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Substrate-controlled [5+1] Annulation of 5-Amino-1*H*-phenylpyrazoles with Alkenes: Divergent Synthesis of Multi-substituted 4,5-Dihydropyrazolo[1,5-*a*]quinazolines

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Dedication

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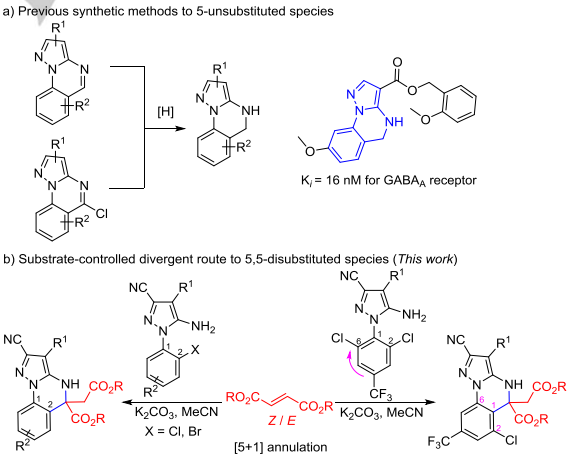
Abstract: A new and efficient [5+1] annulation reaction for the first synthesis of 5,5-disubstituted 4,5-dihydropyrazolo[1,5-*a*]quinazolines is described. This transition-metal-free tandem cyclization was performed with 5-amino-1*H*-phenylpyrazole and readily available electron-deficient olefinic ester. The reaction proceeds *via* an aza-Michael addition/Truce-Smiles rearrangement/S_NAr cyclization pathway, which was verified by DFT calculations. The participation of Truce-Smiles rearrangement is substrate dependent, and could prompt the process of cascade reactions. It is also the first report of alkenes acting as one-carbon synthons for [5+1] hetero-annulations.

Introduction

Quinazolines are nitrogenous heterocycles frequently found in agrochemicals and pharmaceuticals.[1] Among their derivatives, 4,5-dihydropyrazolo[1,5-*a*]quinazolines have attracted broad interests owing to their intriguing structures and unique binding capacities,[2] for example, acting as novel affinity ligands for $GABA_A$ receptor with anxiolytic and antihyperalgesic activities in a selective manner (Scheme 1a).[3] However, efficient synthetic approach to obtain 4,5-dihydropyrazolo[1,5-*a*]quinazolines is rather difficult to achieve. To the best of our knowledge, the only feasible method is the direct reduction of pyrazolo[1,5-*a*]quinazolines, which could only be constructed through multi-step transformation under the assist of metal reductant (Scheme 1a).[3-5] In addition, functionalization at the 5-position of resultant 4,5-dihydropyrazolo[1,5-*a*]quinazolines could not be accomplished. Hence, development of a simple but efficient method for divergent synthesis of multi-substituted 4,5-dihydropyrazolo[1,5-*a*]quinazolines is urgently needed yet remaining challenging.

Herein, we report a transition-metal-free tandem cyclization to achieve the first synthesis of 5,5-disubstituted 4,5-dihydropyrazolo[1,5-*a*]quinazolines using readily available electron-deficient alkenes (Scheme 1b). The participation of Truce-Smiles rearrangement[6] can be controlled by varying the substitution pattern on benzene ring. Notably, it is the first time to use alkenes as one-carbon synthons for such [5+1] hetero-annulations, which provides a new method for 1,1-difunctionalization of alkenes to construct quaternary carbon centers.

