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Synthesis toward CRHR1 Antagonists through 2,7-Dimethylpyrazolo[1,5-α][1,3,5]triazin-4(3*H*)-one C−H Arylation

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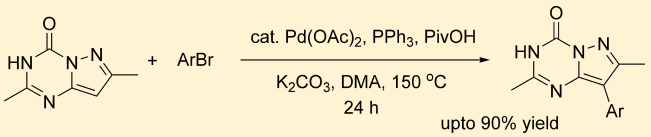
Supporting Information

ABSTRACT: A novel synthetic protocol for 8-aryl substituted pyrazolo[1,5-α][1,3,5]triazin-4(3*H*)-ones was developed employing Pd-catalyzed C−H arylation. The reaction yield was influenced by the presence of a phosphine ligand, pivalic acid, and base selection. With the use of 5−10 mol % catalyst, reactions of **2** with *p*- or *m*-substituted aryl bromides proceeded in moderate to good yields. Lower yields were observed with *o*-substituted aryl bromides. Using this method a precursor for MJL1-109-2, a known nonpeptide CRHR-1 antagonist, was successfully synthesized.



The corticotropin-releasing hormone (CRH), first isolated from ovine hypothalamus by Vale and co-workers[1] in 1981, is a neuropeptide with 41 amino acids. By regulating the hypothalamus-pituitary-adrenal axis (HPA),[2] CRH plays a critical role in the body's response to stress.[3] The CRH hypersecretion is known to trigger chronic stress, which leads to mental disorders such as anxiety and depression.[4] CRH's biological functions are manifested through binding to two classes of G-protein-coupled receptors, called CRHR1 and CRHR2.[2a,5] In particular, CRHR1 densities in the prefrontal cortex are known to have a close relationship with disorders[6] such as depression, anxiety, irritable bowel syndrome, and Alzheimer's disease.[7] Therefore, CRH receptor antagonists may be employed as potential anxiolytic or antidepressant drugs.[8] Additionally, nonpeptide CRHR1 antagonists[9] have been targeted as possible treatments for stress-related illnesses over the past two decades (Figure 1). Our research group has

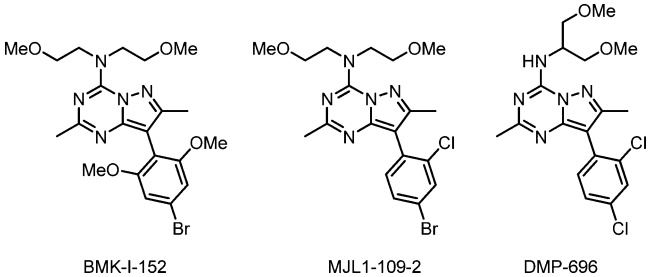


Figure 1. Structures of CRHR1 antagonists.

developed high-affinity [^{76}Br]CRHR1 antagonists and reported on the receptor distribution in the brain through autoradiographic Positron Emission Tomography (PET) imaging studies.[9j,k]

Due to the structural complexity of the CRHR1 antagonists containing the 8-aryl-substituted 2,7-dimethylpyrazolo[1,5-α][1,3,5]triazin-4(3*H*)-one unit, the synthesis of these antagonists in a linear fashion usually requires cumbersome and lengthy synthetic steps. Therefore, many research groups concentrated on convergent synthetic route development for the pyrazolo[1,5-α][1,3,5]triazin-4(3*H*)-one class CRHR1 antagonists.[9g,h,j,k,10] Previously, Griffith[11] and Zuev[12] have successfully accomplished syntheses of the same class compounds by utilizing Suzuki coupling to combine a halogenated *N*-heterocyclic compound and an arylboronic acid. General Pd-catalyzed cross-coupling reactions require prefunctionalized reactants such as ArMgX,[13] ArB(OR)$_2$,[14] or ArSnR$_3$,[15] from which stoichiometric amounts of halogenated and organometallic wastes are produced. In this regard, a direct C−H functionalization of the pyrazolotriazinone would be a more desirable alternative.[11,12] A direct C−H arylation protocol has been developed as an attractive, atom-economical alternative to avoid unwanted side products.[16−18] We previously reported on the development of an environmentally friendly C−H arylation of indole moieties using magnetically recyclable and heterogeneous Pd−Fe$_3$O$_4$ nanocrystal catalysts.[19] We envisioned the use of coupling reactions through C−H activation by utilizing a Pd catalyst to successfully synthesize the pyrazolotriazine class CRHR1 antagonists. Since Sames and co-workers[20] reported the first intermolecular C−H arylation of pyrazoles in 2009, research has concentrated on developing novel ways to synthesize substituted pyrazole derivatives.[21] Contrary to the C5 arylation, the C4 arylation of pyrazoles has not been very efficient.[20−22] In this paper, we reveal the first palladium catalyzed intermolecular C−H arylation for 2,7-dimethylpyrazolo[1,5-α][1,3,5]triazin-4(3*H*)-one as a key step to synthesize key intermediates for pyrazolo[1,5-α][1,3,5]triazine class CRHR1 antagonists.

