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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.

Keywords: Pyrazoles, alkylation, regioselectivity, steric effect, directing group

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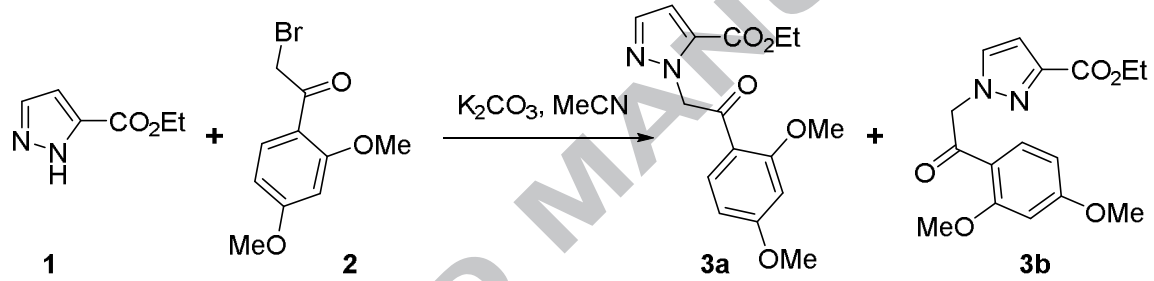
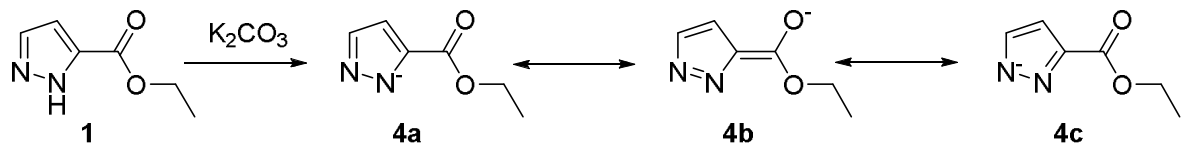
During the course of a recent medicinal chemistry program, our laboratory required 1-phenacyl-5-carboethoxy pyrazoles for further elaboration. A review of the literature showed that similar intermediates were known,[1] and had been prepared by the alkylation of ethyl 1*H*-pyrazole-3-carboxylate (**1**) 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%.



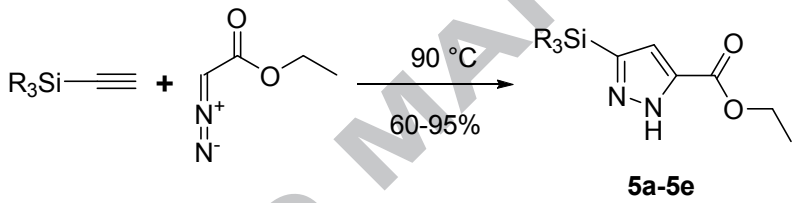
Scheme 1. Regioisomers of pyrazole alkylation with a phenacyl bromide

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]



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

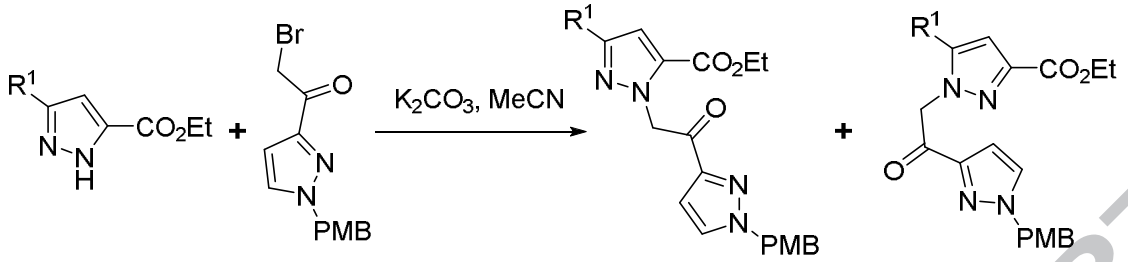
While very small amounts of intermediates could be prepared in this way, further preparation of our desired medicinal chemistry intermediates would clearly be difficult. Accordingly, we sought to develop a solution to help direct the alkylation towards the pyrazole nitrogen atom adjacent to the ester, *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]



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

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).

