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Construction of 2,3,4,5-tetrahydro-1,2,4-triazines via [4 + 2] cycloaddition of α -halogeno hydrazones to imines†

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 In the presence of sodium carbonate, the [4 + 2] cycloaddition of α -halogeno hydrazones to imines proceeded readily, and furnished 2,3,4,5-tetrahydro-1,2,4-triazines in moderate to high chemical yields.

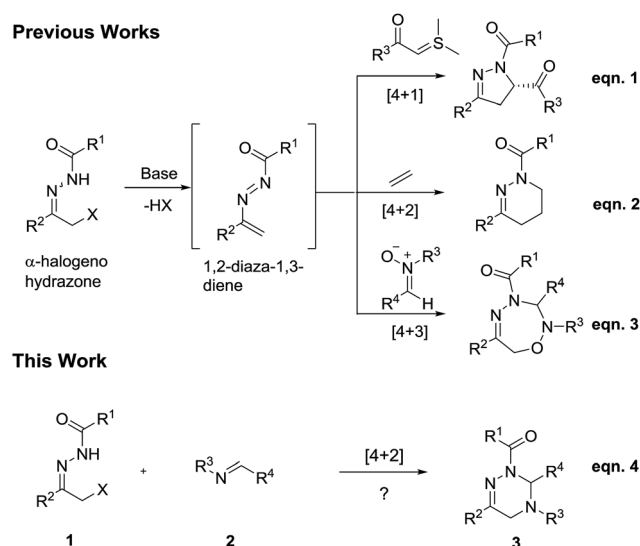
1. Introduction

α -Halogeno hydrazones represent a class of versatile and robust building blocks, which have been widely applied in the construction of structurally diverse and complex N-containing heterocycles possessing varying ring sizes. Normally, α -halogeno hydrazones can undergo [4 + 1],¹ [4 + 2]² or [4 + 3]³ cycloadditions with structurally different dienophiles via the *in situ* formed 1,2-diaza-1,3-diene intermediates under basic reaction conditions. For example, in 2012, Bolm and co-workers realized the enantioselective synthesis of dihydropyrazoles by means of the [4 + 1] cycloaddition of α -halogeno hydrazones to sulphur ylides (Scheme 1, eqn. (1)).⁴ In 2015, the Luo research group reported the [4 + 2] cycloaddition of α -halogeno hydrazones to simple olefins for the preparation of tetrahydropyridazines (Scheme 1, eqn. (2)).⁵ Recently, our research group successfully designed the [4 + 3] cycloaddition of α -halogeno hydrazones to nitrones for the preparation of 1,2,4,5-oxatriazepines (Scheme 1, eqn. (3)).⁶ In particular, most of the previously reported [4 + 2] cycloadditions of α -halogeno hydrazones mainly focused on the use of the differently functionalized olefins as dienophiles.⁷ In addition, only three other pioneering works respectively dealt with the use of arylacetic acids,⁸ methoxyallene⁹ or azodicarboxylates¹⁰ as dienophiles in the [4 + 2] cycloadditions of α -halogeno hydrazones. It is well known that the employment of imines as dienophiles in [4 + 2] cycloaddition of α -halogeno hydrazones has been fully unexplored to date. So, the development of novel [4 + 2] cycloadditions of α -halogeno hydrazones with imines is highly demanded for the synthesis of potentially bioactive heterocycles.

On the basis of the previously published elegant examples, in this work, we first attempted the novel [4 + 2] cycloaddition of α -halogeno hydrazones with synthetically useful and important imines¹¹ for the construction of 2,3,4,5-tetrahydro-1,2,4-triazines bearing potential biological activities¹² (Scheme 1, eqn. (4)). To our delight, under the mild reaction conditions, the [4 + 2] cycloaddition of α -halogeno hydrazones with imines underwent readily, and furnished the target molecules in moderate to high chemical yields. To the best of our knowledge, such a work has not been reported in the literature so far.

2. Results and discussion

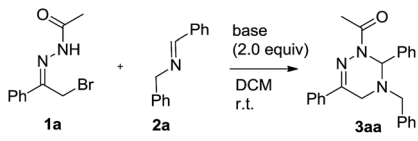
At the outset, we explored the base effects on the chemical yield of the [4 + 2] cycloaddition of α -halogeno hydrazone **1a** with imine **2a** in DCM solvent at room temperature as summarized in Table 1. Indeed, the used base affected the chemical yield of

Scheme 1 Representative cycloadditions of α -halogeno hydrazones.

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† Electronic supplementary information (ESI) available: Copies of NMR spectra for all products related to this article; X-ray single crystal structure analysis data for **3aa**. CCDC 1508810. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ra27767e



Table 1 Screening of bases^a


Entry	Base	Time (h)	Yield ^b (%)
1	Na ₂ CO ₃	25	44
2	K ₂ CO ₃	25	34
3	Cs ₂ CO ₃	25	33
4	NaHCO ₃	36	8
5	KOH	36	13
6	MeONa	36	19
7	Et ₃ N	48	2
8	DBU	48	Trace

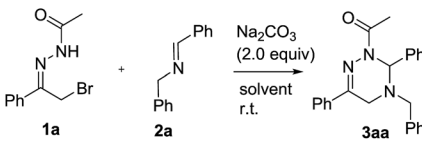
^a Unless otherwise noted, reactions were carried out with **1a** (0.2 mmol), **2a** (0.3 mmol), base (0.4 mmol) in DCM (1.0 mL) at room temperature.

^b Isolated yield.

the [4 + 2] cycloaddition significantly. Using DBU as a base gave product **3aa** in a trace amount after 48 h (entry 8). The choice of NaHCO₃ and Et₃N as bases did not enhance the chemical yield of **3aa** dramatically (entries 4 & 7). By comparison with the former cases, the chemical yield of [4 + 2] cycloaddition increased differently by using KOH and MeONa as bases (entries 5–6). Moreover, when Na₂CO₃, K₂CO₃ and Cs₂CO₃ were examined as bases, the chemical yield of the [4 + 2] cycloaddition ranged from 33% to 44% (entries 1–3). Obviously, among all the bases screened, Na₂CO₃ performed best and delivered product **3aa** in highest chemical yield (entry 1).