The coupling through C−H arylation reaction requires 2,7-dimethylpyrazolo[1,5-α][1,3,5]triazin-4(3*H*)-one (**2**) to be a substrate, and it was synthesized in two steps in 65% overall yield, as reported earlier (Scheme 1).[9k,23] From the

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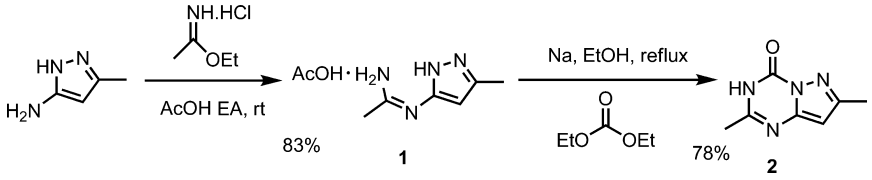
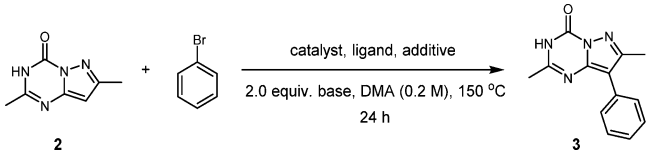
Scheme 1. Synthesis of the 2,7-Dimethylpyrazolo[1,5-α][1,3,5]triazin-4(3H)-one



commercially available starting material, 3-methyl-1*H*-pyrazol-5-amine and ethyl acetimidate hydrochloride, an acetic acid salt of an amidine **1** was obtained in 83% yield. Compound **1** was treated with diethyl carbonate in a basic ethanolic solution to provide the urea **2** in 78% yield.

With the desired pyrazolotriazinone **2**, we carried out an intermolecular coupling reaction with aryl halides through C−H arylation. This intermolecular coupling approach through direct C−H arylation of pyrazoles was previously developed by Kumpulainen et al.[21f] in 2014. We chose bromobenzene as a model coupling partner with the urea **2** for optimal reaction conditions. Because of the poor solubility of **2** in xylenes (the solvent of choice by Kumpulainen et al.), a polar aprotic solvent *N,N*-dimethylacetamide (DMA) was used instead. We first probed various palladium catalysts for the C−H arylation. As seen in Table 1, to our delight, the reaction of **2** (0.20 mmol) with bromobenzene (0.80 mmol, 4 equiv) in the presence of $Pd(OAc)_2$ (0.01 mmol, 5 mol %) and K_2CO_3 in DMA (1.0 mL) produced the desired product **3**, albeit in 24% yield (Table 1, entry 1). It is well-known that *N*-heterocycles can coordinate the Pd catalyst by forming a stable complex, hence reducing the activity.[24] Thus, we carried out the reaction in the presence of an extra ligand and/or an additive. When 30 mol % pivalic acid was added as an additive, a noticeable increase in the yield (47%) was observed (Table 1, entry 2).[21f,25] Adding 30 mol % PPh_3 also dramatically enhanced the coupling reaction reactivity to result in a 56% yield (Table 1, entry 3).[21f] A synergistic effect was observed from the addition of both PPh_3 (0.06 mmol, 30 mol %) and PivOH (0.06 mmol, 30 mol %) in the presence of K_2CO_3 (0.40 mmol, 2 equiv) that led to an 88% yield of the desired coupling product (Table 1, entry 4). These studies demonstrated that both phosphine ligand and pivalic acid in substoichiometric quantities are necessary for optimal reaction yields. We examined other Pd(II) sources, such as $Pd(PPh_3)_2Cl_2$, $(PhCN)_2PdCl_2$, and $PdCl_2$, but no yield improvement was observed (Table 1, entries 5−7, respectively). We also checked Pd[0] catalysts such as $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ (Table 1, entries 8 and 9, respectively) and other phosphine ligands such as $P(Ph)_2Cl$ and $P(n\text{-}Bu)_3$ (Table 1, entries 10 and 11, respectively), but there was no yield improvement. Increasing the palladium catalyst's loading amount up to 20 mol % did not result in yield improvement (Table 1, entries 12 and 13). Finally, the reactions were tested against a series of different inorganic bases. With a strong base, Cs_2CO_3, there was a slightly low yield, while reactions in the presence of Na_2CO_3 or KOAc gave very poor yields (Table 1, entries 14−16, respectively). As a result, we chose entry 4 as the optimized reaction conditions.