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



1, 5a-5e **6** **7a-7f** **8a-8f**

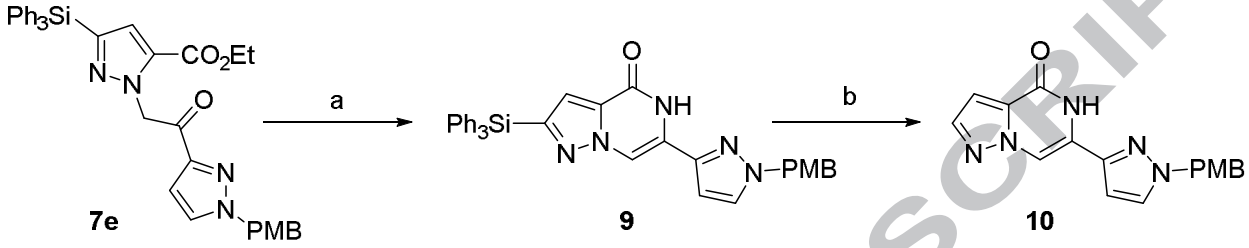
Entry	Pyrazole ester	R^1	Yield **7**[a]	Yield **8**[a]
1	**5a**	Me_3Si	**7a**, 6%[b]	**8a**, 71%
2	**5b**	Et_3Si	**7b**, 5%[b]	**8b**, 72%
3	**5c**	*t*$BuMe_2Si$	**7c**, 16%[b]	**8c**, 42%
4	**5d**	*i*Pr_3Si	**7d**, 37%[b]	**8d**, 25%
5	**5e**	Ph_3Si	**7e**, 38%	**8e**, 52%
6	**5e**	Ph_3Si	**7e**, 50%[c]	**8e**, 40%
7	**1**	H	**7f**, 4%[f]	**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.

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 (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.

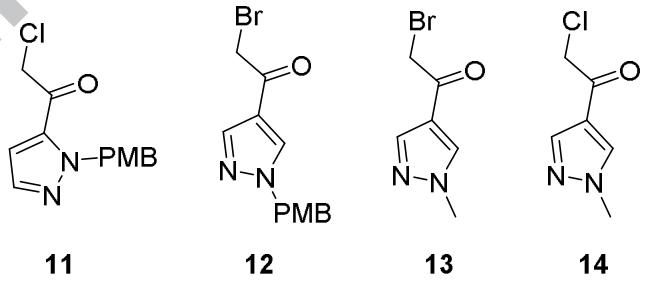
Having identified the capability of the triisopropylsilyl (**5d**) and triphenylsilyl (**5e**) substituted pyrazoles to provide useful amounts of the pyrazole regioisomers **7**, it then remained to determine whether the triisopropylsilyl and/or triphenylsilyl directing groups could be removed. The triisopropylsilyl group

proved to be refractory to protodesilylation even under a variety of forcing conditions and had to be discarded from further consideration.[10] Fortunately, the triphenylsilyl group was readily removed under mild conditions using commercial Bu_4NF in THF solution as the reactant and solvent. For our purposes, this was conveniently accomplished after cyclocondensation with ammonium acetate had been performed to provide the desilylated pyrazole derivative (e.g. **10**) in good yield (Scheme 4).



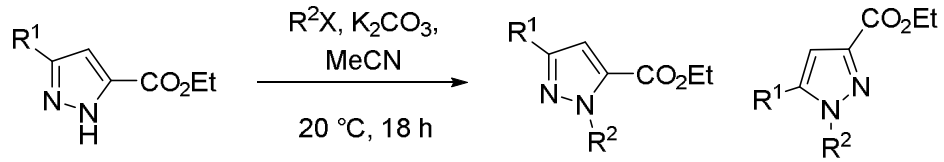
Scheme 4. Cyclocondensation and Ph_3Si removal. (a) NH_4OAc (4 eq.), EtOH, 150 °C (microwave), 1 h, 92%; (b) TBAF (1 M in THF, 20 eq.), 70 °C, 1 h, 96%.