Simultaneously, by using Na₂CO₃ (2.0 equiv.) as base, we investigated the solvent effects on the chemical yield of the [4 + 2] cycloaddition of α -halogeno hydrazone **1a** with imine **2a** as shown in Table 2. Remarkably, the chemical yield of the [4 + 2] cycloaddition was largely influenced by the attempted solvents. In MeOH solvent, the [4 + 2] cycloaddition furnished product **3aa** in 20% chemical yield in 36 h (entry 7). In contrast with the former case, the chemical yield of the [4 + 2] cycloaddition increased to 35% by choosing MeCN as solvent (entries 6 vs. 7). As for solvents DCE, THF, Et₂O and DME, they afforded product **3aa** in similar chemical yields (entries 1–4). Finally, with the use of toluene, PhCl and benzene as solvents, the chemical yield of the [4 + 2] cycloaddition changed from 68% to 75% (entries 5 and 8–9). Therefore, Na₂CO₃ behaved most efficiently in toluene solvent, thus providing **3aa** in the highest chemical yield (entry 5). In addition, we examined other equivalent amounts of Na₂CO₃ in the [4 + 2] cycloaddition by using toluene as solvent, and found that use of 2.0 equiv. of Na₂CO₃ furnished product **3aa** in the highest chemical yield (Table 2, entries 5 vs. 10–11).

Subsequently, under the optimal reaction conditions, we broadened the reaction scope of the [4 + 2] cycloaddition by diversifying α -halogeno hydrazones **1** and imines **2** as outlined in Table 3. Noticeably, the chemical yield of the [4 + 2] cycloaddition highly depended on the structural nature of the used α -halogeno hydrazones **1** and imines **2**. Regarding the [4 + 2]

Table 2 Screening of solvents^a


Entry	Solvent	Time (h)	Yield ^b (%)
1	DCE	24	54
2	THF	24	52
3	Et ₂ O	24	52
4	DME	24	51
5	Toluene	24	75
6	MeCN	24	35
7	MeOH	36	20
8	PhCl	24	68
9	Benzene	24	71
10 ^c	Toluene	24	16
11 ^d	Toluene	24	46

^a Unless otherwise noted, reactions were carried out with **1a** (0.2 mmol), **2a** (0.3 mmol), Na₂CO₃ (0.4 mmol) in the solvent (1.0 mL) at room temperature. ^b Isolated yield. ^c 0.5 equiv. of Na₂CO₃. ^d 1.0 equiv. of Na₂CO₃.

cycloaddition with α -halogeno hydrazone **1a**, most imine substrates **2** well tolerated the structural variation of R³ and R⁴ groups, thus delivering products **3** in 62–88% chemical yields (entries 1–8 & 10–12). In contrast with the former cases, the imines **2i** and **2m** individually bearing a *para*-methoxy-substituted benzyl group or a phenyl group at R³ position furnished products **3ai** and **3am** in the dramatically decreased chemical yields in the [4 + 2] cycloaddition with **1a** (entries 1 vs. 9, 1 vs. 13). Meanwhile, it was noted that in the [4 + 2] cycloaddition with **1a**, the regioisomers **2c–2e**, which derived from the different substitution pattern of nitro group at R⁴ moiety, provided products **3ac–3ae** in the quite different chemical yields (entries 3–5).

In case of the [4 + 2] cycloaddition with **2a**, most α -halogeno hydrazones **1** could better endure the wide variation in R¹ and R² groups, and led to the formation of products **3** in 57–86% chemical yields (entries 14–21 & 24–26). With respect to the imines **1j** with a bulky *tert*-butyl as R² group and **1k** with a phenyl as R¹ group, they preferred to afford products **3** in the relatively lowered chemical yields in the [4 + 2] cycloaddition with **2a** (entries 1 vs. 22, 14 vs. 23). Generally, in the [4 + 2] cycloaddition with **2a**, the imines **1** including an electron-poor phenyl group at R² position usually behaved better than the imines **1** containing an electron-rich phenyl group at R² position, and produced products **3** in higher chemical yields (entries 15–16 vs. 17–20). Simultaneously, it should be addressed that α -halogeno hydrazones **1a** and **1b**, which differ from each other in X group, gave rise to the same product **3aa** in the tremendously different chemical yield in the [4 + 2] cycloaddition with **2a** (entries 1 vs. 14). Moreover, the [4 + 2] cycloaddition of **1f** with **2b** gave product **3fb** in 81% chemical yield (entry 27). At last, we further performed the extension of the reaction scope of the [4 + 2] cycloaddition by treating α -halogeno hydrazone **2f** with



Table 3 Extension of reaction scope^a

Entry	1 (X, R ¹ , R ²)	2 (R ³ , R ⁴)	3	Time (h)	Yield ^b (%)
1	1a (Br, Me, Ph)	2a (Bn, Ph)	3aa	24	75
2	1a (Br, Me, Ph)	2b (Bn, 4-MeOC ₆ H ₄)	3ab	30	85
3	1a (Br, Me, Ph)	2c (Bn, 4-NO ₂ C ₆ H ₄)	3ac	30	67
4	1a (Br, Me, Ph)	2d (Bn, 3-NO ₂ C ₆ H ₄)	3ad	30	62
5	1a (Br, Me, Ph)	2e (Bn, 2-NO ₂ C ₆ H ₄)	3ae	30	75
6	1a (Br, Me, Ph)	2f (Bn, 4-BrC ₆ H ₄)	3af	24	88
7	1a (Br, Me, Ph)	2g (Bn, 2-naphthyl)	3ag	30	66
8	1a (Br, Me, Ph)	2h (Bn, 2-furyl)	3ah	30	80
9	1a (Br, Me, Ph)	2i (4-MeO C ₆ H ₄ CH ₂ , Ph)	3ai	24	29
10	1a (Br, Me, Ph)	2j (4-FC ₆ H ₄ CH ₂ , Ph)	3aj	24	77
11	1a (Br, Me, Ph)	2k (4-ClC ₆ H ₄ CH ₂ , Ph)	3ak	24	77
12	1a (Br, Me, Ph)	2l (Me, Ph)	3al	24	75
13	1a (Br, Me, Ph)	2m (Ph, Ph)	3am	36	33
14	1b (Cl, Me, Ph)	2a (Bn, Ph)	3aa	24	61
15	1c (Br, Me, 4-MeOC ₆ H ₄)	2a (Bn, Ph)	3ca	24	57
16	1d (Br, Me, 4-MeC ₆ H ₄)	2a (Bn, Ph)	3da	24	71
17	1e (Br, Me, 4-BrC ₆ H ₄)	2a (Bn, Ph)	3ea	24	80
18	1f (Br, Me, 4-ClC ₆ H ₄)	2a (Bn, Ph)	3fa	24	86
19	1g (Br, Me, 4-FC ₆ H ₄)	2a (Bn, Ph)	3ga	24	74
20	1h (Br, Me, 3-ClC ₆ H ₄)	2a (Bn, Ph)	3ha	24	80
21	1i (Br, Me, 4-NO ₂ C ₆ H ₄)	2a (Bn, Ph)	3ia	30	71
22	1j (Br, Me, <i>t</i> -Bu)	2a (Bn, Ph)	3ja	36	21
23	1k (Cl, Ph, Ph)	2a (Bn, Ph)	3ka	36	34
24	1l (Cl, MeO, Ph)	2a (Bn, Ph)	3la	30	59
25	1m (Br, MeO, CO ₂ Et)	2a (Bn, Ph)	3ma	30	70
26	 1n	2a (Bn, Ph)	3na	30	64
27	1f (Br, Me, 4-Cl C ₆ H ₄)	2b (Bn, 4-MeOC ₆ H ₄)	3fb	30	81
28	1f (Br, Me, 4-ClC ₆ H ₄)	2f (Bn, 4-BrC ₆ H ₄)	3ff	24	71
29	1h (Br, Me, 3-ClC ₆ H ₄)	2f (Bn, 4-BrC ₆ H ₄)	3hf	24	81
30	1d (Br, Me, 4-MeC ₆ H ₄)	2f (Bn, 4-BrC ₆ H ₄)	3df	24	73