Table 1. Optimization of Reaction Conditions[a]



2 **3**

Entry	Catalyst (mol %)	Phosphine Ligand (mol %)	PivOH (mol %)	Base	Isolated Yield (%)[b]
1	$Pd(OAc)_2$ (5)	–	–	K_2CO_3	24
2	$Pd(OAc)_2$ (5)	–	30	K_2CO_3	47
3	$Pd(OAc)_2$ (5)	PPh_3 (30)	–	K_2CO_3	56
4	**$Pd(OAc)_2$ (5)**	**PPh_3 (30)**	**30**	**K_2CO_3**	**88 (58)**[c]
5	$Pd(PPh_3)_2Cl_2$ (5)	PPh_3 (30)	30	K_2CO_3	65
6	$(PhCN)_2PdCl_2$ (5)	PPh_3 (30)	30	K_2CO_3	50
7	$PdCl_2$ (5)	PPh_3 (30)	30	K_2CO_3	59
8	$Pd(PPh_3)_4$ (5)	PPh_3 (30)	30	K_2CO_3	12
9	$Pd_2(dba)_3$ (5)	PPh_3 (30)	30	K_2CO_3	68
10	$Pd(OAc)_2$ (5)	$P(Ph)_2Cl$ (30)	30	K_2CO_3	11
11	$Pd(OAc)_2$ (5)	$P(n\text{-}Bu)_3$ (30)	30	K_2CO_3	86
12	$Pd(OAc)_2$ (10)	PPh_3 (30)	30	K_2CO_3	87
13	$Pd(OAc)_2$ (20)	PPh_3 (30)	30	K_2CO_3	88
14	$Pd(OAc)_2$ (5)	PPh_3 (30)	30	Cs_2CO_3	75
15	$Pd(OAc)_2$ (5)	PPh_3 (30)	30	Na_2CO_3	10
16	$Pd(OAc)_2$ (5)	PPh_3 (30)	30	KOAc	18

[a]Reaction conditions: starting material (**2**) (0.20 mmol), bromobenzene (0.80 mmol), PPh_3 (0.06 or 0 mmol), PivOH (0.06 or 0 mmol), base (0.40 mmol), Pd complex (0.01 mmol), and DMA (1.0 mL), 150 °C, 24 h. [b]Yields of isolated products. [c]Result with 1.00 g of starting material (unoptimized).

To examine the arene substrate scope, a variety of aryl bromides were used as couplings partners with **2** under the optimized reaction conditions (Table 2). From Table 2, it was evident that both the electronic and steric substrate environments influence the reaction yields. When there was a nitrile (electron-withdrawing) substitution at the *para*-position of the aryl bromide, the reaction led to an excellent yield (90%, Table 2, entry 1). However, the reaction with *m*-cyanobromobenzene produced a moderate yield (44%, Table 1, entry 2). In the reaction of a *para*-formyl substrate, some unknown side products were detected along with the desired product, which led to a moderate 51% yield (Table 2, entry 4). A similar result was observed when the formyl group was at the *meta*-position (Table 2, entry 5). Electron-donating methoxy and methyl groups in *p*- or *m*-substituted bromobenzene derivatives produced moderate yields (Table 2, entries 7−8 and 10−11). When there was a substituent at the *ortho*-position, only trace amounts of desired products were observed regardless of the electronic nature of the substituent (Table 2, entries 3, 6, 9, and 12). However, by increasing the Pd-catalyst amount to 10 mol %, the reaction yields improved noticeably in the case of reactions of all substrates with *m*- or *p*-substituents (Table 2, entries 2, 4−5, 7−8, and 10−11) and *o*-cyano substituents (Table 2, entry 3). However, no enhancements were observed even with an increased amount of Pd catalyst when an electron-donating methoxy- or methyl group was positioned at the *ortho*-

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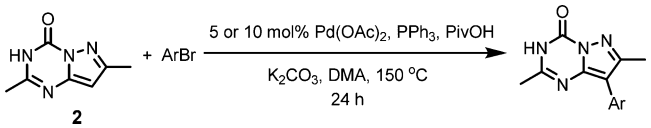
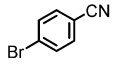
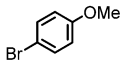
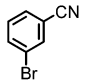
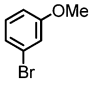
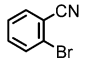
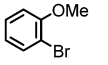
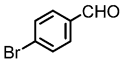
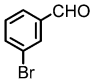
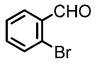
Table 2. Substrate Scope[a]



