30 (CH), 128.25 (CH), 127.03 (CH), 126.22 (CH), 122.76 (C), 118.30 (CH), 110.73 (CH), 84.96 (C), 78.12 (C), 59.16 (CH_2), 13.48 (CH_3) (Found: MH^+ 317.1233, $C_{20}H_{16}N_2O_2$ requires *M*, 316.1211); *m*/*z* 316 (100%, MH^+).

1-Phenyl-5-phenylpropargyl-2*H*-pyrazole-3-carboxylic acid ethyl ester 19b. R_f = 0.6 [light petroleum–EtOAc (10 : 1)]; ν_{max} (Film)/cm^{-1} 2985 (CH), 2932 (CH), 2244 (C≡C), 1732 (CO_2Et); δ_H (200 MHz, $CDCl_3$) 7.59–7.34 (11H, m, Ar and CH), 4.28 (2H, q, *J* = 7 Hz, O-C*H*$_2$CH$_3$), 1.22 (3H, t, *J* = 7 Hz, O-CH$_2$-C*H*$_3$); δ_C (50.3 MHz, $CDCl_3$) 159.51 (C), 148.6 (C), 139.71 (C), 132.71 (CH), 129.15 (CH), 128.22 (CH), 128.10 (CH), 126.11 (C), 126.00 (CH), 122.98 (C), 118.23 (CH), 110.00 (CH), 92.73 (C), 89.86 (C), 59.10 (CH_2), 13.60 (CH_3) (Found: MH^+ 317.1233, $C_{20}H_{16}N_2O_2$ requires *M*, 316.1211); *m*/*z* 316 (100%, MH^+).

Acknowledgements

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Table 2 Preparation of functionalised pyrazoles

Substrate	Compound	R	R^2	Yield of **a**[a](%)	Yield of **b**[a](%)
9	**19a/b**	Ph	Ph	24	48
9	**20a**	Ph	H	89	—
10	**21a/b**	C_3H_7	Ph	20	60
10	**22a**	C_3H_7	H	51	—
11	**23a/b**	C_4H_9	Ph	20	60
11	**24a**	C_4H_9	H	52	—

[a] Isolated yields after chromatography. The structures **a** and **b** were assigned on the basis of ^{1}H NMR three bond correlation (HMBC) and NOE experiments.

Notes and references

† The IUPAC name for propargyl is prop-2-ynyl.

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