^a Unless otherwise noted, reactions were carried out with 1 (0.2 mmol), 2 (0.3 mmol), Na₂CO₃ (0.4 mmol) in toluene (1.0 mL) at room temperature.

^b Isolated yield.

imines **1d**, **1f** and **1h**, and the chemical yield of the [4 + 2] cycloaddition changed from 71–83%. Of course, the α-halogeno hydrazones **1f** and **1d**, where R² group individually has an electron-withdrawing or -donating group attached to the phenyl moiety, did not behaved quite differently in the [4 + 2] cycloaddition with **2f**, and furnished products **3ff** and **3df** in the similar chemical yields (entries 28 vs. 30).

Moreover, the chemical structure of **3aa** was firmly confirmed by single crystal X-ray analysis as depicted in Fig. 1.¹³ The conformational analysis showed that the 2,3,4,5-tetrahydro-1,2,4-triazine ring of **3aa** adopts a highly twisted conformation. By virtue of the non-planar structure of the 2,3,4,5-tetrahydro-1,2,4-triazine ring of **3aa**, as a result, the two protons at C-5 become chemically non-equivalent: one proton occupies the pseudo-oxial position; the other one resides in the pseudo-equatorial position. This fact was clearly identified by the ¹H

NMR performance of the two protons at C-5: one proton resonates at 3.48 ppm; the other one signals at 3.55 ppm (see details in ESI†). These observations proved that the inversion barrier of

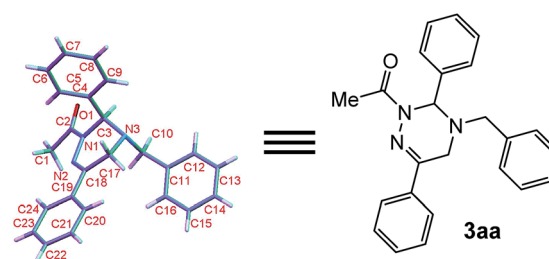


Fig. 1 X-ray single crystal structure of **3aa** (with thermal ellipsoid shown at the 50% probability level).



2,3,4,5-tetrahydro-1,2,4-triazine ring is big enough at room temperature, and as a consequence, the two protons exchange pretty slowly at ^1H NMR timescale. Meanwhile, we proposed the reaction mechanism for the formation of **3aa** (Scheme 2). In the presence of Na_2CO_3 , the elimination reaction of **1a** takes place to give 1,2-diaza-1,3-diene **4**. Then, two possible transition states **TS1** and **TS2** will be produced for the $[4 + 2]$ cycloaddition between **4** and **2a**. With the aid of the molecular model, it was found that in **TS2** phenyl group at C-6 sterically repulse benzyl group at N-4 severely; whereas, this strong destabilizing interaction does not exist in **TS1** at all. Therefore, the transition state **TS1** is more stable than the transition state **TS2**, and mainly accounts for the formation of the desired cycloadduct **3aa**.

3. Conclusions

In conclusion, the $[4 + 2]$ cycloaddition of α -halogeno hydrazones with imines underwent efficiently, and provided the easy access to the novel potentially bioactive 2,3,4,5-tetrahydro-1,2,4-triazines in the reasonable chemical yields. Furthermore, the exploration of other novel cycloadditions of α -halogeno hydrazones with various 1,3-, 1,4- and 1,5-dipoles is ongoing in our laboratory, and will be reported in due course.

4. Experimental section

4.1 General information

Proton (^1H) and carbon (^{13}C) NMR spectra were recorded on 400 MHz instrument (400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR) and calibrated using tetramethylsilane (TMS) as internal reference. High resolution mass spectra (HRMS) were recorded

under electrospray ionization (ESI) conditions. Flash column chromatography was performed on silica gel (0.035–0.070 mm) using compressed air. Thin layer chromatography (TLC) was carried out on 0.25 mm SDS silica gel coated glass plates (60F254). Eluted plates were visualized using a 254 nm UV lamp. Unless otherwise indicated, all reagents were commercially available and used without further purification. All solvents were distilled from the appropriate drying agents immediately before using. α -Chloro- or α -bromo hydrazones (**1a–1n**) were prepared according to literature procedures.^{3c,4,7b} Imines (**2a–2m**) were synthesized according to known procedures.¹⁴

4.2 Procedure for the synthesis of products 3

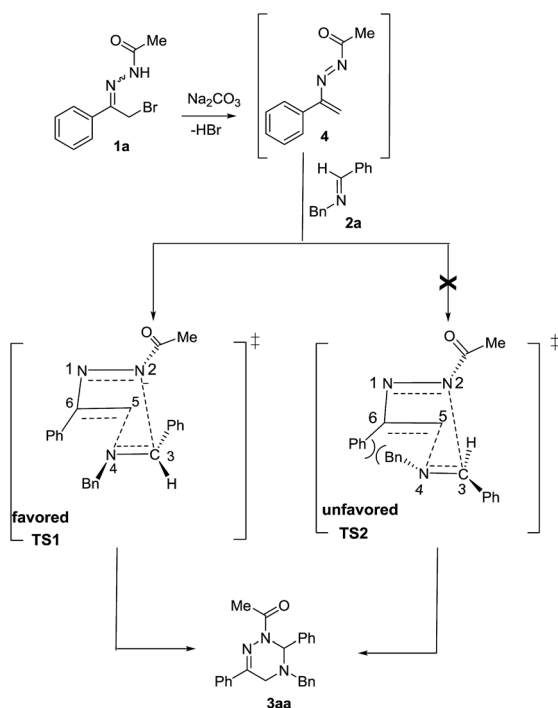
Na_2CO_3 (2.0 equiv., 0.4 mmol) was added to a solution of α -chloro- or α -bromo hydrazone **1** (1.0 equiv., 0.2 mmol) and imine **2** (1.5 equiv., 0.3 mmol) in toluene (1.0 mL). The mixture was monitored by TLC plate and stirred for 24–36 h at room temperature. The crude products were purified by flash column chromatography on silica gel using EtOAc–petroleum as eluent to give products **3** (21–88% yield).