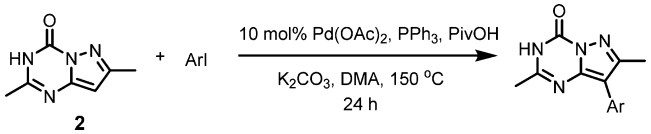
Entry	Substrate	Product	% Yield[b]	Entry	Substrate	Product	% Yield[b]
1		**4**	90	7		**10**	45 65[c]
2		**5**	44 79[c]	8		**11**	44 61[c]
3		**6**	trace 53[c]	9			trace[c]
4		**7**	51 72[c]	10		**12**	42 74[c]
5		**8**	47 68[c]	11		**13**	40 67[c]
6		**9**	trace 33[c]	12			trace[c]

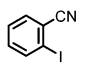
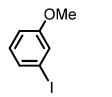
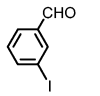
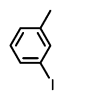
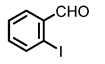
[a]Reaction conditions: starting material (**2**) (0.20 mmol), substrate (0.80 mmol), PPh_3 (0.06 mmol), PivOH (0.06 mmol), K_2CO_3 (0.40 mmol), $Pd(OAc)_2$ (0.01 mmol, 5 mol %), and DMA (1.0 mL), 150 °C, 24 h. [b]Yields of isolated products. [c]10 mol % $Pd(OAc)_2$ was used.

position (Table 2, entries 9 and 12, respectively). All of the yields are essentially the same for meta and para substitution and irrelevant of electronics (apart from the outlying *p*-CN). Only ortho substitution seems to hinder; hence, only sterics are the limitation. Increasing the catalyst loading to 15 and 20 mol % did not improve the reaction yields presumably due to unwanted side reactions.

Employment of aryl iodides instead of aryl bromides did not improve the reaction yields as indicated in Table 3. Except for the case of 2-cyanophenyl iodide, where a 60% yield was achieved with 10 mol % catalyst (Table 3, entry 1), all the other cases examined showed a small amount or trace of the desired product. Instead, large amounts of aryl−aryl coupling products and reduced (C−I to C−H) aryl compounds were observed.

Table 3. Results on the Reaction with Aryl Iodides



Entry	Substrate	Product	% Yield[a]	Entry	Substrate	Product	% Yield[a]
1		**6**	60	4		**11**	13
2		**8**	trace	5		**13**	17
3		**9**	trace				

[a]Yields of isolated products.

This indicates that the rate-determining step of the reaction may reside in the activation of the C−H bond of the pyrazolotriazinone **2**.

With the optimized reaction conditions for the C−H activation-mediated coupling, we carried out the coupling reaction of **2** and *O*-benzyl 4-bromo-3-chlorophenol (**14**) to yield compound **15**. Compound **15** is an intermediate in the construction of MJL1-109-2, a known CRHR1 antagonist (Scheme 2). Considering the steric effects of compound **14**, we employed 10 mol % $Pd(OAc)_2$ as a catalyst, which resulted in product **15** in 31% yield. By increasing the catalyst loading to 15 mol %, the yield was raised to 56%. The chlorine substituent next to the Br remained intact after the reaction. This result exemplifies the utility of the developed methodology, allowing for the simple synthesis of compound **15**, which is a synthetic precursor for MJL1-109-2.[9k]

In summary, we have developed a novel synthetic protocol for the synthesis of 8-aryl substituted pyrazolo[1,5-α][1,3,5]-triazinones employing a palladium-catalyzed intermolecular direct C−H arylation. The coupling reaction yield was directly dependent upon a phosphine ligand, pivalic acid additive, and base selection. By using 5−10 mol % catalyst, we were successful in achieving coupling reactions of compound **2** with both electron-rich and -poor aryl bromides that have substituents at *para*- or *meta*-positions in moderate to excellent yields. *Ortho*-substituted aryl bromides, using 10−15 mol % $Pd(OAc)_2$, produced the desired products in moderate yields. Using this method we were able to prepare a synthetic precursor for MJL1-109-2, a known nonpeptide CRHR-1 antagonist. Variations in the aryl bromide can provide convenient ways to synthesize potential pyrazolo[1,5-α][1,3,5]-triazine class CRHR1 antagonists.

EXPERIMENTAL SECTION

General. All the reactions were carried out using oven-dried glassware. Commercial reagents were used without further purification unless otherwise noted. Thin layer chromatography (TLC) plates were used to check the reactions using dichloromethane and methanol (95:5) as eluent, and the spots were visualized under UV light. Flash column chromatography was used to isolate eluted products with a mixture of dichloromethane and methanol. ^1H and ^{13}C NMR spectra were acquired at 400 MHz. High-resolution mass spectra were obtained on a mass spectrometer in ESI mode using a quadrupole mass analyzer.

Synthesis of 2,7-Dimethylpyrazolo[1,5-α][1,3,5]triazin-4(3*H*)-one (2). (i) Ethyl acetimidate hydrochloride (5.86 g, 47.4 mmol) was added to a 200 mL round-bottom flask containing K_2CO_3 (10.57 g, 76.5 mmol) dissolved in water (25 mL). Ethyl acetate (38 mL) was added to the suspension, and the two-phase system was stirred forcefully for about 5 min. The aqueous phase (and some undissolved salts) was removed by a separatory funnel. The organic phase was dried over anhydrous $MgSO_4$, filtered, and then transferred to the round-bottom flask containing commercially available 3-amino-5-methylpyrazole (2.48 g, 25.5 mmol) and a stirring bar. The mixture was stirred for 1 h until TLC did not show any more starting material. Acetic acid (2.2 mL, 38.3 mmol) was then added to the reaction mixture, and solids began to appear 15 min later. After 30 min, the white solids were filtered and washed with ethyl acetate before being dried in a vacuum oven (4.19 g, 83% yield). ^1H NMR (CD_3OD-d_4, δ = 3.31 ppm, 400 MHz): δ 5.90 (s, 1H), 2.38 (s, 3H), 2.31 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (CD_3OD-d_4, δ = 49.00 ppm, 100 MHz) δ 180.0, 163.6, 149.0, 142.1, 95.9, 24.1, 19.0, 10.6.

(ii) Sodium pellets (0.47 g, 20.4 mmol) were added portionwise to dry ethanol (18 mL) in a two-necked 50 mL round-bottom flask equipped with a condenser. After all sodium pellets dissolved, the solution was cooled to room temperature. Acetic acid salt **1** (0.30 g,

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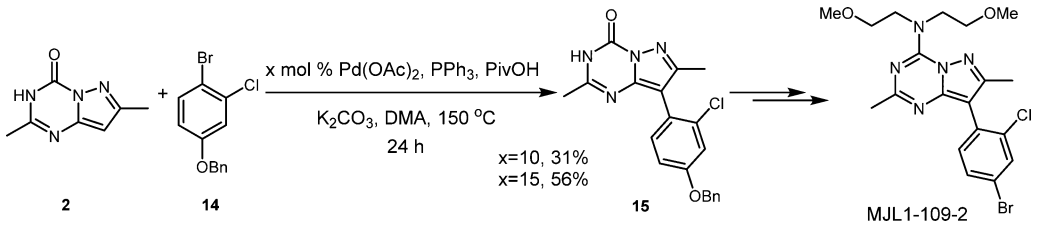
Scheme 2. Synthesis of MJL1-109-2 Intermediate



1.51 mmol) and diethyl carbonate (1.9 mL, 15.7 mmol) were added in sequence, and the mixture was heated to reflux overnight. After the mixture cooled to room temperature, the solvent was evaporated. The remaining solid was dissolved in water and acidified by 6 N aq HCl solution. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography using 95:5 (v/v) dichloromethane/methanol as an eluent to give 194.3 mg of product (78% yield) as a white solid. ^{1}H NMR (DMSO-d_6, δ = 2.50 ppm, 400 MHz): δ 12.30 (s, 1H), 6.18 (s, 1H), 2.28 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (DMSO-d_6, δ = 39.5 ppm, 100 MHz) δ 154.7, 154.0, 149.4, 143.8, 97.6, 20.7, 14.2. HRMS (ESI-quadrupole) m/z: [M + H]$^+$ Calcd for $C_7H_8N_4O$ 165.0698; Found 165.0772.

