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Steric redirection of alkylation in 1*H*-pyrazole-3-carboxylate esters

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ABSTRACT

The alkylation of ethyl 1*H*-pyrazole-3-carboxylate with a variety of alkylating agents in the presence of K_2CO_3 was found to largely favor the formation of ethyl 1-substituted pyrazole-3-carboxylates. The alkylation could be sterically redirected by the use of a triphenylsilyl group (ethyl 3-(triphenylsilyl)-1*H*-pyrazole-5-carboxylate) to provide synthetically useful yields of ethyl 1-substituted-3-(triphenylsilyl)-1*H*-pyrazole-5-carboxylates. The triphenylsilyl group could be removed with Bu_4NF. Other triorganosilyl groups (TMS, TES, TBDMS) failed to provide significant redirection, while TIPS proved refractory to protodesilylation.

During the course of a recent medicinal chemistry program, our laboratory required 1-phenacyl-5-carboethoxy pyrazoles for further elaboration. A review of the literature showed that similar intermediates were known,[1] and had been prepared by the alkylation of ethyl 1*H*-pyrazole-3-carboxylate (**1**) with an appropriate phenacyl bromide such as **2** as might be anticipated. The yields for these transformations were not specified, although it could be inferred from the experimental procedures provided that the isolated yields of desired 1-phenacyl-5-carboethoxy regioisomer **3a** might be on the order of 5% to 8% (Scheme 1).

We repeated these transformations with **2** and similar phenacyl halides, and were disappointed to find that indeed the yields of the desired 1-substituted pyrazole-5-carboxylate products such as **3a** were less than 10%. In all cases, the predominant products were the undesired 1-substituted pyrazole-3-carboxylate regioisomer such as **3b**. The reasons for this outcome are likely both steric and electronic. The carboethoxy group might be expected to sterically shield the adjacent pyrazole nitrogen to a greater extent than the distal pyrazole nitrogen. Simultaneously, the delocalization of negative charge in the presumed deprotonated pyrazole intermediate (Scheme 2) would be expected to favor the tautomer **4c** to a greater extent than tautomer **4a**, due to the greater separation of mutually repulsive partial negative charges on the carboethoxy group and the distal pyrazole nitrogen in tautomers **4b** and **4c**.[2]

While very small amounts of intermediates could be prepared in this way, further preparation of our desired medicinal chemistry intermediates would clearly be difficult. Accordingly, we sought to develop a solution to help direct the alkylation towards the pyrazole nitrogen atom adjacent to the ester, *via* the imposition of steric constraints on the deprotonated pyrazole tautomers. In as much as our desired medicinal chemistry targets were required to contain hydrogen substituents at the remaining positions of the pyrazole ring, any substituent used to control the alkylation step would necessarily need to be convenient to introduce and to subsequently remove.[3] Further, removal conditions would ideally be accomplished in a single step, under mild conditions, and with high functional group compatibility. We were naturally drawn to the possible use of a bulky silyl substituent, due to the ease of synthesis of silyl substituted pyrazoles **5** by the [3+2]-cycloaddition of ethyl diazoacetate with a suitable triorganosilyl alkyne (Scheme 3),[4] and by the precedented use of silyl groups as "traceless" linkers in solid phase synthesis.[5]

The trimethylsilyl (**5a**), triethylsilyl (**5b**), and *t*-butyldimethylsilyl (**5c**) pyrazole esters were known in the literature, while the triisopropylsilyl (**5d**) and triphenylsilyl (**5e**) pyrazoles were prepared by the extension of established methods.[6] We then explored the feasibility of our steric redirection concept by screening the regioselectivity of alkylation of the set of pyrazole esters (**1**, **5a**–**5e**) using 2-bromo-1-(1-(4-methoxybenzyl)-1*H*-pyrazol-3-yl)ethan-1-one **6** (Table 1).[7] The structures of the alkylation isomers **7a**–**7f** and **8a**–**8f** were established by 2D NMR experiments and further confirmed by cyclization of the 1-substituted pyrazole-5-carboxylate regioisomers **7a**–**7f** with ammonium acetate,[8] a reaction that regioisomers **8a**–**8f** cannot undergo (Scheme 4).