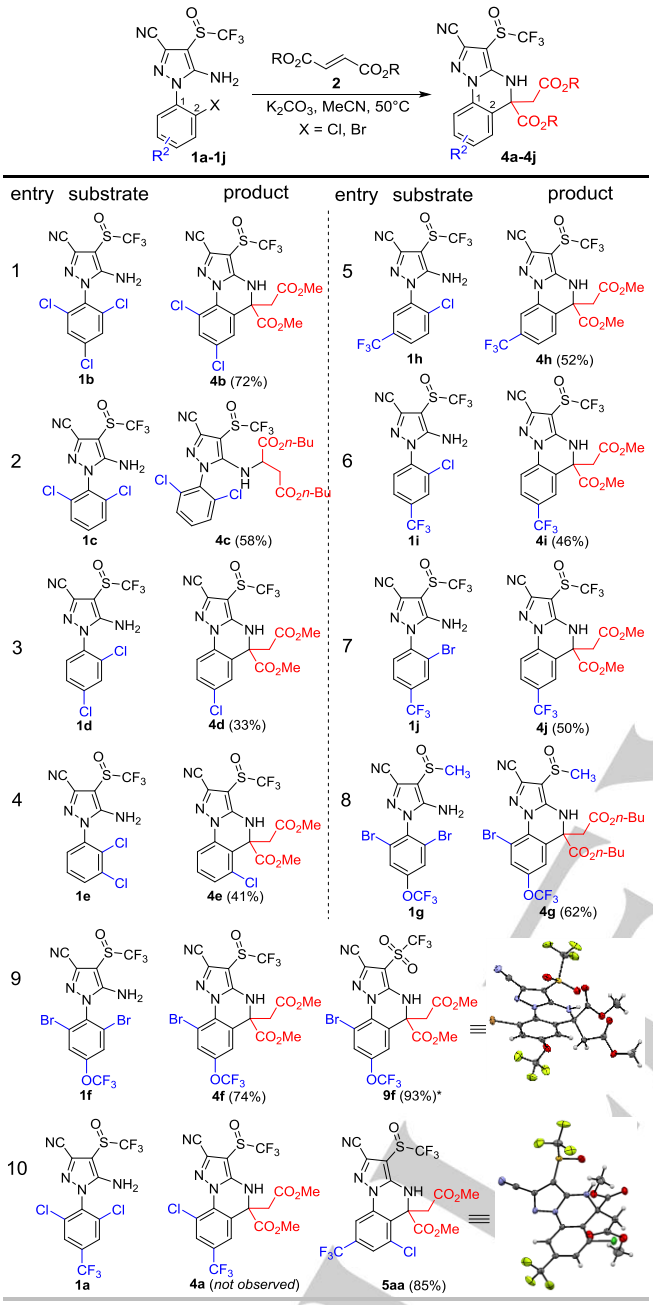


Scheme 1. Synthetic approaches for 4,5-dihydropyrazolo[1,5-*a*]quinazolines.

Results and Discussion

A variety of 5,5-disubstituted 4,5-dihydropyrazolo[1,5-*a*]quinazolines were synthesized through one-pot reactions in acceptable yields under mild condition (Table 1). Direct [5+1] hetero-annulation between dimethyl fumarate (**2a**) and 5-amino-1*H*-phenylpyrazoles bearing electron-withdrawing groups on benzene ring (**1b**-**1j**) have resulted in the expected tricyclic products (**4b**-**4j**) which were unambiguously confirmed using 2D NMR spectroscopy and X-ray crystallographic.[7] The reaction may start with an aza-Michael addition between the olefin and 5-amino-1*H*-phenylpyrazole, then the resulting adducts underwent a direct intramolecular S_NAr cyclization to obtain products **4**.

Table 1. Substrate scope of 5-amine-1*H*-phenylpyrazoles with various substitutions on benzene ring for the formation of 5,5-disubstituted 4,5-dihydropyrazolo[1,5-*a*]quinazolines.[a]



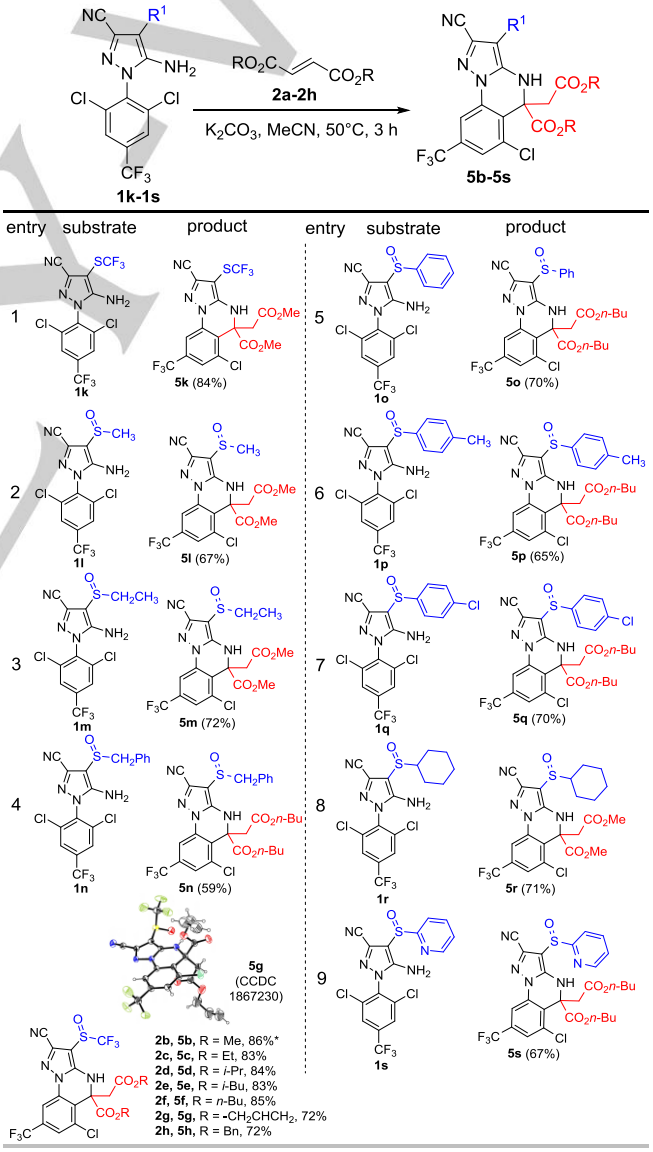
[a] Experiments were performed with **1a**-**1j** (1.0 mmol), **2a**-**2f** (1.1 equiv.), K_2CO_3 (2.5 equiv.) in 15 mL of MeCN. Isolated yields were shown. ***9f** was derived from **4f** by *m*CPBA oxidation.

Reaction of **1c** with **2a** did not afford the target product under present conditions. It is possibly due to the inferior electrophilicity at C-2 position was not enough for the intramolecular S_NAr cyclization.