A General Procedure for Coupling through C−H Arylation. Synthesis of 2,7-Dimethyl-8-phenylpyrazolo[1,5-*α*][1,3,5]-triazin-4(3*H*)-one Preparation (3). 2,7-Dimethylpyrazolo[1,5-*α*]-[1,3,5]triazin-4(3*H*)-one **2** (32.8 mg, 0.20 mmol), potassium carbonate (55.3 mg, 0.40 mmol), pivalic acid (6.1 mg, 0.06 mmol), palladium acetate (2.2 mg, 0.01 mmol, 5 mmol %), and triphenylphosphine (15.7 mg, 0.06 mmol) were added to a 25 mL oven-dried vial equipped with a stir bar and rubber septum. The flask was evacuated and backfilled with argon three times before DMA (1.0 mL) and bromobenzene (84 μL, 0.80 mmol) were added via a syringe. The reaction mixture was stirred at room temperature for about 5 min and then heated to 150 °C for 24 h. The reaction was cooled to room temperature, and solvent was removed under reduced pressure. The crude product was purified on a chromatographic column with DCM/MeOH as an eluent to yield 42.2 mg (88% yield) of product as a pale yellow solid. ^{1}H NMR (DMSO-d_6, δ = 2.50 ppm, 400 MHz): δ 12.42 (s, 1H), 7.61 (d, J = 7.2 Hz, 2H), 7.45 (t, J = 7.2 Hz, 2H), 7.31 (t, J = 7.2 Hz, 1H), 2.43 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (DMSO-d_6, δ = 39.5 ppm, 100 MHz) δ 154.5, 152.6, 145.7, 143.8, 131.3, 128.6, 128.4, 126.5, 110.2, 20.9, 14.2. HRMS (ESI-quadrupole) m/z: [M + H]$^+$ Calcd for $C_{13}H_{12}N_4O$ 241.1011; Found 241.1083. IR (KBr) 1585, 1756, 2973, 3144 cm^{-1}; mp 263−265 °C.

4-(2,7-Dimethyl-4-oxo-3,4-dihydropyrazolo[1,5-*α*][1,3,5]-triazin-8-yl)benzonitrile (4). The same procedure was used as for the preparation of compound **3**. A pale yellow solid, 47.6 mg (90% yield). ^{1}H NMR (DMSO-d_6, δ = 2.50 ppm, 400 MHz): δ 12.59 (s, 1H), 7.90 (s, 2H), 7.89 (s, 2H), 2.48 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (DMSO-d_6, δ = 39.52 ppm, 100 MHz) δ 155.8, 152.5, 146.6, 143.7, 136.6, 132.3, 128.7, 119.1, 108.5, 108.2, 21.1, 14.6. HRMS (ESI-quadrupole) m/z: [M + H]$^+$ Calcd for $C_{14}H_{11}N_5O$ 266.0964; Found 266.1038. IR (KBr) 1598, 1736, 2219, 2753, 3038 cm^{-1}; mp 287−289 °C.

3-(2,7-Dimethyl-4-oxo-3,4-dihydropyrazolo[1,5-*α*][1,3,5]-triazin-8-yl)benzonitrile (5). The same procedure was used as for the preparation of compound **3** except for the use of 10 mol % Pd catalyst. A pale yellow solid, 42.1 mg (79% yield). ^{1}H NMR (DMSO-d_6, δ = 2.50 ppm, 400 MHz): δ 12.55 (s, 1H), 8.06 (dd, J = 2.1, 1.1 Hz, 1H), 8.01−7.96 (m, 1H), 7.77 (ddd, J = 7.8, 2.1, 1.1 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 2.47 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (DMSO-d_6, δ = 39.52 ppm, 100 MHz) δ 155.5, 152.5, 146.3, 143.7, 133.0, 132.8, 131.4, 130.1, 129.8, 118.9, 111.6, 108.0, 21.0, 14.2. HRMS (ESI-quadrupole) m/z: [M + H]$^+$ Calcd for $C_{14}H_{11}N_5O$ 266.0964; Found 266.1038. IR (KBr) 1623, 1747, 2230, 2924, 3142 cm^{-1}; mp 268−270 °C.

2-(2,7-Dimethyl-4-oxo-3,4-dihydropyrazolo[1,5-*α*][1,3,5]-triazin-8-yl)benzonitrile (6). The same procedure was used as for the preparation of compound **3** except for the use of 10 mol % Pd catalyst. A brown solid, 28.2 mg (53% yield). ^{1}H NMR (DMSO-d_6, δ = 2.50 ppm, 400 MHz): δ 12.59 (s, 1H), 7.98−7.94 (m, 1H), 7.79 (td, J = 7.7, 1.2 Hz, 1H), 7.60 (dd, J = 7.7, 1.2 Hz, 1H), 7.58−7.54 (m, 1H), 2.30 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (DMSO-d_6, δ = 39.52 ppm, 100 MHz) δ 155.5, 152.9, 146.9, 143.7, 134.7, 133.3, 133.2, 131.9, 128.3, 118.2, 112.7, 108.2, 20.9, 13.2. HRMS (ESI-quadrupole) m/z: [M + H]$^+$ Calcd for $C_{14}H_{11}N_5O$ 266.0964; Found 266.1037. IR (KBr) 1619, 1753, 2226, 2943, 3065 cm^{-1}; mp 251−254 °C.