1-(4-Benzyl-3,6-diphenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethanone (3aa). White solid, yield: 55.6 mg, 75%; mp = 164.0–165.2 °C ^1H NMR (400 MHz, CDCl_3): δ 7.66–7.64 (m, 2H), 7.45 (d, J = 7.2 Hz, 2H), 7.42–7.38 (m, 5H), 7.36–7.29 (m, 6H), 6.45 (s, 1H), 3.93 (d, J = 13.2 Hz, 1H), 3.77 (d, J = 13.2 Hz, 1H), 3.58–3.46 (m, 2H), 2.66 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.6, 145.4, 137.6, 137.5, 135.8, 129.7, 129.1, 128.8, 128.7, 128.6, 128.1, 127.8, 126.4, 125.0, 69.6, 58.7, 43.0, 20.8 ppm; HRMS (ESI) calculated for $\text{C}_{24}\text{H}_{24}\text{N}_3\text{O}$ $[\text{M} + \text{H}]^+$: 370.19139, found 370.19046.

1-(4-Benzyl-3-(4-methoxyphenyl)-6-phenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3ab). Oil, yield: 68.1 mg, 85%; ^1H NMR (400 MHz, CDCl_3): δ 7.65–7.63 (m, 2H), 7.43 (d, J = 7.2 Hz, 2H), 7.40–7.37 (m, 5H), 7.34–7.31 (m, 1H), 7.21 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.39 (s, 1H), 3.90 (d, J = 13.2 Hz, 1H), 3.79 (s, 3H), 3.73 (d, J = 13.2 Hz, 1H), 3.55–3.46 (m, 2H), 2.63 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.5, 159.5, 145.4, 137.7, 135.8, 129.7, 129.6, 129.0, 128.7, 128.6, 127.8, 127.6, 125.0, 114.1, 69.3, 58.5, 55.3, 42.9, 20.9 ppm; HRMS (ESI) calculated for $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_2$ $[\text{M} + \text{H}]^+$: 400.20195, found 400.20111.

1-(4-Benzyl-3-(4-nitrophenyl)-6-phenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3ac). Light yellow solid, yield: 55.5 mg, 67%; mp = 143.4–144.9 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.21 (d, J = 8.8 Hz, 2H), 7.64–7.62 (m, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.42–7.36 (m, 8H), 6.45 (s, 1H), 3.92 (d, J = 13.2 Hz, 1H), 3.80 (d, J = 12.8 Hz, 1H), 3.64–3.39 (m, 2H), 2.66 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.7, 147.9, 145.7, 144.9, 136.9, 135.2, 130.1, 129.1, 128.8, 128.7, 128.1, 127.7, 124.9, 124.0, 68.6, 58.9, 43.2, 20.8 ppm; HRMS (ESI) calculated for $\text{C}_{24}\text{H}_{23}\text{N}_4\text{O}_3$ $[\text{M} + \text{H}]^+$: 415.17647, found 415.17526.

1-(4-Benzyl-3-(3-nitrophenyl)-6-phenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3ad). Light yellow solid, yield: 51.4 mg, 62%; mp = 129.4–131.1 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.20–8.16 (m, 2H), 7.65–7.61 (m, 3H), 7.53 (t, J = 8.0 Hz, 1H), 7.45–7.43 (m, 3H), 7.41–7.36 (m, 5H), 6.46 (s,



Scheme 2 Proposed mechanism for the formation of **3aa**.



1H), 3.95–3.79 (m, 2H), 3.65–3.41 (m, 2H), 2.68 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 172.8, 148.9, 145.7, 140.1, 136.9, 135.3, 132.7, 130.0, 129.9, 129.2, 128.8, 128.7, 128.1, 125.0, 123.3, 121.9, 68.4, 58.8, 43.0, 20.8 ppm; HRMS (ESI) calculated for C₂₄H₂₃N₄O₃ [M + H]⁺: 415.17647, found 415.17505.

1-(4-Benzyl-3-(2-nitrophenyl)-6-phenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3ae). White solid, yield: 62.5 mg, 75%; mp = 153.3–154.5 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.88–7.86 (m, 1H), 7.56–7.54 (m, 2H), 7.51–7.45 (m, 2H), 7.40–7.31 (m, 6H), 7.27–7.24 (m, 3H), 7.05–7.03 (m, 1H), 4.07 (d, *J* = 12.8 Hz, 1H), 3.52 (d, *J* = 12.8 Hz, 1H), 3.43–2.91 (m, 2H), 2.66 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 172.6, 149.2, 145.3, 137.0, 135.3, 132.3, 131.7, 130.0, 129.4, 129.2, 128.7, 128.6, 127.9, 127.2, 125.5, 125.0, 68.1, 59.0, 40.4, 20.9 ppm; HRMS (ESI) calculated for C₂₄H₂₃N₄O₃ [M + H]⁺: 415.17647, found 415.17542.

1-(4-Benzyl-3-(4-bromophenyl)-6-phenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3af). Oil, yield: 78.6 mg, 88%; ¹H NMR (400 MHz, CDCl₃): δ 7.65–7.63 (m, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.44–7.38 (m, 7H), 7.36–7.33 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.38 (s, 1H), 3.92–3.74 (m, 2H), 3.59–3.44 (m, 2H), 2.65 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 172.6, 145.5, 137.4, 136.7, 135.6, 131.9, 129.9, 129.1, 128.7, 128.7, 128.3, 127.9, 125.0, 122.2, 68.9, 58.7, 43.0, 20.8 ppm; HRMS (ESI) calculated for C₂₄H₂₃BrN₃O [M + H]⁺: 448.10190, found 448.10135.

1-(4-Benzyl-3-(naphthalen-2-yl)-6-phenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3ag). White solid, yield: 55.2 mg, 66%; mp = 52.3–53.6 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.87 (d, *J* = 8.4 Hz, 1H), 7.85–7.80 (m, 2H), 7.65–7.63 (m, 2H), 7.59–7.56 (m, 2H), 7.50–7.46 (m, 4H), 7.45–7.41 (m, 2H), 7.39–7.34 (m, 4H), 6.60 (s, 1H), 4.00–3.80 (m, 2H), 3.59–3.47 (m, 2H), 2.73 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 172.6, 145.6, 137.6, 135.8, 134.9, 133.3, 133.2, 129.7, 129.2, 128.9, 128.7, 128.6, 128.3, 127.9, 127.6, 126.2, 126.2, 125.2, 125.0, 124.6, 69.7, 58.8, 43.2, 21.0 ppm; HRMS (ESI) calculated for C₂₈H₂₆N₃O [M + H]⁺: 420.20704, found 420.20602.