As observed from the results in Table 1, a very significant steric demand must be imposed to effect a meaningful change in the ratio of **7** to **8** in the alkylation reaction. A trimethylsilyl group

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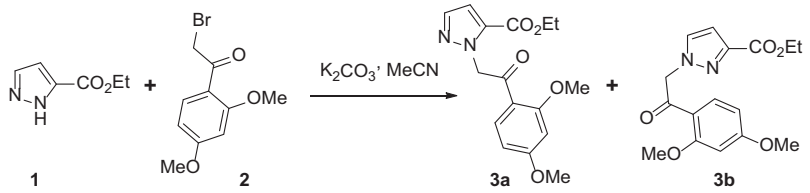
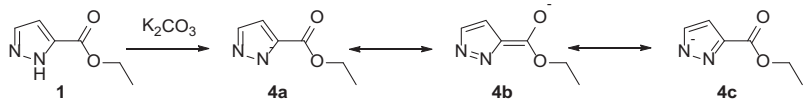
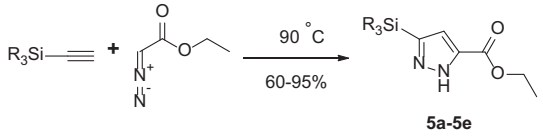


Scheme 1. Regioisomers of pyrazole alkylation with a phenacyl bromide.



Scheme 2. Charge distribution tautomers in deprotonated pyrazole **1**.

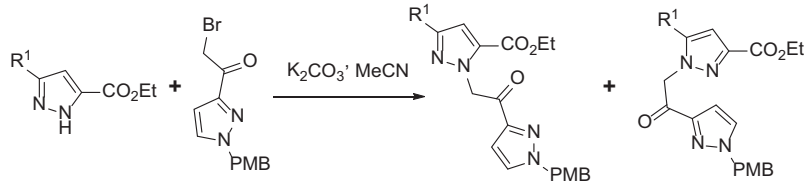


Scheme 3. Synthesis of 3-silyl substituted 5-carboethoxy pyrazoles by [3+2]-cycloaddition.

(Entry 1) offered no benefit.[9] We were surprised to find that triethylsilyl (Entry 2) and *t*-butyldimethylsilyl (Entry 3) substituents likewise failed to significantly redirect alkylation in favor of regioisomer **7**. Fortunately, the triisopropylsilyl (Entry 4) and triphenylsilyl (Entry 5) groups had a significant effect, resulting in a marked increase in the proportion of the desired regioisomer **7e** produced in the reaction. The selectivity in favor of regioisomer **7e** was marginally increased at 100 °C (Entry 6). Further, the triphenylsilyl substituted products **7e** and **8e** proved to be the most amenable to chromatographic purification. Separation of recovered **5a**–**5d** from **7a**–**7d** proved to be difficult, hence the yields of **7a**–**7d** in Table 1 have been corrected based on the sample purity as estimated by ^{1}H NMR. In all cases, the isomers **7** were eluted prior to the isomers **8** during chromatographic purification on silica gel using a heptane – ethyl acetate solvent gradient.

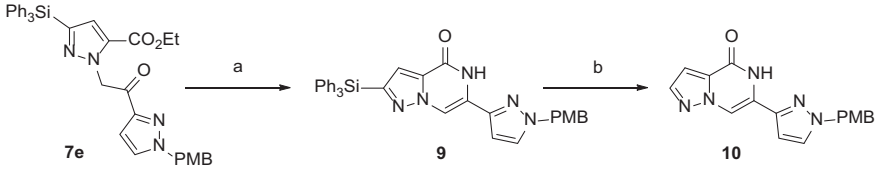
Having identified the capability of the triisopropylsilyl (**5d**) and triphenylsilyl (**5e**) substituted pyrazoles to provide useful amounts

Table 1
Alkylation of ethyl 3-(triorganosilyl)substituted-1*H*-pyrazole-5-carboxylates.



Entry	Pyrazole ester	R^1	Yield **7**[a]	Yield **8**[a]
1	**5a**	Me_3Si	**7a**, 6%[b]	**8a**, 71%
2	**5b**	Et_3Si	**7b**, 5%[b]	**8b**, 72%
3	**5c**	$tBuMe_2Si$	**7c**, 16%[b]	**8c**, 42%
4	**5d**	iPr_3Si	**7d**, 37%[b]	**8d**, 25%
5	**5e**	Ph_3Si	**7e**, 38%	**8e**, 52%
6	**5e**	Ph_3Si	**7e**, 50%[c]	**8e**, 40%
7	**1**	H	**7f**, 4%	**8f**, 74%

[a] All alkylations were conducted using 1 eq. each of pyrazole esters (**1**, **5a**–**5e**) and bromoketone **6** with 1.2 eq. powdered K_2CO_3 in CH_3CN at 0.1 M and 20 °C for 18 h. Yields represent isolated yields of purified products.
[b] Corrected yield based on ^{1}H NMR of isolated material.
[c] Reaction carried out at 100 °C in a sealed tube.



Scheme 4. Cyclocondensation and Ph_3Si removal. (a) NH_4OAc (4 eq.), EtOH, 150 °C (microwave), 1 h, 92%; (b) TBAF (1 M in THF, 20 eq.), 70 °C, 1 h, 96%.