Having shown that the triphenylsilyl pyrazole **5e** could redirect alkylation by bromoketone **6** and that the triphenylsilyl group could then be removed to provide useful yields of the cyclized alkylation products such as **10**, we then examined the regiochemical outcome of the alkylation of **5e** using a variety of α-halo ketones, α-halo esters, benzyl halides, and α-halo pyrazolyl ketones (Scheme 5, ketones **11** – **14**).[11] By way of comparison, we conducted parallel alkylation reactions using **1** (Table 2). All reactions were carried out with continuous magnetic stirring at 0.1 M concentration of the pyrazole ester with 1.1 equivalents of the halide and 1.2 equivalents of -325 mesh powdered K_2CO_3 in MeCN solvent for 18 hours at 20 °C.



Scheme 5. Additional α-halo pyrazolyl ketones studied

Table 2. Alkylation of **1** and **5e**



1, R^1 = H
5e, R^1 = Ph_3Si

15 **16**

Entry[a]	R^1	R^2	X	Yield **15**[b]	Yield **16**[b]
1	H	**11**	Cl	not found	**16a**, 72%
2	Ph_3Si	**11**	Cl	**15b**, 64%	**16b**, 11%
3	H	**12**	Br	**15c**, 11%	**16c**, 40%
4	Ph_3Si	**12**	Br	**15d**, 52%	**16d**, 41%
5	H	**13**	Br	**15e**, <5%	**16e**, 46%
6	Ph_3Si	**13**	Br	**15f**, 31%	**16f**, 18%
7	H	**14**	Cl	**15e**, 14%	**16e**, 65%
8	Ph_3Si	**14**	Cl	**15f**, 52%	**16f**, 30%
9	H	MeO_2CCH_2	Cl	**15g**, 9%	**16g**, 91%
10	Ph_3Si	MeO_2CCH_2	Cl	**15h**, 27%	not found
11	H	MeO_2CCH_2	Br	**15g**, 11%	**16g**, 78%
12	Ph_3Si	MeO_2CCH_2	Br	**15h**, 42%	**16h**, 17%
13	H	$C_6H_5COCH_2$	Br	**15i**, 8%	**16i**, 65%
14	Ph_3Si	$C_6H_5COCH_2$	Br	**15j**, 45%	**16j**, 35%
15	H	$C_6H_5CH_2$	Br	**15k**, 28%	**16k**, 62%
16	Ph_3Si	$C_6H_5CH_2$	Br	**15l**, 47%	**16l**, 13%
17	H	$C_6H_5CH_2$	Cl	**15k**, 40%	**16k**, 60%
18	Ph_3Si	$C_6H_5CH_2$	Cl	**15l**, 27%	**16l**, 3%
19	H	2,5-$(MeO)_2C_6H_5COCH_2$	Br	**15m**, 3%	**16m**, 91%
20	Ph_3Si	2,5-$(MeO)_2C_6H_5COCH_2$	Br	**15n**, 46%	**16n**, 23%
21	H	**2**	Br	**3a**, <5%	**3b**, 85%

22	Ph_3Si	**2**	Br	**15o**, 34%	**16o**, 33%

[a]All alkylations were conducted using 1 eq. of **1** or **5e** and 1.1 eq. of alkyl halide R^2X with 1.2 eq. powdered K_2CO_3 in CH_3CN at 0.1 M and 20 °C for 18 h. [b]All yields refer to isolated yields of purified products. All products gave satisfactory ^1H NMR and mass spectral data.