1-(4-Benzyl-3-(furan-2-yl)-6-phenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3ah). White solid, yield: 57.3 mg, 80%; mp = 91.3–92.7 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.71–7.68 (m, 2H), 7.43–7.41 (m, 6H), 7.39–7.34 (m, 3H), 6.46 (s, 1H), 6.34–6.33 (m, 1H), 6.26 (d, *J* = 3.2 Hz, 1H), 3.87–3.79 (m, 2H), 3.68 (s, 2H), 2.56 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 171.9, 150.2, 145.0, 142.9, 137.0, 135.6, 129.8, 129.0, 128.7, 128.6, 127.8, 125.0, 110.3, 108.6, 64.0, 58.2, 44.0, 20.9 ppm; HRMS (ESI) calculated for C₂₂H₂₂N₃O₂ [M + H]⁺: 360.17065, found 360.16971.

1-(4-(4-Methoxybenzyl)-3,6-diphenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3ai). White solid, yield: 23.2 mg, 29%; mp = 126.2–127.9 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.66–7.64 (m, 2H), 7.40–7.38 (m, 3H), 7.36–7.32 (m, 4H), 7.29–7.28 (m, 3H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.42 (s, 1H), 3.85–3.82 (m, 4H), 3.70 (d, *J* = 12.8 Hz, 1H), 3.57–3.44 (m, 2H), 2.65 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 172.6, 159.3, 145.4, 137.6, 135.8, 130.3, 129.7, 129.6, 128.7, 128.6, 128.1, 126.4, 125.0, 114.1, 69.2, 58.0, 55.3, 42.9, 20.8 ppm; HRMS

(ESI) calculated for C₂₅H₂₆N₃O₂ [M + H]⁺: 400.20195, found 400.20111.

1-(4-(4-Fluorobenzyl)-3,6-diphenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3aj). White solid, yield: 59.3 mg, 77%; mp = 132.1–133.7 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.66–7.64 (m, 2H), 7.43–7.38 (m, 5H), 7.35 (d, *J* = 7.2 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 3H), 7.11–7.07 (m, 2H), 6.42 (s, 1H), 3.89–3.72 (m, 2H), 3.56–3.46 (m, 2H), 2.66 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 172.6, 163.7, 161.2, 145.3, 137.4, 135.7, 133.3, 133.3, 130.7, 130.6, 129.8, 128.8, 128.6, 128.2, 126.4, 124.9, 115.6, 115.4, 69.3, 57.9, 43.1, 20.8 ppm; HRMS (ESI) calculated for C₂₄H₂₃FN₃O [M + H]⁺: 388.18197, found 388.18085.

1-(4-(4-Chlorobenzyl)-3,6-diphenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3ak). White solid, yield: 62.2 mg, 77%; mp = 175.7–176.4 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.65–7.63 (m, 2H), 7.40–7.37 (m, 7H), 7.34 (d, *J* = 7.2 Hz, 2H), 7.31–7.27 (m, 3H), 6.41 (s, 1H), 3.89–3.71 (m, 2H), 3.50 (s, 2H), 2.64 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 172.5, 145.3, 137.3, 136.1, 135.7, 133.6, 130.4, 129.8, 128.9, 128.8, 128.6, 128.2, 126.4, 124.9, 69.4, 57.9, 43.1, 20.8 ppm; HRMS (ESI) calculated for C₂₄H₂₃ClN₃O [M + H]⁺: 404.15242, found 404.15152.

1-(4-Methyl-3,6-diphenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3al). White solid, yield: 44.0 mg, 75%; mp = 92.7–93.2 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.69–7.67 (m, 2H), 7.40 (t, *J* = 3.2 Hz, 3H), 7.37–7.33 (m, 2H), 7.31–7.27 (m, 3H), 6.35 (s, 1H), 3.55–3.40 (m, 2H), 2.61 (s, 3H), 2.60 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 172.7, 145.0, 137.3, 135.9, 129.7, 128.7, 128.6, 128.2, 126.4, 124.9, 71.3, 45.1, 42.7, 20.7 ppm; HRMS (ESI) calculated for C₁₈H₂₀N₃O [M + H]⁺: 294.16009, found 294.15924.

1-(3,4,6-Triphenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3am). White solid, yield: 23.4 mg, 33%; mp = 131.1–132.7 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.74–7.71 (m, 2H), 7.42 (t, *J* = 3.2 Hz, 3H), 7.37–7.34 (m, 5H), 7.32–7.30 (m, 3H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.02–6.99 (m, 1H), 4.42–3.96 (m, 2H), 2.58 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 171.8, 148.8, 146.1, 136.6, 135.1, 129.9, 129.7, 129.0, 128.7, 128.6, 128.4, 128.2, 126.2, 125.0, 121.7, 117.9, 67.6, 43.5, 32.6, 20.8 ppm; HRMS (ESI) calculated for C₂₃H₂₂N₃O [M + H]⁺: 356.17574, found 356.17426.

1-(4-Benzyl-6-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3ca). Oil, yield: 45.2 mg, 57%; ¹H NMR (400 MHz, CDCl₃): δ 7.59 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 6.8 Hz, 2H), 7.41–7.38 (m, 2H), 7.35–7.30 (m, 6H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.44 (s, 1H), 3.92 (d, *J* = 12.8 Hz, 1H), 3.84 (s, 3H), 3.75 (d, *J* = 13.2 Hz, 1H), 3.54–3.42 (m, 2H), 2.64 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 172.4, 160.9, 145.2, 137.7, 137.6, 129.1, 128.7, 128.6, 128.5, 128.1, 127.8, 126.4, 126.4, 113.9, 69.5, 58.6, 55.4, 42.9, 20.8 ppm; HRMS (ESI) calculated for C₂₅H₂₆N₃O₂ [M + H]⁺: 400.20195, found 400.20105.

1-(4-Benzyl-3-phenyl-6-(*p*-tolyl)-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3da). White solid, yield: 54.5 mg, 71%; mp = 93.3–94.7 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 6.8 Hz, 2H), 7.42–7.38 (m, 2H), 7.36–7.29 (m, 6H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.45 (s, 1H), 3.94–3.75 (m, 2H), 3.56–3.44 (m, 2H), 2.65 (s, 3H), 2.39 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃): δ 172.5, 145.5, 139.9, 137.7, 137.6, 133.1, 129.3, 129.1,



128.7, 128.7, 128.1, 127.8, 126.4, 124.9, 69.5, 58.7, 43.0, 21.4, 20.9 ppm; HRMS (ESI) calculated for $C_{25}H_{26}N_3O$ $[M + H]^+$: 384.20704, found 384.20621.

