Catalyst-Free 1,3-Dipolar Cycloaddition: An Efficient Route for the Formation of the 1,2,3-Triazole-Fused Diazepinone Framework

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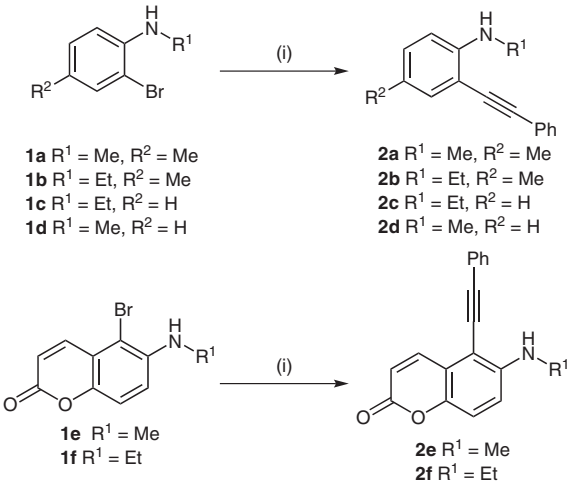
Abstract: A catalyst-free, effective method for the synthesis of the hitherto unreported 1,2,3-triazole-fused diazepinone framework in good to excellent yield through 1,3-dipolar cycloaddition is reported. The generality of the reaction is demonstrated by the synthesis of an array of [1,2,3]triazolodiazepinones. The methodology offers a clean reaction and easy isolation of the products in good to excellent yield.

Key words: triazoles, diazepinones, 1,3-dipolar cycloaddition

Heterocycles containing the 1,2,3-triazole ring system are reported to possess several biological activities including anti-HIV,[1] antiallergic,[2] antifungal,[3] antiviral,[4] antimicrobial[5] and antihistamine activity.[2] 1,2,3-Triazoles have also found industrial application such as their use as dyes, corrosion inhibitors, photostabilizers, photographic materials and agrochemicals.[6] Therefore, importance has been given to the development of new and more efficient synthetic pathways to a diverse array of 1,2,3-triazole pharmacophores. The most popular method for the construction of the 1,2,3-triazole framework is the Huisgen 1,3-dipolar cycloaddition reaction of azides with alkynes.[7] This methodology has been widely used by many research groups for the synthesis of several bicyclic, as well as polycyclic, triazole-fused nitrogen-containing heterocycles,[8] and also in the synthesis of triazole-fused oxygen-rich heterocycles.[9] There are also some other reports for the formation of this framework which include the use of copper(I) systems in the presence of a base[10] or in aqueous poly(ethylene glycol),[11] and the redox couple copper(II)/ascorbic acid[12] in organic or organoaqueous systems and in the solid phase.[13]

Apart from this, benzodiazepinones have emerged as a particularly fascinating class of scaffold in medicinal chemistry and have been viewed repeatedly as the prototype of a 'privileged structure' as they hit various classes of pharmacologically relevant targets such as GPCRs, ion channels and enzymes.[14] Prominent examples include the $GABA_A$ agonists Diazepam[15] (sedative) and Zolpidem[16] (nonadditive hypnotic), the antitumour antibiotic chicamycin A,[17] and the cholecystokinin antagonist asperlicin,[18] respectively. There are some reports[19] for the synthesis of 1,4-benzodiazepinone derivatives but 1,2,3-triazole-fused 1,4-benzodiazepinones are still lacking in the literature. Considering the utility of both 1,2,3-triazoles and 1,4-benzodiazepinones, we have undertaken a study to synthesize fused triazolobenzodiazepinones using the Huisgen 1,3-dipolar cycloaddition reaction. The results are reported here.

The precursors **3a–f** required for our present investigation were synthesized from compounds **2a–f**, which were in turn synthesized in one step by Sonogashira coupling of the corresponding bromo derivatives **1a–f** with phenylacetylene using $PdCl_2(PPh_3)_2$ as catalyst and copper(I) iodide as cocatalyst in anhydrous *N*,*N*-dimethylformamide containing triethylamine as base, at 120 °C (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) PhC≡CH, $PdCl_2(PPh_3)_2$, CuI, Et_3N, anhyd DMF, 120 °C, 4–6 h.