The results of this study showed that under these conditions (powdered K_2CO_3 in CH_3CN at 20 °C) the alkylation of **1** consistently favored the formation of the regioisomer **16**, whereas the alkylation of **5e** favored the formation of the regioisomer **15**. Not surprisingly, the ratio of **15** to **16** in any given experiment depended upon the particular alkylating agent employed. The alkylation of **5e** occurred more slowly than that of **1**, and reactions of **5e** with some rather less reactive alkylating agents such as methyl chloroacetate (Entry 10) and benzyl chloride (Entry 18) were incomplete at the 18 hour time point. As might be expected, the decomposition of the alkylating agent by base could be a significant side reaction, and this was particularly true for the bromoketone **13** (Entries 5 and 6). The corresponding chloroketone **14** was more tolerant of the reaction conditions and returned higher yields (Entries 7 and 8). It should be noted that under the conditions used in Table 2 (powdered K_2CO_3 in CH_3CN at 20 °C for 18 h), the alkylation of either **1** or **5e** by a simple primary alkyl bromide or chloride such as 1-bromobutane or 1-chlorobutane did not proceed to any significant extent. In all cases, the isomers **15** were eluted prior to the isomers **16** during chromatographic purification on silica gel using a heptane – ethyl acetate solvent gradient as noted previously. Clear differences were observed between isomers **15** and **16** in their ^1H NMR spectra. In isomers **15**, the carboethoxy CH_2 is observed at about 4.25 ppm while in isomers **16** it is found closer to 4.45 ppm. Similarly, in isomers **15** the newly installed *N*-CH_2 substituent occurs downfield from that in the corresponding isomer **16**.

In conclusion, we have shown that the alkylation of ethyl 1*H*-pyrazole-3-carboxylate proceeds largely in favor of the formation of ethyl 1-substituted pyrazole-3-carboxylates. The use of a triphenylsilyl substituted pyrazole resulted in significant steric bias of the alkylation to favor the formation of ethyl 1-substituted-3-(triphenylsilyl)-1*H*-pyrazole-5-carboxylates. The triphenylsilyl directing group could be removed with Bu_4NF.

Acknowledgements

The authors thank Pfizer Worldwide Research and Development for support of this work. The authors declare no competing financial interest.

A. Supplementary material

Experimental procedures for the preparation of silylpyrazoles **5d** and **5e**, haloketones **6**, **11**, and **14**, typical procedures for the alkylation of **5e** (Table 2), cyclization with NH4OAc (**9**), and protodesilylation with TBAF (**10**), ^1H NMR spectra for products **3**, **7**, **8**, **15**, and **16**.

References and Notes

1. Currie, K. S.; Du, Z.; Farand, J.; Guerrero, J. A.; Katana, A. A.; Kato, D.; Lazerwith, S. E.; Li, J.; Link, J. O.; Mai, N.; Notte, G.; Pyun, H.-J.; Sangi, M.; Schmitt, A. C.; Schrier, A. J.; Stevens, K. L.; Venkataramani, C.; Watkins, W. J.; Yang, Z.-Y.; Zablocki, J.; Zipfel, S. WO 2015/017610 A1, 2015; *Chem. Abstr*. **2015**, *162*, 300251.

2. (a) The preference of substrates such as **1** to undergo preferential alkylation at the distal nitrogen to the pyrazole 3-substituent has recently been studied in detail, see Huang, A.; Wo, K.; Lee, S. Y. C.; Kneitschel, N.; Chang, J.; Zhu, K.; Mello, T.; Bancroft, L.; Norman, N. J.; Zheng, S. –L. *J. Org. Chem.* **2017**, *82*, 8864 - 8872. For recent efforts to circumvent this phenomenon, see also (b) Lindsay-Scott, P. J.; Charlesworth, N. G.; Grozavu, A. *J. Org. Chem.* **2017**, *82*, 11295 - 11303; (c) Dorsch, D.; Radtki, D.; Buchstaller, H.-P. *Abstracts of Papers*, 254th ACS National Meeting of the American Chemical Society, Washington, DC, August 20-24, 2017; American Chemical Society: Washington, DC, 2017; ORGN-622622.

3. It should be appreciated that the alkylation regioselectivity issue can be obviated by the use of a symmetrical pyrazole diester, such as diethyl 1*H*-pyrazole-3,5-dicarboxylate, followed by removal of the extra ester group by saponification and decarboxylation. However, the decarboxylation requires forcing conditions and consequently suffers from poor functional group compatibility. See (a) Dorsch, D.; Buchstaller, H.-P.; Moinet, G.; Wegener, A. WO 2013/143663 A1, 2013; *Chem. Abstr*. **2013**, *159*, 546837; (b) Allen, S.; Boys, M. L.; Chicarelli, M. J.; Fell, J. B.; Fischer, J. P.; Gaudino, J.; Hicken, E. J.; Hinklin, R. J.; Kraser, C. F.; Laird, E.; Robinson, J. E.; Tang, T. P.; Burgess, L. E.; Rieger, R. A.; Pheneger, J.; Satoh, Y.; Leftheris, K.; Raheja, R. K.; Bennett, B. L. WO 2016/090285 A1, 2016; *Chem. Abstr*. **2016**, *165*, 69040.