4-(2,7-Dimethyl-4-oxo-3,4-dihydropyrazolo[1,5-*α*][1,3,5]-triazin-8-yl)benzaldehyde (7). The same procedure was used as for the preparation of compound **3** except for the use of 10 mol % Pd catalyst. A yellow solid, 38.6 mg (72% yield). ^{1}H NMR ($CDCl_3$-*d*, δ = 7.26 ppm, 400 MHz): δ 10.60 (s, 1H), 10.06 (s, 1H), 7.98 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H), 2.62 (s, 3H), 2.57 (s, 3H). ^{13}C NMR ($CDCl_3$-*d*, δ = 77.16 ppm, 100 MHz) δ 192.0, 155.4, 153.5, 146.2, 145.5, 137.4, 135.0, 130.2, 129.3, 111.9, 21.9, 14.9. HRMS (ESI-quadrupole) m/z: [M + H]$^+$ Calcd for $C_{14}H_{12}N_4O_2$ 269.0960; Found 269.1034. IR (KBr) 1600, 1699, 1753, 2925, 3155 cm^{-1}; mp 273−276 °C.

3-(2,7-Dimethyl-4-oxo-3,4-dihydropyrazolo[1,5-*α*][1,3,5]-triazin-8-yl)benzaldehyde (8). The same procedure was used as for the preparation of compound **3** except for the use of 10 mol % Pd catalyst. A pale green solid, 36.3 mg (68% yield). ^{1}H NMR ($CDCl_3$-*d*, δ = 7.26 ppm, 400 MHz): δ 11.00 (s, 1H), 10.09 (s, 1H), 8.13 (t, J = 1.5 Hz, 1H), 7.92−7.84 (m, 2H), 7.65 (t, J = 7.7 Hz, 1H), 2.59 (s, 3H), 2.57 (s, 3H). ^{13}C NMR ($CDCl_3$-*d*, δ = 77.16 ppm, 100 MHz) δ 192.4, 155.4, 153.7, 146.0, 145.8, 136.9, 134.9, 132.1, 130.1, 129.5, 128.6, 111.6, 21.7, 14.6. HRMS (ESI-quadrupole) m/z: [M + H]$^+$ Calcd for $C_{14}H_{12}N_4O_2$ 269.0960; Found 269.1036. IR (KBr) 1614, 1751, 2830, 2941, 3346 cm^{-1}; mp 198−202 °C.

2-(2,7-Dimethyl-4-oxo-3,4-dihydropyrazolo[1,5-*α*][1,3,5]-triazin-8-yl)benzaldehyde (9). The same procedure was used as for the preparation of compound **3** except for the use of 10 mol % Pd catalyst. A brown solid, 17.7 mg (33% yield). ^{1}H NMR ($CDCl_3$-*d*, δ = 7.26 ppm, 400 MHz): δ 11.23 (s, 1H), 9.88 (s, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.73−7.64 (m, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H), 2.49 (s, 3H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$-*d*, δ = 77.16 ppm, 100 MHz) δ 191.8, 156.2, 154.2, 146.8, 145.6, 134.5, 134.1, 133.5, 131.9, 128.7, 128.6, 109.5, 21.7, 13.7. HRMS (ESI-quadrupole) m/z: [M + H]$^+$ Calcd for $C_{14}H_{12}N_4O_2$ 269.0960; Found 269.1035. IR (KBr) 1620, 1750, 2830, 2934, 3279 cm^{-1}; mp 175−178 °C.

8-(4-Methoxyphenyl)-2,7-dimethylpyrazolo[1,5-*α*][1,3,5]-triazin-4(3*H*)-one (10). The same procedure was used as for the preparation of compound **3** except for the use of 10 mol % Pd catalyst. A pale brown solid, 35.2 mg (65% yield). ^{1}H NMR ($CDCl_3$-*d*, δ = 7.26 ppm, 400 MHz): δ 10.74 (s, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 2.54 (s, 3H), 2.53 (s, 3H). ^{13}C NMR ($CDCl_3$-*d*, δ = 77.16 ppm, 100 MHz) δ 159.0, 155.7, 152.2, 148.6, 130.3, 129.1, 128.8, 123.1, 114.4, 55.5, 21.8, 14.5. HRMS (ESI-quadrupole) m/z: [M + H]$^+$ Calcd for $C_{14}H_{14}N_4O_2$ 271.1117; Found 271.1190.

8-(3-Methoxyphenyl)-2,7-dimethylpyrazolo[1,5-*α*][1,3,5]-triazin-4(3*H*)-one (11). The same procedure was used as for the preparation of compound **3** except for the use of 10 mol % Pd catalyst. A light brown solid, 32.9 mg (61% yield). ^{1}H NMR ($CDCl_3$-*d*, δ = 7.26 ppm, 400 MHz): δ 11.34 (s, 1H), 7.38 (t, J = 8.2 Hz, 1H), 7.21−7.15 (m, 2H), 6.90 (dd, J = 8.2, 1.6 Hz, 1H), 3.86 (s, 3H), 2.57 (s, 3H), 2.55 (s, 3H). ^{13}C NMR ($CDCl_3$-*d*, δ = 77.16 ppm, 100 MHz) δ 159.8, 155.8, 152.9, 146.1, 132.1, 129.8, 129.1, 128.8, 121.5, 115.1,

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112.8, 55.4, 21.8, 14.6. HRMS (ESI-quadrupole) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}N_4O_2$ 271.1117; Found 271.1189. IR (KBr) 1021, 1784, 2833, 2932, 3259 cm^{-1}; mp 234−236 °C.

2,7-Dimethyl-8-*p*-tolylpyrazolo[1,5-α][1,3,5]triazin-4(3*H*)-one (12). The same procedure was used as for the preparation of compound **3** except for the use of 10 mol % Pd catalyst. A pale yellow solid, 37.7 mg (74% yield). ^1H NMR (DMSO-d_6, δ = 2.50 ppm, 400 MHz): δ 12.39 (s, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 2.40 (s, 3H), 2.33 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (DMSO-d_6, δ = 39.52 ppm, 100 MHz) δ 154.2, 152.6, 145.5, 143.8, 135.7, 129.0, 128.5, 128.3, 110.2, 20.9, 20.8, 14.2. HRMS (ESI-quadrupole) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}N_4O$ 255.1168; Found 255.1241. IR (KBr) 1333, 1726, 2849, 2926, 3081 cm^{-1}; mp 269−272 °C.

2,7-Dimethyl-8-*m*-tolylpyrazolo[1,5-α][1,3,5]triazin-4(3*H*)-one (13). The same procedure was used as for the preparation of compound **3** except for the use of 10 mol % Pd catalyst. A pale yellow solid, 34.1 mg (67% yield). ^1H NMR (DMSO-d_6, δ = 2.50 ppm, 400 MHz): δ 12.40 (s, 1H), 7.38 (d, J = 7.6 Hz, 2H), 7.32 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 7.2 Hz, 1H), 2.41 (s, 3H), 2.35 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (DMSO-d_6, δ = 39.52 ppm, 100 MHz) δ 154.4, 152.6, 145.6, 143.8, 137.4, 131.2, 129.2, 128.3, 127.2, 125.8, 110.3, 21.2, 21.0, 14.2. HRMS (ESI-quadrupole) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}N_4O$ 255.1168; Found 255.1241. IR (KBr) 1032, 1619, 1752, 2832, 2943, 3157 cm^{-1}; mp 245−248 °C.

8-(4-(Benzyloxy)-2-chlorophenyl)-2,7-dimethylpyrazolo[1,5-α][1,3,5]triazin-4(3*H*)-one (15). The same procedure was used as for the preparation of compound **3** except for the use of 15 mol % Pd catalyst. A yellow solid, 42.7 mg (56% yield). ^1H NMR ($CDCl_3$-*d*, δ = 7.26 ppm, 400 MHz): δ 7.47−7.33 (m, 5H), 7.23 (d, J = 8.5 Hz, 1H), 7.15 (d, J = 2.6 Hz, 1H), 6.97 (dd, J = 8.5, 2.6 Hz, 1H), 5.09 (s, 2H), 2.51 (s, 3H), 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$-*d*, δ = 77.16 ppm, 100 MHz) δ 159.5, 157.0, 153.0, 146.3, 146.0, 136.4, 135.5, 133.3, 128.9, 128.4, 127.7, 121.8, 116.3, 114.0, 111.4, 70.5, 21.7, 13.8. HRMS (ESI-quadrupole) m/z: $[M + H]^+$ Calcd for $C_{20}H_{17}ClN_4O_2$ 381.1040; Found 381.1115. IR (KBr) 1277, 1620, 1749, 2941, 3164 cm^{-1}; mp 108−111 °C.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The ^1H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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