1-(4-Benzyl-6-(4-bromophenyl)-3-phenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3ea). White solid, yield: 71.1 mg, 80%; mp = 159.4–160.8 °C; 1H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 4H), 7.45–7.40 (m, 3H), 7.38–7.35 (m, 4H), 7.31–7.29 (m, 3H), 6.46 (s, 1H), 3.94–3.73 (m, 2H), 3.52–3.42 (m, 2H), 2.65 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 144.3, 137.4, 137.4, 134.6, 131.7, 129.1, 128.8, 128.7, 128.2, 127.9, 126.4, 126.4, 124.0, 69.6, 58.7, 42.8, 20.8 ppm; HRMS (ESI) calculated for $C_{24}H_{23}BrN_3O$ $[M + H]^+$: 448.10190, found 448.10092.

1-(4-Benzyl-6-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3fa). White solid, yield: 69.2 mg, 86%; mp = 138.5–139.9 °C; 1H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 8.4 Hz, 2H), 7.45–7.39 (m, 5H), 7.36–7.34 (m, 4H), 7.32–7.30 (m, 3H), 6.46 (s, 1H), 3.93 (d, J = 12.8 Hz, 1H), 3.75 (d, J = 13.2 Hz, 1H), 3.53–3.43 (m, 2H), 2.65 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 144.3, 137.4, 137.4, 135.7, 134.2, 129.1, 128.8, 128.7, 128.2, 127.9, 126.4, 126.2, 69.6, 58.7, 42.8, 20.8 ppm; HRMS (ESI) calculated for $C_{24}H_{23}ClN_3O$ $[M + H]^+$: 404.15242, found 404.15161.

1-(4-Benzyl-6-(4-fluorophenyl)-3-phenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3ga). White solid, yield: 57.1 mg, 74%; mp = 121.9–123.6 °C; 1H NMR (400 MHz, $CDCl_3$): δ 7.64–7.60 (m, 2H), 7.45–7.43 (m, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.36–7.29 (m, 6H), 7.09–7.04 (m, 2H), 6.44 (s, 1H), 3.94–3.73 (m, 2H), 3.53–3.42 (m, 2H), 2.64 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 164.9, 162.4, 144.4, 137.5, 137.4, 132.0, 132.0, 129.1, 128.8, 128.7, 128.2, 127.8, 126.9, 126.8, 126.4, 115.7, 115.5, 69.5, 58.7, 42.9, 20.8 ppm; HRMS (ESI) calculated for $C_{24}H_{23}FN_3O$ $[M + H]^+$: 388.18197, found 388.18100.

1-(4-Benzyl-6-(3-chlorophenyl)-3-phenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3ha). White solid, yield: 64.9 mg, 80%; mp = 126.2–127.3 °C; 1H NMR (400 MHz, $CDCl_3$): δ 7.66 (s, 1H), 7.46–7.42 (m, 4H), 7.40–7.38 (m, 2H), 7.37–7.35 (m, 3H), 7.32–7.28 (m, 4H), 6.45 (s, 1H), 3.93–3.73 (m, 2H), 3.48 (s, 2H), 2.65 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 144.1, 137.5, 137.4, 137.3, 134.8, 129.9, 129.6, 129.1, 128.8, 128.7, 128.2, 127.9, 126.4, 125.0, 123.1, 69.6, 58.7, 43.0, 20.9 ppm; HRMS (ESI) calculated for $C_{24}H_{23}ClN_3O$ $[M + H]^+$: 404.15242, found 404.15158.

1-(4-Benzyl-6-(4-nitrophenyl)-3-phenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3ia). Light yellow solid, yield: 58.7 mg, 71%; mp = 116.2–117.5 °C; 1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 8.8 Hz, 2H), 7.77 (d, J = 8.8 Hz, 2H), 7.43–7.39 (m, 4H), 7.37–7.33 (m, 3H), 7.31–7.27 (m, 3H), 6.46 (s, 1H), 3.94–3.73 (m, 2H), 3.52 (s, 2H), 2.66 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 148.1, 143.0, 141.4, 137.2, 137.1, 129.0, 128.9, 128.8, 128.4, 128.0, 126.3, 125.6, 123.9, 69.9, 58.7, 42.9, 20.8 ppm; HRMS (ESI) calculated for $C_{24}H_{23}N_4O_3$ $[M + H]^+$: 415.17647, found 415.17514.

1-(4-Benzyl-6-(tert-butyl)-3-phenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3ja). White solid, yield: 14.7 mg, 21%; mp = 63.1–63.7 °C; 1H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 7.2 Hz, 2H), 7.41–7.37 (m, 2H), 7.35–7.29 (m, 4H), 7.24 (d, J = 7.2 Hz, 2H), 6.30 (s, 1H), 3.85–3.56 (m, 2H), 3.04 (s, 2H), 2.51 (s, 3H), 1.08 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5,

156.2, 137.9, 137.8, 129.0, 128.6, 127.9, 127.7, 126.3, 69.4, 58.2, 41.0, 37.5, 27.5, 20.7 ppm; HRMS (ESI) calculated for $C_{22}H_{28}N_3O$ $[M + H]^+$: 350.22269, found 350.22183.

(4-Benzyl-3,6-diphenyl-4,5-dihydro-1,2,4-triazin-2(3H)-yl)-(phenyl)methanone (3ka). Light yellow solid, yield: 29.6 mg, 34%; mp = 134.0–135.3 °C; 1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, J = 6.8 Hz, 2H), 7.61–7.55 (m, 3H), 7.51–7.49 (m, 4H), 7.45–7.37 (m, 6H), 7.35–7.30 (m, 5H), 6.61 (s, 1H), 4.12–3.90 (m, 2H), 3.65–3.55 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 145.6, 137.5, 137.3, 135.6, 134.5, 130.8, 130.4, 129.7, 129.1, 128.9, 128.8, 128.6, 128.2, 127.9, 127.6, 126.5, 125.0, 70.4, 58.9, 43.3, 27.0 ppm; HRMS (ESI) calculated for $C_{29}H_{26}N_3O$ $[M + H]^+$: 432.20704, found 432.20627.

Methyl 4-benzyl-3,6-diphenyl-4,5-dihydro-1,2,4-triazine-2(3H)-carboxylate (3la). White solid, yield: 45.8 mg, 59%; mp = 55.7–56.4 °C; 1H NMR (400 MHz, $CDCl_3$): δ 7.66 (s, 2H), 7.48 (d, J = 6.8 Hz, 2H), 7.44–7.40 (m, 2H), 7.38–7.31 (m, 9H), 6.20 (s, 1H), 4.02–3.84 (m, 5H), 3.56–3.43 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.0, 146.8, 137.9, 137.6, 135.9, 129.6, 129.1, 128.8, 128.7, 128.5, 128.2, 127.8, 126.3, 125.2, 72.0, 58.6, 53.7, 43.1 ppm; HRMS (ESI) calculated for $C_{24}H_{24}N_3O_2$ $[M + H]^+$: 386.18630, found 386.18539.

6-Ethyl 2-methyl 4-benzyl-3-phenyl-4,5-dihydro-1,2,4-triazine-2,6(3H)-dicarboxylate (3ma). Oil, yield: 53.5 mg, 70%; 1H NMR (400 MHz, $CDCl_3$): δ 7.41–7.39 (m, 4H), 7.37–7.32 (m, 4H), 7.25 (d, J = 7.2 Hz, 2H), 6.07 (s, 1H), 4.34–4.29 (m, 2H), 3.96 (s, 3H), 3.82–3.73 (m, 2H), 3.56–3.51 (m, 1H), 3.26 (d, J = 19.2 Hz, 1H), 1.39–1.35 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 154.2, 140.2, 137.2, 137.0, 129.0, 128.9, 128.7, 128.5, 127.9, 126.1, 72.3, 62.0, 58.3, 54.3, 42.6, 14.1 ppm; HRMS (ESI) calculated for $C_{21}H_{24}N_3O_4$ $[M + H]^+$: 382.17613, found 382.17499.

4-Benzyl-3,6-diphenyl-2-tosyl-2,3,4,5-tetrahydro-1,2,4-triazine (3na). White solid, yield: 61.3 mg, 64%; mp = 110.5–111.3 °C; 1H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.4 Hz, 2H), 7.61–7.58 (m, 2H), 7.42–7.39 (m, 1H), 7.38–7.36 (m, 9H), 7.34–7.31 (m, 5H), 6.12 (s, 1H), 3.72 (d, J = 13.6 Hz, 1H), 3.50–3.43 (m, 2H), 3.35 (d, J = 18.4 Hz, 1H), 2.49 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.2, 144.0, 138.5, 137.3, 135.7, 129.5, 129.4, 129.0, 128.6, 128.5, 128.4, 128.3, 127.8, 126.9, 124.9, 74.4, 58.4, 42.1, 27.0, 21.7 ppm; HRMS (ESI) calculated for $C_{29}H_{28}N_3O_2S$ $[M + H]^+$: 482.18967, found 482.18881.

1-(4-Benzyl-6-(4-chlorophenyl)-3-(4-methoxyphenyl)-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3fb). Oil, yield: 70.0 mg, 81%; 1H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 8.8 Hz, 2H), 7.43–7.37 (m, 4H), 7.35–7.33 (m, 3H), 7.21 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 6.39 (s, 1H), 3.90 (d, J = 13.2 Hz, 1H), 3.79 (s, 3H), 3.71 (d, J = 12.8 Hz, 1H), 3.46 (s, 2H), 2.63 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 159.5, 144.2, 137.5, 135.6, 134.2, 129.4, 129.0, 128.8, 128.7, 127.8, 127.6, 126.2, 114.2, 69.4, 58.5, 55.3, 42.7, 20.8 ppm; HRMS (ESI) calculated for $C_{25}H_{25}ClN_3O_2$ $[M + H]^+$: 434.16298, found 434.16229.

1-(4-Benzyl-3-(4-bromophenyl)-6-(4-chlorophenyl)-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3ff). White solid, yield: 68.3 mg, 71%; mp = 153.2–154.0 °C; 1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.40–7.39 (m, 4H), 7.36–7.34 (m, 3H), 7.17 (d, J = 8.4 Hz, 2H), 6.37 (s, 1H), 3.91–3.71 (m, 2H), 3.52–3.39 (m, 2H), 2.62 (s, 3H) ppm;



^{13}C NMR (100 MHz, CDCl_3): δ 172.5, 144.4, 137.2, 136.6, 135.8, 134.0, 132.0, 129.0, 128.8, 128.7, 128.2, 128.0, 126.2, 122.2, 69.0, 58.7, 42.8, 20.8 ppm; HRMS (ESI) calculated for $\text{C}_{24}\text{H}_{22}\text{BrClN}_3\text{O}$ $[\text{M} + \text{H}]^+$: 482.06293, found 482.06226.

1-(4-Benzyl-3-(4-bromophenyl)-6-(3-chlorophenyl)-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3hf). Oil, yield: 77.8 mg, 81%; ^1H NMR (400 MHz, CDCl_3): δ 7.65 (s, 1H), 7.49 (s, 1H), 7.47–7.43 (m, 2H), 7.41–7.40 (m, 4H), 7.38–7.36 (m, 2H), 7.31 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.4 Hz, 2H), 6.37 (s, 1H), 3.90–3.72 (m, 2H), 3.53–3.41 (m, 2H), 2.64 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.5, 144.1, 137.3, 137.1, 136.5, 134.9, 132.0, 129.9, 129.7, 129.0, 128.8, 128.2, 128.0, 125.0, 123.0, 122.3, 69.0, 58.7, 43.0, 20.8 ppm; HRMS (ESI) calculated for $\text{C}_{24}\text{H}_{22}\text{BrClN}_3\text{O}$ $[\text{M} + \text{H}]^+$: 482.06293, found 482.06238.

1-(4-Benzyl-3-(4-bromophenyl)-6-(*p*-tolyl)-4,5-dihydro-1,2,4-triazin-2(3H)-yl)ethan-1-one (3df). White solid, yield: 67.5 mg, 73%; mp = 133.9–134.7 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.54 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H), 7.44–7.33 (m, 5H), 7.21–7.19 (m, 4H), 6.38 (s, 1H), 3.92–3.74 (m, 2H), 3.57–3.42 (m, 2H), 2.65 (s, 3H), 2.40 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3): δ 172.5, 145.6, 140.1, 137.4, 136.8, 132.8, 131.9, 129.3, 129.1, 128.7, 128.3, 127.9, 124.9, 122.1, 68.9, 58.6, 42.9, 21.4, 20.8 ppm; HRMS (ESI) calculated for $\text{C}_{25}\text{H}_{25}\text{BrN}_3\text{O}$ $[\text{M} + \text{H}]^+$: 462.11755, found 462.11670.

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References

- For selected examples, see: (a) O. A. Attanasi, L. De Crescentini, G. Favi, F. Mantellini, S. Mantenuto and S. Nicolini, *J. Org. Chem.*, 2014, **79**, 8331; (b) O. A. Attanasi, P. Filippone, B. Guidi, T. Hippe, F. Mantellini and L. F. Tietze, *Tetrahedron Lett.*, 1999, **40**, 9277.
- For selected examples, see: (a) A. M. Shelke and G. Suryavanshi, *Org. Lett.*, 2016, **18**, 3968; (b) R. Huang, X. Chang, J. Li and C. J. Wang, *J. Am. Chem. Soc.*, 2016, **138**, 3998; (c) S. M. M. Lopes, M. S. C. Henriques, J. A. Paixao and T. M. V. D. P. E. Melo, *Eur. J. Org. Chem.*, 2015, **2015**, 6146; (d) J. Li, R. Huang, Y. K. Xing, G. Qiu, H. Y. Tao and C. J. Wang, *J. Am. Chem. Soc.*, 2015, **137**, 10124; (e) M. C. Tong, X. Chen, J. Li, R. Huang, H. Tao and C. J. Wang, *Angew. Chem., Int. Ed. Engl.*, 2014, **53**, 4680; (f) S. M. M. Lopes, A. Lemos and T. M. V. D. P. E. Melo, *Eur. J. Org. Chem.*, 2014, **2014**, 7039; (g) F. Palacios, D. Aparicio, Y. Lopez, J. M. D. Santos and C. Alonso, *Eur. J. Org. Chem.*, 2005, **2005**, 1142.
- For selected examples, see: (a) W. Yang, C. Yuan, Y. Liu, B. Mao, Z. Sun and H. Guo, *J. Org. Chem.*, 2016, **81**, 7597; (b) C. Guo, B. Sahoo, C. G. Daniliuc and F. Glorius, *J. Am. Chem. Soc.*, 2014, **136**, 17402; (c) X. Q. Hu, J. R. Chen, S. Gao, B. Feng, L. Q. Lu and W. J. Xiao, *Chem. Commun.*, 2013, **49**, 7905.
- J. R. Chen, W. R. Dong, M. Candy, F. F. Pan, M. Jorres and C. Bolm, *J. Am. Chem. Soc.*, 2012, **134**, 6924.
- X. Zhong, J. Lv and S. Luo, *Org. Lett.*, 2015, **17**, 1561.
- H.-W. Zhao, H.-L. Pang, T. Tian, B. Li, X.-Q. Chen, X.-Q. Song, W. Meng, Z. Yang, Y.-Y. Liu and Y.-D. Zhao, *Adv. Synth. Catal.*, 2016, **358**, 1826.
- For selected examples, see: (a) L. Wei and C. J. Wang, *Chem. Commun.*, 2015, **51**, 15374; (b) S. Gao, J. R. Chen, X. Q. Hu, H. G. Cheng, L. Q. Lu and W. J. Xiao, *Adv. Synth. Catal.*, 2013, **355**, 3539; (c) S. M. M. Lopes, A. F. Brigas, F. Palacios, A. Lemos and T. M. V. D. P. E. Melo, *Eur. J. Org. Chem.*, 2012, **2012**, 2152; (d) A. Lemos and J. P. Lourenco, *Tetrahedron Lett.*, 2009, **50**, 1311; (e) H. Salaheddine, S. L. Titouani, M. Soufiaoui and A. Tahdi, *Tetrahedron Lett.*, 2002, **43**, 4351.
- X. Li, K. Gai, Z. Yuan, J. Wu, A. Lin and H. Yao, *Adv. Synth. Catal.*, 2015, **357**, 3479.
- O. A. Attanasi, G. Favi, F. Mantellini, S. Mantenuto, G. Moscatelli and S. Nicolini, *Synlett*, 2015, **26**, 193.
- H.-W. Zhao, H.-L. Pang, B. Li, T. Tian, X.-Q. Chen, X.-Q. Song, W. Meng, Z. Yang, Y.-Y. Liu and Y.-D. Zhao, *RSC Adv.*, 2016, **6**, 25562.
- For selected reviews, see: (a) J. Vesely and R. Rios, *Chem. Soc. Rev.*, 2014, **43**, 611; M. González-López and J. T. Shaw, *Chem. Rev.*, 2009, **109**, 164.; S. Kobayashi and H. Ishitani, *Chem. Rev.*, 1999, **99**, 1069. For selected examples, see: (d) H. W. Zhao, B. Li, H. L. Pang, T. Tian, X. Q. Chen, X. Q. Song, W. Meng, Z. Yang, Y. D. Zhao and Y. Y. Liu, *Org. Lett.*, 2016, **18**, 848; (e) J. Xu, S. Yuan and M. Miao, *Org. Lett.*, 2016, **18**, 3822; (f) L. Cai, K. Zhang and O. Kwon, *J. Am. Chem. Soc.*, 2016, **138**, 3298; (g) D. Xie, L. Yang, Y. Lin, Z. Zhang, D. Chen, X. Zeng and G. Zhong, *Org. Lett.*, 2015, **17**, 2318; (h) B. M. Trost and S. M. Silverman, *J. Am. Chem. Soc.*, 2012, **134**, 4941; (i) X. Han, F. Zhong, Y. Wang and Y. Lu, *Angew. Chem., Int. Ed. Engl.*, 2012, **51**, 767.
- For selected examples, see: (a) R. Luciani, P. Saxena, S. Surade, M. Santucci, A. Venturelli, C. Borsari, G. Marverti, G. Ponterini, S. Ferrari, T. L. Blundell and M. P. Costi, *J. Med. Chem.*, 2016, **59**, 9269; (b) M. Stefek, M. Soltesova Prnova, M. Majekova, C. Rechlin, A. Heine and G. Klebe, *J. Med. Chem.*, 2015, **58**, 2649; (c) N. Oi, M. Tokunaga, M. Suzuki, Y. Nagai, Y. Nakatani, N. Yamamoto, J. Maeda, T. Minamimoto, M. R. Zhang, T. Suhara and M. Higuchi, *J. Med. Chem.*, 2015, **58**, 8444; (d) F. Lopez-Tapia, K. A. Walker, C. Brotherton-Pleiss, J. Caroon, D. Nitzan, L. Lowrie, S. Gleason, S. H. Zhao, J. Berger, D. Cockayne, D. Phippard, R. Suttman, W. L. Fitch, D. Bourdet, P. Rege, X. Huang, S. Broadbent, C. Dvorak, J. Zhu, P. Wagner, F. Padilla, B. Loe, A. Jahangir and A. Alker, *J. Med. Chem.*, 2015, **58**, 8413; (e) N. Hin,



- B. Duvall, D. Ferraris, J. Alt, A. G. Thomas, R. Rais, C. Rojas, Y. Wu, K. M. Wozniak, B. S. Slusher and T. Tsukamoto, *J. Med. Chem.*, 2015, **58**, 7258; (f) H. L. Maslen, D. Hughes, M. Hursthouse, E. De Clercq, J. Balzarini and C. Simons, *J. Med. Chem.*, 2004, **47**, 5482.
- 13 CCDC 1508810 contains the supplementary crystallographic data for compound **3aa**.
- 14 Z. Yang, N. Chen and J. Xu, *J. Org. Chem.*, 2015, **80**, 3611.