4. (a) For the synthesis of **5a**, see: Zrinski, I.; Juribasic, M.; Eckert-Maksic, M. *Heterocycles*, **2006**, *68*, 1961 - 1967. (b) For the syntheses of **5b** and **5c**, see: Fyfe, M. C.; Meghani, P.; Thom, S. M.; WO 2014/33449 A1, 2014; *Chem. Abstr*. **2014**, *160*, 399206.

5. See, for example: (a) Hone, N. D.; Davies, S. G.: Devereux, N. J.; Taylor, S. L.; Baxter, A. D. *Tetrahedron Let.* **1998**, *39*, 897 - 900; (b) Routledge, A.; Stock, H. T.; Flitsch, S. L.; Turner, N. J. *Tetrahedron Let.* **1997**, *38*, 8287 - 8290.

6. **5d**: Prepared in 61% recrystallized (hexanes) yield from ethyl diazoacetate (1 eq.) and triisopropylsilylacetylene (1 eq.) at 115 °C for 24 h, melting point 105 - 107 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.30 (br. s., 1 H), 6.84 (s, 1 H), 4.27 (q, J=7.28 Hz, 2 H), 1.39 (quin, J=7.41 Hz, 3 H), 1.29 (t, J=7.22 Hz, 3 H), 1.02 (d, J=7.41 Hz, 18 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.14, 143.14, 137.81, 116.35, 59.86, 18.21, 14.19, 10.24. **5e:** Prepared in 76% recrystallized (*n*-octane) yield from ethyl diazoacetate (1 eq.) and triphenylsilylacetylene (1 eq.) in *n*-octane at 90 °C for 24 h, melting point 153 - 154 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.83 (br. s., 1 H), 7.36 - 7.66 (m, 15 H), 6.67 (d, J=1.56 Hz, 1 H), 4.25 (q, J=7.02 Hz, 2 H), 1.26 (t, J=7.02 Hz, 3 H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.88, 143.23, 137.99, 135.51, 132.09, 130.30, 128.25, 118.58, 60.02, 14.17.

7. Bromoketone **6** was prepared from 1-(1-(4-methoxybenzyl)-1*H*-pyrazol-3-yl)ethan-1-one by bromination with pyridinium perbromide in $CHCl_3$ (see ESI).

8. See references 1 and 2(b); see also: Di Fabio, R.; Gentile, G.; Pozzan, A.; Tarsi, L.; Terreni, S.; Tonelli, F. WO 2009/130232 A1, 2009; *Chem. Abstr.* **2009**, *151,* 491158.

9. This observation is consistent with the reported description of the alkylation of **5a** by 2-bromo-1-(2,5-dimethoxyphenyl)ethan-1-one; see: Beeson, C. C.; Lindsey, C. C.; Peterson, Y. K.; Rohrer, B. WO 2014/160181 A1, 2014; *Chem. Abstr.* **2014**, *161*, 551158.

10. A screen of fluoride reagents was conducted to study their ability to effect protodesilylation, including Bu_4NF, KHF_2, $Et_3N \bullet 3$ HF, HF (*aq*), and pyridine HF.

11. The preparation of the bromoketones**12** and **13** has been described, see Brown, M. F.; Dermenci, A.; Fensome, A.; Gerstenberger, B. S.; Hayward, M. M.; Owen, R. R.; Wright, S. W.; Xing, L. H.; Yang, X. WO 2017/144995 A1, 2017; *Chem. Abstr.* **2017**, 1374563.

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Highlights

- Alkylation of 1*H*-pyrazole-3-carboxylate esters favors distal pyrazole ring nitrogen atom
- It is possible to bias the alkylation reaction towards the adjacent pyrazole ring nitrogen atom
- A triphenylsilyl substituent can bias the alkylation reaction in useful yields
- A triphenylsilyl substituent can be removed with fluoride ion after use

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Graphical abstract: