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Unusual multiple insertion of diazo carbonyl compounds into (purin-6-yl)benzene derivative

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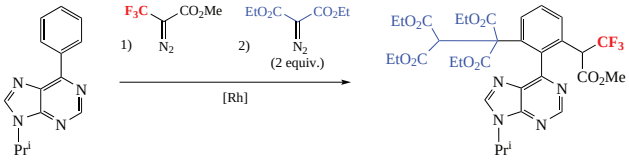
The consecutive alkylation of 9-isopropyl-6-phenyl-9*H*-purine with methyl 2-diazo-3,3,3-trifluoropropionate and diethyl diazomalonate proceeds at the phenyl substituent firstly *via ortho*-C–H activation under chelation-assistance of the purine core, followed by classical electrophilic metal carbenoid insertion to the C−H bond of a malonate moiety.

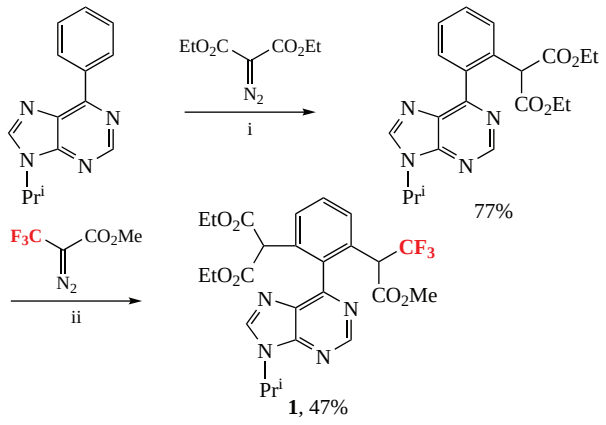


Keywords: carbenoids, C–H functionalization, diazo compounds, organofluorine compounds, homogeneous catalysis, nitrogen heterocycles, purines.

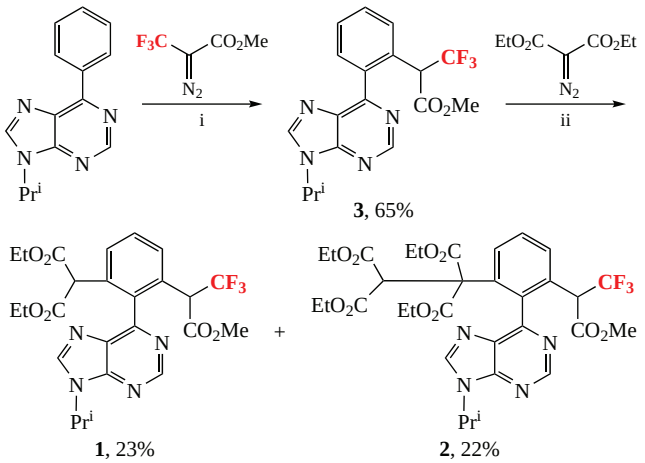
α-Diazo carbonyl compounds have proved to be useful alkylation reagents,[1,2] and their transition metal activation is of a special interest due to atom- and step-economy. Recently, we have reported selective C–H alkylation of 6-arylpurines using diethyl diazomalonate or methyl 2-diazo-3,3,3-trifluoropropionate as the second coupling partner.[3] This reaction proceeded under chelation-assistance of the purine core that provided high regioselectivity at the *ortho*-position of aryl substituent.[4] Catalyst screening showed that the dimeric rhodium complex $[Cp^*RhCl_2]_2$ is the best one. On the one example, we have demonstrated the possibility of consecutive double alkylation of 9-isopropyl-6-phenyl-9*H*-purine with two different α-diazo carbonyl compounds, primarily with diethyl diazomalonate and then with methyl 2-diazo-3,3,3-trifluoropropionate (Scheme 1). The corresponding dialkylation product **1** was obtained as a mixture of diastereomers in 47% yield.[3]

In the present work, we reinvestigated the synthesis of compound **1** using the reverse sequence of α-diazo carbonyl compounds (Scheme 2) when intermediate 2-aryl-3,3,3-trifluoropropionate **3** was reacted with diazomalonate. The mixture of $[Cp^*RhCl_2]_2$ (2.5 mol%) and $AgSbF_6$ (10 mol%) was used as a catalytic system without the addition of pivalic acid because this additive would not considerably impact the yield.[3] Unexpectedly, along with target compound **1**, the product **2** of double insertion of diethyl diazomalonate was isolated in 22% yield at the second stage. A double set of all characteristic signals that corresponded to a mixture of two diastereomers has been observed in a ratio 1:3 in ^{1}H and ^{13}C NMR spectra of **2**. The structure of **2** was ultimately established by X-ray diffraction (Figure 1).† Similarly to compound **1**, the aryl substituent in **2** is not coplanar with the purine moiety; the dihedral angle being 66.0°. At the same time, the C(19)−C(37) bond in **2** (1.557 Å) is considerably longer than in **1** (1.518 Å), which can be caused by electron-withdrawing and steric effects of additional malonate moiety.

To study the pathway for the formation of pentaester **2**, we initially proposed two possible pathways, namely, simple electrophilic metal carbenoid insertion into the C_{sp^3}−H bond of compound **1**



Scheme 1 *Reagents and conditions*: i, $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), Bu^tCO_2H (50 mol%), 1,2-dichloroethane, 80 °C, 4 h; ii, $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), 1,2-dichloroethane, 80 °C, 4 h (see ref. 3).



Scheme 2 *Reagents and conditions*: i, $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), 1,2-dichloroethane, 80 °C, 4 h; ii, $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), 1,2-dichloroethane, 85−95 °C, 4 h.

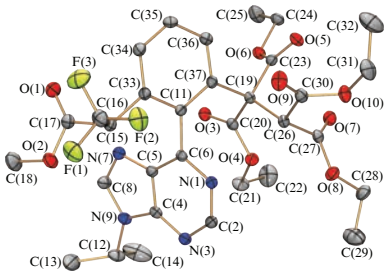


Figure 1 Molecular structure of **2** with atoms shown as thermal ellipsoids at 50% probability level. Hydrogen atoms are omitted for clarity.

(Scheme 3, pathway *a*) or preliminary formation of tetraethyl ethene-1,1,2,2-tetracarboxylate from diethyl diazomalonate with its subsequent addition to intermediate 3,3,3-trifluoro-2-[2-(9-isopropyl-9*H*-purin-6-yl)phenyl]propanoate **3** *via* C_{sp^2}–H activation process (pathway *b*). Noteworthy, the alkene formation under thermal decomposition of dialkyl diazomalonates[8] as well as the Rh-catalyzed alkylation of arenes with alkenes have been known.[9] To verify the second pathway, we treated compound **3** with electron-deficient O^1,O^1-diethyl O^2-methyl 3,3,3-trifluoroprop-1-ene-1,1,2-tricarboxylate,[10] which is closely related to tetraethyl ethene-1,1,2,2-tetracarboxylate, in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol%) and $AgSbF_6$ (10 mol%). Only starting materials were isolated after the processing, which would confirm that pathway *a* is more plausible. Indeed, the reaction of **1** with diethyl diazomalonate occurred under the same conditions to afford compound **2** in 72% yield. To elucidate the selectivity of the diethyl diazomalonate insertion, we performed the DFT calculations at the B3LYP/DZP level (Table 1). It was found that, in general, the CH proton at the malonate moiety is more acidic than that of trifluoropropionate (entries 1 *vs.* 2 and 3 *vs.* 4), suggesting more nucleophilic nature of carbon atom in the first case. To the best of our knowledge, metal carbenoid insertion without chelation-assistance of directing groups preferably proceeds *via* an electrophilic attack on the most nucleophilic site of organic compounds.[11] Although the deprotonation of malonates and trifluororopionates is endothermic, the proton elimination at CH group of the malonate moiety of compound **1** is less endothermic (entry 3), thus additionally confirming the reaction pathway *a*.

In summary, we demonstrated the feasibility of multiple alkylation of 6-arylpurines with α-diazo carbonyl compounds. It was shown that the first and second functionalizations proceed *via* C–H activation of *ortho*-hydrogen atoms of aryl substituent under chelation-assistance of the purine core, while the third alkylation occurs as a result of simple electrophilic metal carbenoid insertion to the C–H bond of the malonate moiety.

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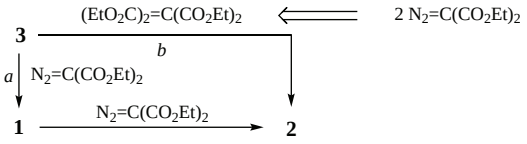
† *Crystal data for* **2**. $C_{32}H_{37}F_3N_4O_{10}$ (M = 694.65), monoclinic, space group $P2_1/c$, at 120 K: a = 13.5252(6), b = 10.1119(5) and c = 24.7730(11) Å, β = 100.3370(10)°, V = 3333.1(3) Å^3, Z = 4, d_{calc} = 1.384 g cm^{-3}, μ(MoKα) = = 1.94 cm^{-1}, F(000) = 1456. Total of 55759 reflections were collected (7277 independent reflections, R_{int} = 0.0781) and used in the refinement, which converged to wR_2 = 0.1226 and GOOF = 1.018 for all the independent reflections [R_1 = 0.0452 was calculated for 5187 reflections with $I>2\sigma(I)$].

The X-ray diffraction data were collected with a Bruker APEX2 CCD diffractometer (MoKα radiation, λ = 0.71072 Å, graphite monochromator). Raw data were integrated, scaled, merged, and corrected for Lorentz-polarization effects using the APEX2 package. Using Olex2,[5] the structure was solved with the ShelXT structure solution program[6] using Intrinsic Phasing and refined with the XL refinement package[7] using Least-Squares minimisation in the anisotropic approximation for non-hydrogen atoms.

CCDC 1983328 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.



Scheme 3

Table 1 Calculated reaction energies of deprotonation of malonate and trifluoropropionate moieties in alkylation products at the B3LYP/DZP level with corrections for solvation in 1,2-dichloroethane (the COSMO model).[a]

Entry	Reaction	ΔE/ kcal mol^{-1}
1	[Pur-CH(COOEt)$_2$] + H_2O → [Pur-C(COOEt)$_2$]$^-$ + [H_3O]$^+$	69.46
2	[Pur-CH(CF$_3$)(COOMe)] (**3**) + H_2O → [Pur-C(CF$_3$)(COOMe)]$^-$ + [H_3O]$^+$	70.74
3	[Pur-CH(COOEt)$_2$CH(CF$_3$)(COOMe)] (**1**) + H_2O → [Pur-C(COOEt)$_2$CH(CF$_3$)(COOMe)]$^-$ + [H_3O]$^+$	69.25
4	[Pur-CH(COOEt)$_2$CH(CF$_3$)(COOMe)] (**1**) + H_2O → [Pur-CH(COOEt)$_2$C(CF$_3$)(COOMe)]$^-$ + [H_3O]$^+$	71.41

[a] Pur is 2-(9-isopropyl-9*H*-purin-6-yl)phenyl; the eliminated proton is marked red.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2020.07.029.

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