Compounds **2a–f** were subsequently treated with chloroacetyl chloride under phase-transfer catalysis conditions using tetrabutylammonium hydrogen sulfate (TBAHS) as catalyst and potassium carbonate as base to give the amide derivatives **3a–f** in good yield (Scheme 2).

Treatment of compound **3a** with an excess amount of sodium azide (2.5 equiv) in *N*,*N*-dimethylformamide at 100 °C for 1 hour gave the azide derivative **4a**. Azide **4a** was isolated and heated in *N*,*N*-dimethylformamide at 110 °C for four hours to afford the desired product **5a** in 90% yield. The same sequence of two steps (iii and iv) has been conducted in one step without isolating the azide derivative **4a** to give the 1,2,3-triazole-fused 1,4-benzodiaz-

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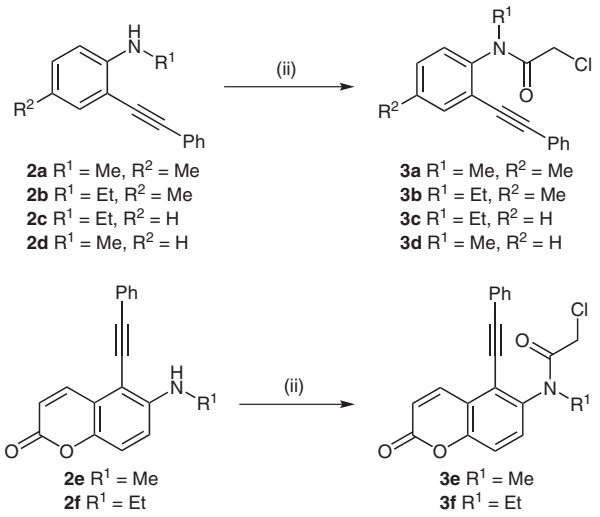
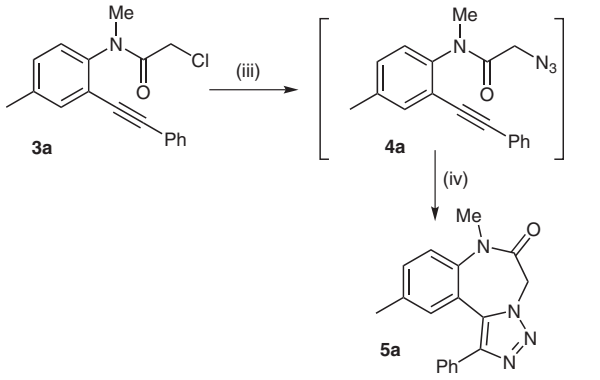


Scheme 2 *Reagents and conditions*: (ii) $ClCH_2COCl$, TBAHS, K_2CO_3, CH_2Cl_2–H_2O, r.t., 0.5 h.



Scheme 3 *Reagents and conditions*: (iii) NaN_3, DMF, 100 °C; (iv) 110 °C.

epinone **5a** without affecting the yield of the cycloaddition reaction (Scheme 3).

We have also attempted the same reaction in other solvents, such as dimethyl sulfoxide and 1,4-dioxane, but none of these solvents afforded the desired cyclized product. *N*,*N*-Dimethylformamide is the best choice, with the cycloaddition taking place in one pot to give the desired cyclized products in high yield. The other substrates **3b–f** were treated similarly to give the desired 1,3-dipolar cycloaddition products **5b–f** in 86–92% yield (Table 1).

Ko and Lee[20] synthesized substituted triazolobenzazepine derivatives in 72–77% yield from the Baylis–Hillman adducts of 2-alkynylbenzaldehydes by a 1,3-dipolar cycloaddition reaction. Recently, Chandrasekaran and coworkers reported the synthesis of [1,2,3]triazolopyrazinones in above 90% yield from amines and amino acids.[8g] Therefore, triazole-fused nitrogen heterocycles have attracted much attention from both biological and medicinal interests. In view of the importance of both the triazole and the 1,4-benzodiazepinone moiety, we have described the synthesis of some complex 1,2,3-triazole-fused 1,4-benzodiazepinone heterocycles using 1,3-dipolar cycloaddition in good to excellent yield.

In conclusion, we have achieved a catalyst-free 1,3-dipolar cycloaddition reaction of alkynes with azides for the synthesis of various complex 1,2,3-triazole-fused diazepinone derivatives of potential utility.

Melting points were determined in open capillaries and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer 120-000A instrument using KBr disks. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as internal standard (chemical shifts in δ) on either a Bruker DPX 400-MHz or a Bruker DPX 500-MHz spectrometer. MS data were recorded on a Qtof Micro YA263 mass spectrometer. Silica gel (60–120 mesh; Spectrochem, India) was used for chromatographic separations. Silica gel G (Spectrochem, India) was used for TLC. Petroleum ether refers to the fraction boiling between 60 and 80 °C.

CAUTION: Although we encountered no problems during the course of our studies, azides can be explosive compounds and should be handled with great care.[21]

Amide 3a; Typical Procedure

To a stirred soln of chloroacetyl chloride (383 mg, 3.39 mmol) in CH_2Cl_2 (20 mL), a mixture of amine **2a** (500 mg, 2.26 mmol) and a catalytic amount of TBAHS in CH_2Cl_2 (20 mL) was added. To this mixture, a soln of K_2CO_3 (468 mg, 3.39 mmol) in H_2O (10 mL) was added slowly. After the mixture was stirred for 30 min, a TLC check indicated completion of the reaction. Then, the reaction mixture was washed with 5% aq HCl (2 × 20 mL) and then with 5% aq NaOH (2 × 20 mL). Finally, the organic layer was washed with brine (20 mL), dried (anhyd Na_2SO_4) and filtered. The filtrate was concentrated and the crude product was purified by column chromatography over silica gel (60–120 mesh) using petroleum ether–EtOAc (4:1) as eluant to give **3a** in 72% yield. Amides **3b–f** were prepared accordingly.

Compound 3a

Yield: 72%; solid; mp 78–80 °C.

IR (KBr): 1673, 2218 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.48 (m, 2 H), 7.42 (br s, 1 H), 7.33–7.34 (m, 3 H), 7.17–7.22 (m, 2 H), 3.85 (q, *J* = 13.1 Hz, 2 H), 3.31 (s, 3 H), 2.38 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.9, 37.2, 41.9, 84.5, 95.0, 122.2, 127.9, 128.5, 128.9, 130.7, 131.7, 133.5, 138.9, 141.2, 166.7.

TOFMS (ES^+): *m*/*z* = 298.10 $[M + H]^+$.

Anal. Calcd for $C_{18}H_{16}ClNO$: C, 72.60; H, 5.42; N, 4.70. Found: C, 72.51; H, 5.39; N, 4.83.

Compound 3b

Yield: 74%; solid; mp 82–84 °C.

IR (KBr): 1674, 2213 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.48 (m, 3 H), 7.32–7.34 (m, 3 H), 7.20 (d, *J* = 8.0 Hz, 1 H), 7.13 (d, *J* = 8.2 Hz, 1 H), 3.74–3.94 (m, 4 H), 2.38 (s, 3 H), 1.14 (t, *J* = 7.4 Hz, 3 H).

MS: *m*/*z* = 311 $[M^+]$.

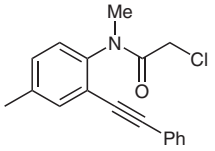
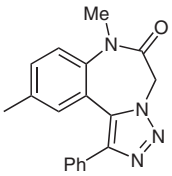
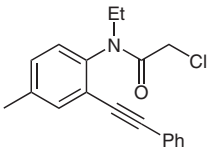
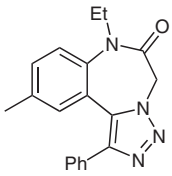
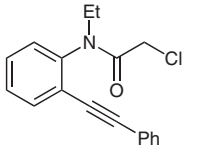
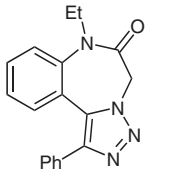
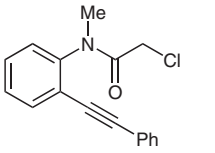
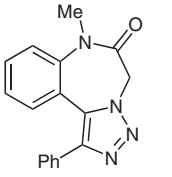
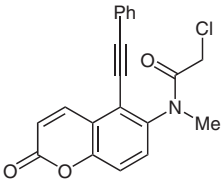
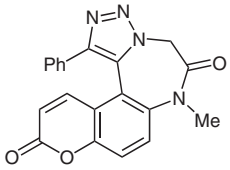
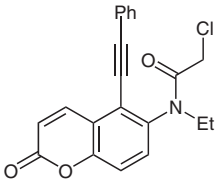
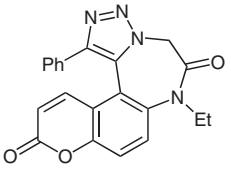
Anal. Calcd for $C_{19}H_{18}ClNO$: C, 73.19; H, 5.82; N, 4.49. Found: C, 73.31; H, 5.89; N, 4.31.

Compound 3c

Yield: 78%; solid; mp 92–94 °C.

IR (KBr): 1680, 2215 cm^{-1}.

Table 1 Summarized Results of the 1,3-Dipolar Cycloaddition Reactions

Starting material		Time (h)	Product		Yield (%)
3a		5	**5a**		90
3b		5.1	**5b**		88
3c		5	**5c**		86
3d		5	**5d**		92
3e		5.3	**5e**		87
3f		5.3	**5f**		89

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.42 (m, 3 H), 7.26–7.29 (m, 3 H), 7.07–7.16 (m, 3 H), 3.64–3.89 (m, 4 H), 1.08 (t, *J* = 7.0 Hz, 3 H).

MS: *m*/*z* = 297 [M$^+$].

Anal. Calcd for $C_{18}H_{16}ClNO$: C, 72.60; H, 5.42; N, 4.70. Found: C, 72.42; H, 5.32; N, 4.89.

Compound 3d
Yield: 72%; solid; mp 80–82 °C.

IR (KBr): 1676, 2218 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.63 (m, 1 H), 7.48–7.50 (m, 2 H), 7.39–7.42 (m, 2 H), 7.31–7.37 (m, 4 H), 3.85 (q, *J* = 13.1 Hz, 2 H), 3.34 (s, 3 H).

MS: *m*/*z* = 283 [M$^+$].

Anal. Calcd for $C_{17}H_{14}ClNO$: C, 71.96; H, 4.97; N, 4.94. Found: C, 71.77; H, 4.88; N, 4.75.

Compound 3e
Yield: 68%; solid; mp 204–206 °C.

IR (KBr): 1673, 1716, 2212 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 9.7 Hz, 1 H), 7.54 (d, *J* = 7.3 Hz, 2 H), 7.48 (d, *J* = 8.7 Hz, 1 H), 7.36–7.41 (m, 4 H), 6.57 (d, *J* = 9.7 Hz, 1 H), 3.85 (q, *J* = 13.2 Hz, 2 H), 3.35 (s, 3 H).

MS: *m*/*z* = 351 [M$^+$].

Anal. Calcd for $C_{20}H_{14}ClNO_3$: C, 68.28; H, 4.01; N, 3.98. Found: C, 68.11; H, 4.08; N, 4.11.

Compound 3f
Yield: 70%; solid; mp 156–158 °C.

IR (KBr): 1676, 1737, 2213 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 9.76 Hz, 1 H), 7.53 (d, *J* = 7.36 Hz, 2 H), 7.36–7.46 (m, 5 H), 6.57 (d, *J* = 9.72 Hz, 1 H), 3.79–3.94 (m, 4 H), 1.17 (t, *J* = 6.96 Hz, 3 H).

MS: *m*/*z* = 365 [M$^+$].

Anal. Calcd for $C_{21}H_{16}ClNO_3$: C, 68.95; H, 4.41; N, 3.83. Found: C, 69.11; H, 4.33; N, 3.77.

1,2,3-Triazole-Fused 1,4-Benzodiazepinone 5a; Typical Procedure

To a soln of amide **3a** (200 mg, 0.67 mmol) in DMF (5 mL) was added NaN_3 (110 mg, 1.68 mmol). The mixture was then heated to 100 °C for 1 h, and then at 110 °C for a further 4 h. After completion of the reaction (monitored by TLC), the mixture was cooled and H_2O (5 mL) was added. The mixture was then extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was dried (anhyd Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography over silica gel (60–120 mesh) using PE–EtOAc (3:1) as eluant to obtain the pure product **5a** in 90% yield. Similarly, the other amides **3b–f** were subjected to the same reaction conditions to give the products **5b–f** in good to excellent yield.

Compound 4a

Yield: 83%; solid; mp 150–152 °C.