Interestingly, when compound **1a** bearing 2,6-dichloro-4-trifluoromethyl phenyl group was used as reactant, the expected product **4a** was not formed. A rearranged product **5aa** was the sole product instead (Table 1, entry 10) as verified by 2D NMR spectroscopy and X-ray crystallographic analysis (CCDC 1868710, see Supporting Information). It is possible that a Truce-Smiles rearrangement leading to migration of benzene ring has occurred before the intramolecular S_NAr cyclization process. Given the ubiquity of quinazoline structures in pharmaceutical studies, this rearranged [5+1] annulation could contribute to the structural diversity of 5,5-disubstituted 4,5-dihydropyrazolo[1,5-*a*]quinazolines and is therefore of great importance.

With optimal reaction conditions being established (Table S1, see SI), structural factors that may interfere the rearrangement were then explored to speculate the mechanism (Table 2). Configuration of alkene was found not to affect the occurrence of rearrangement. Reaction of **1a** with dimethyl maleate (**2b**), which is the *Z*- isomer of compound **2a**, would afford the same product (**5b**, Table 2) with similar yield. Choice of ester groups at ends of alkenes would neither impede the rearranging process. When applying various olefinic alkyl or benzyl esters, rearranged products (**5c**-**5h**, Table 2) were obtained in high yields.

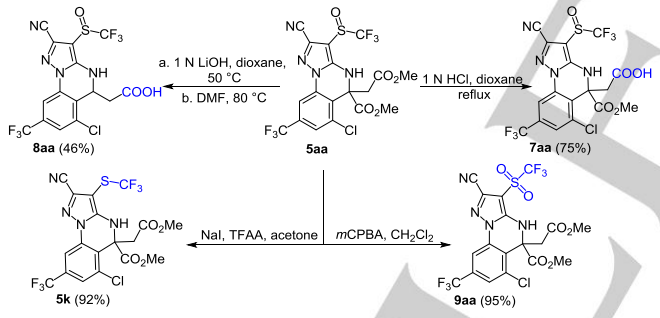
Table 2. Substrate scope of different olefinic esters and various substituted pyrazoles.[a]



[a] Experiments were performed with **1k**-**1s** (5.0 mmol), **2a**-**2h** (1.1 equiv.), K_2CO_3 (2.5 equiv.) in 35 mL of MeCN. Isolated yields were shown. *Dimethyl maleate was used as starting material.

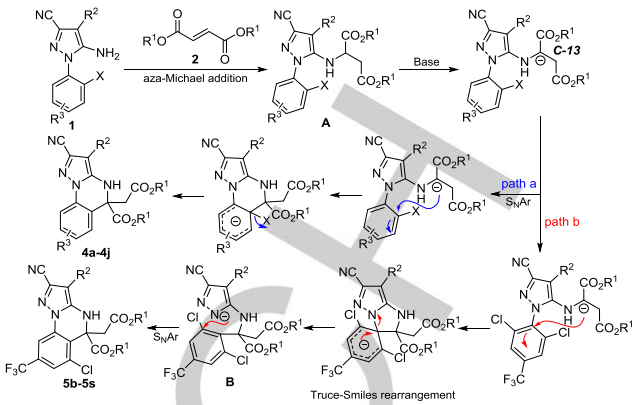
5-Amino-1*H*-phenylpyrazoles with different sulfur-containing substituents on 4-position of pyrazole moiety but the same 2,6-dichloro-4-trifluoromethyl phenyl ring (**1k**-**1s**) were all able to react with dialkyl 2-butenedioates and produced corresponding rearranged products (**5k**-**5s**, Table 2). Apparently, the electronic nature of the substituent linked to sulfoxide could influence the efficiency of the cyclization. Compared to compound **1a** with strong electron-withdrawing trifluoromethyl group (**5aa** 85%), substrates (**1l**-**1n**) with electron-donating groups (methyl, ethyl, or benzyl) on sulfoxide displayed relatively lower reactivity, leading to moderate yields from 59%-72% (**5l**-**5n**). Besides, substrates with bulky cycloalkyl groups or aromatic rings were also compatible with the rearranged process in yields from 65%-71% (**5p**-**5r**). Other phenylpyrazoles substituted with aromatic heterocycles, such as 2-pyridinyl group, also worked well (**5s**).

The protocol to synthesize 4,5-dihydropyrazolo[1,5-*a*]quinazolines was scalable to hectograms. Large-scale reaction of 250 mmol compound **1a** with dimethyl fumarate (**2a**, 275 nmmol) was also performed, and the yield was up to 81% (see SI). Moreover, the 4,5-dihydropyrazolo[1,5-*a*]quinazolines with ester substitution at 5-position enabled more flexible post-synthetic transformations to construct derivatives with potential bioactivities. As illustrated in Scheme 2, treatment of **5aa** with 1N hydrochloric acid enabled the site-selective hydrolysis of the distalis methyl ester in 75% yield (**7aa**). Decarboxylation of **5aa** could proceed in moderate yield to give the corresponding 5-monosubstituted 4,5-dihydropyrazolo[1,5-*a*]quinazoline product (**8aa**). Furthermore, reduction and oxidation of the trifluoromethyl sulfonyl group on **5aa** could also be achieved to afford the corresponding thioether (**5k**) and sulphonyl derivative (**9aa**) in high yields.



Scheme 2. Examples of post-synthetic transformations with compound **5aa**.

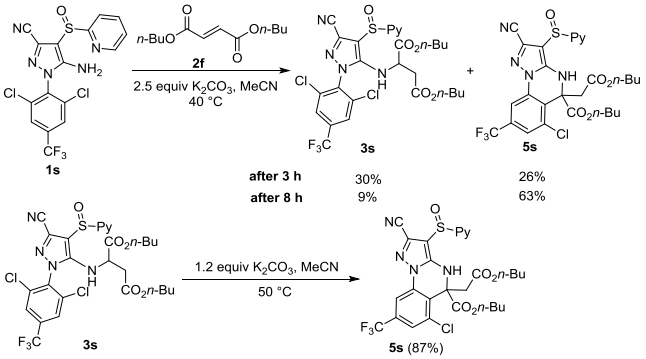
Experiments showed that when applying phenylpyrazole with 2,6-dichloro-4-trifluoromethyl phenyl moiety as reactant, the reaction would lead to rearranged product; otherwise, the direct cyclization product would be obtained. Based on the above observations and literature precedents,[8] a plausible mechanism of this divergent [5+1] annulation reaction was outlined in Scheme 3. The reaction may start with an aza-Michael addition between olefin and 5-amino-1*H*-phenylpyrazole to form adduct **A**, which is then deprotonated at C-13 position. The 2,6-dichloro and 4-trifluoromethyl substituents on phenyl ring have provided sufficient electrophilicity at C-1 position for the formation of a spirocyclic transition state, which enables the 1,4-migration of benzene ring *via* intramolecular nucleophilic Truce-Smiles aromatic rearrangement to generate intermediate **B**. The resulting pyrazolyl anion would then undergo an intramolecular S_NAr to



Scheme 3. Proposed reaction pathways to 4,5-dihydropyrazolo[1,5-*a*]quinazolines with (path **b**) or without (path **a**) 1,4-aryl rearrangement.

displace one of the halide groups on aryl ring, leading to the final cyclization products **5** with trifluoromethyl group located at *meta*- rather than *para*- position of pyrazole ring (path b). When the phenylpyrazole bears less electron-withdrawing substitutions on phenyl ring, direct S_NAr cyclization of deprotonated adduct **A** tends to be favored and affords the tricyclic products **4** without 1,4-aryl rearrangement (path a).

To verify the above mechanism, preliminary studies were conducted by trapping possible intermediates during the transformation (Scheme 4). When **1s** was treated with dibutyl fumarate under conditions with relatively lower temperature (40 °C) and shorter period of time (3 h), aza-Michael adduct **A** (**3s**, 30% yield) could be isolated along with the rearranged cyclization product **5s** (26% yield). Upon prolonged heating, the yield of product **5s** increased to 63% along with the decreased yield of adduct **3s** to 9%. Furthermore, treatment of adduct **3s** under similar conditions could afford the tricyclic product **5s** in high yield (87%), providing further evidence for adduct **3s** being an intermediate in the reaction pathway.



Scheme 4. Capture and post-transformation of intermediate from aza-Michael adduction of **1s** and **2f**.

The proposed reaction pathways were further supported theoretically by conducting DFT computation for the potential energy surfaces (Figure 1).[9] First, a simplified molecule (**C1**) of adduct **A** from aza-Michael addition was deprotonated to get intermediate **IM-1**. In the Truce-Smiles rearrangement/S_NAr cyclization pathway (path **b**, in blue), **IM-1** was then transformed

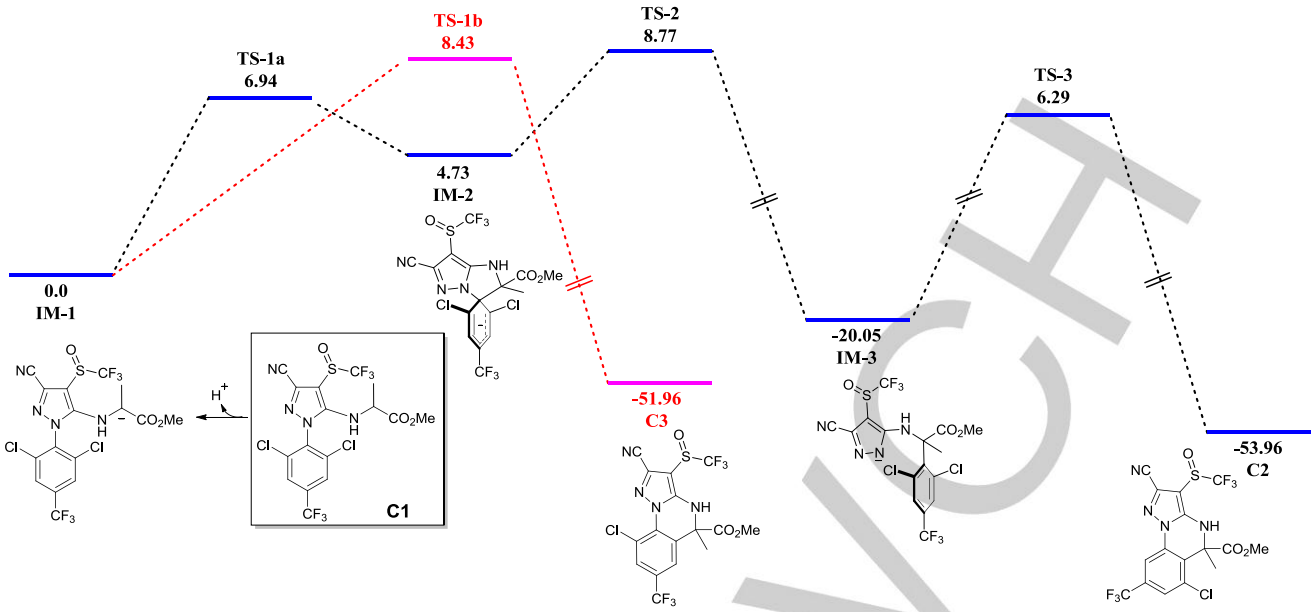


Figure 1. Computational analysis of potential energy surfaces (Δ*G*, kcal/mol) of transition states and intermediates during the formation of 5,5-disubstituted 4,5-dihydropyrazolo[1,5-*a*]quinazolines using DFT [B3LYP-D3/6-311+G (2d,p)].

to a 1,3-spirocyclic imidazolidine (**IM-2**) through transition state **TS-1a** (Figure 2), which was identified to be 6.94 kcal·mol^{-1}. The cleavage of C-N bond of **IM-2** then led to **IM-3** with pyrazolyl anion, and the corresponding transition state **TS-2** (8.77 kcal·mol^{-1}) was determined to be the rate-determining step throughout the process. The S_NAr cyclization product was then achieved with **TS-3** (6.29 kcal·mol^{-1}) as the last barrier. In comparison, if the reaction ran through a direct intramolecular nucleophilic cyclization from **IM-1** to **C3** *via* **TS-1b** (path **a**, in red), its energy barrier (8.43 kcal·mol^{-1}) was slightly higher than that of path **b**. In addition, as shown in Figure 2, the distance between reactive sites in **TS-1a** (2.123 Å) was closer to that in **TS-1b** (2.369 Å), which enables less steric hindrance and higher efficiency for the nucleophile anion to attack C-1 position. Thus, path **b** with Truce-Smiles rearrangement was both energetically and conformationally preferred in the transformation. IRC analysis results of **TS-1a**, **TS-1b**, **TS-2**, and **TS-3** are shown in Figure S8, NPA charges of relevant atoms in the computed intermediates were listed in Table S2.

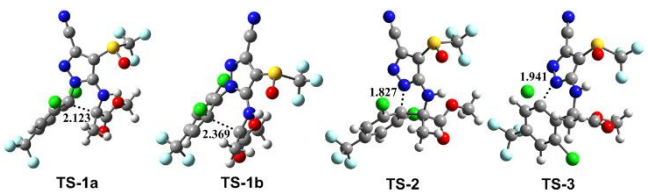


Figure 2. Illustrations of transition-state structures in figure 1. Distances between atoms involved in bond formation (Å) were indicated by dash lines.

Similar calculations were performed for the transformation of substrate **1b** without trifluoromethyl substitution on aryl ring (Figure S9). Results suggested that the energetically preferred pathway passed through a direct intramolecular nucleophilic cyclization from **IM-4** to **C6** *via* **TS-4b** (in red), which was of lower energy barrier (3.02 kcal·mol^{-1}) than the one with Truce-Smiles rearrangement (in blue). It fit well with our experimental observations that the participation of Truce-Smiles rearrangement depends on the strong electron-withdrawing groups on aryl ring, which could promote and stabilize the formation of 1,3-spirocyclic imidazolidine intermediate (**IM-2**), leading to the migration of aryl moiety.

Conclusion

We have developed a novel [5+1] annulation reaction between 5-amino-1*H*-phenylpyrazoles and readily available electron-deficient olefinic esters for the first synthesis of 5,5-disubstituted 4,5-dihydropyrazolo[1,5-*a*]quinazolines. It is also the first-time using electron-deficient alkenes as one-carbon synthon for [5+1] hetero-annulation. The mechanism has been investigated theoretically and experimentally to confirm the tandem aza-Michael addition/Truce-Smiles rearrangement/S_NAr cyclization pathway. The participation of Truce-Smiles rearrangement was substrate dependent, and has prompted the process of cascade reactions verified by DFT calculations. This approach features simple operation, mild reaction conditions, great structural tunability, and satisfactory atom economy. Given the ubiquity of the quinazoline structures in pharmaceuticals, this [5+1] annulation may have broad applications in the synthesis of bioactive molecules.

Experimental Section

General information for synthesis. All reagents and solvents were used as received from commercial sources. All reactions were carried out under air atmosphere and monitored by thin-layer chromatography (TLC) performed on 0.25 mm silica gel plates (GF254) purchased from Haiyang Chemical Industry Co., Ltd (Qingdao, China). The TLC plates were visualized with a ZF-20D ultraviolet analyser. Column chromatographic

purifications were carried out on silica gel (200-300 mesh) using petroleum ether (PE) and ethyl acetate (EA) as eluents. All ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker AV-600 instrument. Chemical shifts (δ) were expressed in parts per million (ppm) with TMS used as an internal standard. Coupling constants (*J*) were quoted in hertz (Hz). ^{1}H NMR splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q), and broad (brs). Splitting patterns that could not be interpreted or easily visualized were designated as multiplet (m). High resolution electro-spray ionization mass spectra (HRMS-ESI) were obtained using a Waters SYNAPT Q-TOF instrument.

Typical experimental procedure of 5,5-disubstituted 4,5-dihydropyrazolo[1,5-*a*]quinazolines (4b-4j). To a solution of 5-amino-1*H*-phenylpyrazole (**1a**-**1j**, 1.0 mmol, 1.0 equiv) and dialkyl 2-butenedioate (**2a** or **2f**, 1.1 equiv) in acetonitrile (35 mL) was added K_2CO_3 (2.5 equiv) under air. The reaction mixture was then heated to 50 °C. After completion of the reaction, acetonitrile was removed in vacuo and the resulting residue was purified *via* flash column chromatography to afford the 5,5-disubstituted 4,5-dihydropyrazolo[1,5-*a*]quinazolines (**4b**-**4j**). The characterization data for representative compounds **4b**, **4e** and **4h** are shown below.

Methyl-7,9-dichloro-2-cyano-5-(2-methoxy-2-oxoethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-a]quinazoline-5-carboxylate (4b): 75:25 d.r.; R_f: 0.3 (EA:PE = 1:7, v/v); white solid; 368 mg, 72% yield; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.86 (brs, 0.75H), 7.84 (brs, 0.25H), 7.58 (d, *J* = 2.2 Hz, 0.75H), 7.57 (d, *J* = 2.1 Hz, 0.25H), 7.33 (d, *J* = 2.2 Hz, 0.75H), 7.32 (d, *J* = 2.2 Hz, 0.25H), 3.80 (s, 2.25H), 3.79 (s, 0.75H), 3.77 (s, 0.75H), 3.73 (s, 2.25H), 3.68 (dd, *J* = 32.0, 17.1 Hz, 1H), 3.00 (dd, *J* = 32.4, 17.1 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 170.14, 170.10, 148.29, 134.02, 133.57, 127.83, 127.21, 125.45 (q, *J* = 336.2 Hz), 125.27, 124.85, 124.14, 110.81, 94.41, 60.98, 54.48, 53.09, 42.82. (major diastereomer) ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 170.41, 170.01, 147.26, 134.39, 134.15, 127.69, 126.62, 125.33 (q, *J* = 336.2 Hz), 125.20, 124.76, 124.43, 110.75, 94.71, 61.02, 54.68, 53.27, 42.97. (minor diastereomer) HRMS (ESI): calcd. for $C_{17}H_{10}Cl_2F_3N_4O_5S$ $[M-H]^-$ 508.9701, found 508.9692.

Methyl-6-chloro-2-cyano-5-(2-methoxy-2-oxoethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-a]quinazoline-5-carboxylate (4e): 55:45 d.r.; R_f: 0.3 (EA:PE = 1:4, v/v); white solid; 196 mg, 41% yield; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 7.91 (dd, *J* = 8.2, 1.3 Hz, 0.55H), 7.90 (dd, *J* = 8.2, 1.3 Hz, 0.45H), 7.45 (t, *J* = 8.2 Hz, 0.45H), 7.44 (t, *J* = 8.2 Hz, 0.55H), 7.42 (brs, 0.45H), 7.36 (dd, *J* = 2.0, 1.3 Hz, 0.55H), 7.34 (dd, *J* = 2.0, 1.3 Hz, 0.45H), 6.93 (brs, 0.55H), 3.82 (s, 1.35H), 3.81 (s, 1.65H), 3.68 (s, 1.35H), 3.63 (s, 1.65H), 3.56 – 3.21 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 169.75, 168.73, 144.33, 133.70, 132.20, 131.02, 129.99, 125.51 (q, *J* = 336.6 Hz), 124.92, 120.22, 114.46, 110.75, 93.49, 61.56, 54.23, 52.14, 41.91. (major diastereomer) ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 170.14, 168.87, 144.38, 133.53, 132.33, 131.10, 130.07, 125.52 (q, *J* = 336.6 Hz), 125.08, 120.24, 114.59, 109.73, 93.93, 61.62, 54.15, 52.40, 41.23. (minor diastereomer) HRMS (ESI): calcd. for $C_{17}H_{11}ClF_3N_4O_5S$ $[M-H]^-$ 475.0091, found 475.0093.

Methyl-2-cyano-5-(2-methoxy-2-oxoethyl)-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-a]quinazoline-5-carboxylate (4h): 55:45 d.r.; R_f: 0.35 (EA:PE = 1:3, v/v); white solid; 265 mg, 52% yield; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.12 (dd, *J* = 4.0, 1.7 Hz, 1H), 7.66 (brs, 0.55H), 7.62 – 7.58 (m, 1H), 7.58 (brs, 0.45H), 7.56 (s, 0.55H), 7.55 (s, 0.45H), 3.80 (s, 1.65H), 3.79 (s, 1.35H), 3.77 (s, 1.35H), 3.76 (s, 1.65H), 3.73 (d, *J* = 1.1 Hz, 1H), 3.09 (dd, *J* = 20.9, 17.2 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 170.65, 170.26, 146.13, 133.46 (q, *J* = 34.0 Hz), 132.06, 126.98, 125.57 (q, *J* = 336.1 Hz), 125.29, 124.76 (q, *J* = 3.4 Hz), 124.70, 122.97 (q, *J* = 273.0 Hz), 113.39 (q, *J* = 3.9 Hz), 110.63, 94.86, 60.89, 54.48, 53.05, 43.53. (major diastereomer) ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 170.26, 170.21, 145.71, 133.49 (q, *J* = 34.0 Hz), 131.99, 126.98, 125.55, 125.36 (q, *J* = 336.0 Hz), 124.76 (q, *J* = 3.4 Hz), 124.42, 122.95 (q, *J* = 272.9 Hz), 113.31 (q, *J* = 3.9 Hz), 110.60, 94.60, 60.85, 54.34, 52.98, 43.72.(minor diastereomer) HRMS (ESI): calcd. for $C_{18}H_{11}F_6N_4O_5S$ $[M-H]^-$ 509.0354, found 509.0361.

Typical experimental procedure of 5,5-disubstituted 4,5-dihydropyrazolo[1,5-*a*]quinazolines (5b-5s). To a solution of 5-amino-1*H*-phenylpyrazole (**1k**-**1s**, 5.0 mmol, 1.0 equiv.) and dialkyl 2-butenedioate (**2a**-**2j**, 1.1 equiv.) in acetonitrile (35 mL) was added K_2CO_3 (2.5 equiv.) under air. The reaction mixture was then heated to 50 °C for 3 h. After completion of the reaction, acetonitrile was removed in vacuo and the resulting residue was purified *via* flash column chromatography to afford the 5,5-disubstituted 4,5-dihydropyrazolo[1,5-*a*]quinazolines (**5b**-**5s**). The characterization data for representative compounds **5b, 5g, 5k** and **5r** are shown below.

Methyl-6-chloro-2-cyano-5-(2-methoxy-2-oxoethyl)-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-a]quinazoline-5-carboxylate (5aa or 5b): 50:50 d.r.; R_f: 0.3 (EA:PE = 1:6, v/v); white solid; 2.33 g, 86% yield; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.14 (d, *J* = 1.8 Hz, 0.5H), 8.13 (d, *J* = 1.8 Hz, 0.5H), 7.57 (d, *J* = 1.7 Hz, 1H), 7.28 (brs, 0.5H), 6.83 (brs, 0.5H), 3.82 (s, 1.5H), 3.81 (s, 1.5H), 3.66 (s, 1.5H), 3.62 (s, 1.5H), 3.57 – 3.25 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 169.48, 168.05, 144.64, 134.50, 133.72 (q, *J* = 34.9 Hz), 133.19, 126.39 (q, *J* = 3.9 Hz), 125.72, 125.58 (q, *J* = 336.2 Hz), 123.69, 122.38 (q, *J* = 273.4 Hz), 111.66 (q, *J* = 3.8 Hz), 110.39, 93.69, 61.75, 54.46, 52.51, 41.85. (A diastereomer) ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 169.75, 168.21, 144.69, 134.36, 133.62 (q, *J* = 34.6 Hz), 133.03, 126.46 (q, *J* = 3.9 Hz), 125.57, 125.52 (q, *J* = 336.5 Hz), 123.71, 122.41 (q, *J* = 273.2 Hz), 111.80 (q, *J* = 3.8 Hz), 110.39, 94.05, 61.70, 54.38, 52.27, 41.14. (B diastereomer) HRMS (ESI): calcd. for $C_{18}H_{11}ClF_6N_4NaO_5S$ $[M+Na]^+$ 566.9941, found 566.9918.

Allyl-5-[2-(allyloxy)-2-oxoethyl]-6-chloro-2-cyano-8-(trifluoromethyl)-3-[(trifluoromethyl)sulfinyl]-4,5-dihydropyrazolo[1,5-*a*]quinazoline-5-carboxylate (5g): 85:15 d.r.; R_f: 0.3 (EA:PE = 1:12, v/v); white solid; 2.16 g, 72% yield; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.12 (d, *J* = 1.8 Hz, 1H), 7.57 (d, *J* = 1.9 Hz, 1H), 7.23 (s, 0.85H), 6.85 (s, 0.15H), 5.88 – 5.74 (m, 2H), 5.33 – 5.19 (m, 4H), 4.70 (ddd, *J* = 75.0, 12.8, 6.1 Hz, 2H), 4.56 – 4.47 (m, 2H), 3.56 – 3.35 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 168.90, 167.28, 144.66, 134.36, 133.74 (q, *J* = 34.8 Hz), 133.27, 131.28, 130.43, 126.42 (q, *J* = 3.8 Hz), 125.80 (q, *J* = 336.2 Hz), 125.74, 123.58, 122.39 (q, *J* = 273.2 Hz), 120.46, 119.50, 111.80 (q, *J* = 3.7 Hz), 110.39, 94.01, 68.16, 66.31, 61.96, 41.54. (major diastereomer) ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 168.63, 167.16, 144.60, 134.52, 133.66 (q, *J* = 34.8 Hz), 133.13, 131.14, 130.43, 126.38 (q, *J* = 3.2 Hz), 125.59, 125.53 (q, *J* = 336.7 Hz), 123.64, 122.41 (q, *J* = 273.1 Hz), 120.55, 119.64, 111.67 (q, *J* = 3.8 Hz), 110.39, 93.71, 68.29, 66.21, 61.92, 42.09. (minor diastereomer) HRMS (ESI): calcd. for $C_{22}H_{14}ClF_6N_4O_5S$ $[M-H]^-$ 595.0278, found 595.0259.

Methyl-6-chloro-2-cyano-5-(2-methoxy-2-oxoethyl)-8-(trifluoromethyl)-3-[(trifluoromethyl)thio]-4,5-dihydropyrazolo[1,5-a]quinazoline-5-carboxylate (5k): R_f: 0.35 (EA:PE = 1:6, v/v); white solid, 2.22 g, 84% yield; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.16 (d, *J* = 1.8 Hz, 1H), 7.56 (d, *J* = 0.3 Hz, 1H), 6.84 (s, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.51 (d, *J* = 16.9 Hz, 1H), 3.10 (d, *J* = 16.9 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 170.42, 168.68, 145.37, 134.71, 133.90 (q, *J* = 34.7 Hz), 133.44, 133.24, 128.57 (q, *J* = 312.4 Hz), 126.09 (q, *J* = 3.6 Hz), 123.71, 122.43 (q, *J* = 273.3 Hz), 111.73 (q, *J* = 3.8 Hz), 111.30, 84.06 (d, *J* = 2.6 Hz), 62.19, 54.34, 52.51, 40.55. HRMS (ESI): calcd. for $C_{18}H_{10}ClF_6N_4O_5S$ $[M-H]^-$ 527.0015, found 527.0002.

Methyl-6-chloro-2-cyano-3-(cyclohexylsulfinyl)-5-(2-methoxy-2-oxoethyl)-8-(trifluoromethyl)-4,5-dihydropyrazolo[1,5-a]quinazoline-5-carboxylate (5r): 80:20 d.r.; R_f: 0.3 (EA:PE = 1:5, v/v); white solid; 1.99 g, 71% yield; ^{1}H NMR (600 MHz, $CDCl_3$) *δ* 8.16 – 8.10 (m, 0.8H), 8.12 (d, *J* = 1.6 Hz, 0.2H), 7.53 (d, *J* = 3.6 Hz, 0.2H), 7.52 (s, 0.8H), 7.43 (s, 0.2H), 6.90 (s, 0.8H), 3.82 (s, 0.6H), 3.79 (s, 2.4H), 3.63 (s, 0.6H), 3.58 (s, 2.4H), 3.56 – 3.37 (m, 2H), 2.92 (tt, *J* = 11.8, 3.4 Hz, 1H), 2.07 – 1.98 (m, 2H), 1.97 – 1.86 (m, 2H), 1.77 – 1.69 (m, 1H), 1.52 – 1.43 (m, 2H), 1.44 – 1.34 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) *δ* 169.71, 168.21, 143.32, 134.75,

133.22 (q, *J* = 34.7 Hz), 132.71, 125.62 (q, *J* = 3.7 Hz), 124.75, 123.69, 122.33 (q, *J* = 273.3 Hz), 111.63, 111.24 (q, *J* = 3.7 Hz), 98.63, 63.14, 61.13, 54.16, 52.04, 41.79, 31.43, 30.19, 25.40, 25.38, 24.46. (major diastereomer) ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.52, 168.63, 143.50, 134.59, 133.22 (q, *J* = 34.7 Hz), 132.92, 125.62 (q, *J* = 3.7 Hz), 124.45, 123.95, 122.33 (q, *J* = 273.3 Hz), 111.63, 111.24 (q, *J* = 3.7 Hz), 99.22, 63.49, 61.33, 54.02, 52.32, 41.03, 31.92, 29.35, 25.26, 25.14, 24.72. (minor diastereomer) HRMS (ESI): calcd. for $C_{23}H_{21}ClF_3N_4O_5S$ $[M-H]^-$ 557.0873, found 557.0878.

Acknowledgements

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Keywords: [5+1] Annulation • 4,5-Dihydropyrazolo[1,5-*a*]quinazolines • Nucleophilic aromatic substitution • Truce-Smiles rearrangement • Alkenes

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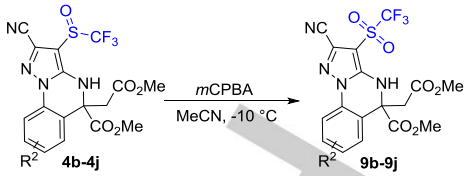

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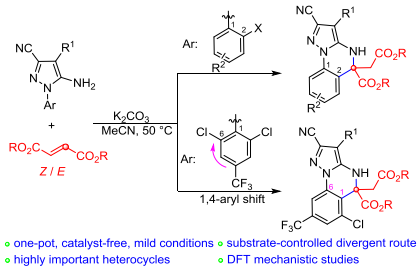
Annulation Reactions



With C=C double bonds as one-carbon synthons, an efficient [5+1] hetero-annulation of 5-amino-1*H*-phenylpyrazoles with electron-deficient olefinic esters was developed, allowing the first and divergent synthesis of 5,5-disubstituted 4,5-dihydropyrazolo[1,5-*a*]quinazolines.

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Substrate-controlled [5+1] Annulation of 5-Amino-1*H*-phenylpyrazoles with Alkenes: Divergent Synthesis of Multi-substituted 4,5-Dihydropyrazolo[1,5-a]quinazolines