IR (KBr): 1671, 2106, 2211 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.53 (m, 2 H), 7.45 (d, *J* = 1.2 Hz, 1 H), 7.36–7.39 (m, 3 H), 7.22 (dd, *J* = 2.0, 8.4 Hz, 1 H), 7.14 (d, *J* = 8.0 Hz, 1 H), 3.73 (d, *J* = 16.0 Hz, 1 H), 3.58 (d, *J* = 16.0 Hz, 1 H), 3.34 (s, 3 H), 2.41 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 36.7, 50.8, 84.4, 95.0, 122.2, 122.3, 127.7, 128.5, 129.0, 130.8, 131.7, 133.6, 139.0, 140.8, 167.7.

TOFMS (ES^+): *m*/*z* = 327.0 $[M + Na]^+$.

Anal. Calcd for $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41. Found: C, 71.11; H, 5.22; N, 18.60.

Compound 5a

Yield: 90%; solid; mp 182–184 °C.

IR (KBr): 1385, 1684 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.74 (m, 2 H), 7.34–7.42 (m, 5 H), 7.28 (s, 1 H), 5.45 (d, *J* = 14.4 Hz, 1 H), 4.53 (d, *J* = 14.4 Hz, 1 H), 3.43 (s, 3 H), 2.28 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.6, 37.1, 52.1, 120.6, 123.5, 127.3, 128.4, 128.8, 129.8, 129.9, 130.4, 131.7, 136.3, 138.1, 143.7, 165.9.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{17}N_4O$: 305.1397; found: 305.1406.

Compound 5b

Yield: 88%; solid; mp 172–174 °C.

IR (KBr): 1383, 1678 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 14.0 Hz, 2 H), 7.34–7.42 (m, 6 H), 5.41 (d, *J* = 14.0 Hz, 1 H), 4.52 (d, *J* = 14.0 Hz, 1 H), 4.27–4.36 (m, 1 H), 3.67–3.75 (m, 1 H), 2.30 (s, 3 H), 1.09 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 20.6, 44.2, 52.4, 122.2, 124.3, 127.2, 128.4, 128.7, 129.7, 129.8, 130.9, 131.8, 136.6, 136.8, 143.7, 164.9.

TOFMS (ES^+): *m*/*z* = 319.08 $[M + H]^+$.

Anal. Calcd for $C_{19}H_{18}N_4O$: C, 71.68; H, 5.70; N, 17.60. Found: C, 71.77; H, 5.66; N, 17.87.

Compound 5c

Yield: 86%; solid; mp 176–178 °C.

IR (KBr): 1393, 1682 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.74 (m, 2 H), 7.55–7.59 (m, 2 H), 7.48 (d, *J* = 8.0 Hz, 1 H), 7.36–7.44 (m, 3 H), 7.26–7.30 (m, 1 H), 5.44 (d, *J* = 14.0 Hz, 1 H), 4.54 (d, *J* = 14.0 Hz, 1 H), 4.28–4.37 (m, 1 H), 3.72–4.28 (m, 1 H), 1.12 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.2, 44.4, 52.4, 122.4, 124.5, 126.6, 127.4, 128.5, 128.8, 129.7, 129.8, 130.3, 130.9, 139.1, 143.9, 164.8.

MS: *m*/*z* = 304 $[M^+]$.

Anal. Calcd for $C_{18}H_{16}N_4O$: C, 71.04; H, 5.30; N, 18.41. Found: C, 71.16; H, 5.37; N, 18.65.

Compound 5d

Yield: 92%; solid; mp 210–212 °C.

IR (KBr): 1382, 1682 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.73–7.76 (m, 2 H), 7.54–7.59 (m, 1 H), 7.47–7.52 (m, 2 H), 7.36–7.44 (m, 3 H), 7.25–7.29 (m, 1 H), 5.50 (d, *J* = 14.4 Hz, 1 H), 4.57 (d, *J* = 14.8 Hz, 1 H), 3.48 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.2, 52.1, 120.7, 123.7, 126.3, 127.4, 127.6, 128.5, 128.7, 129.8, 130.3, 130.9, 140.4, 143.9, 165.9.

MS: *m*/*z* = 290 $[M^+]$.

Anal. Calcd for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30. Found: C, 70.11; H, 4.79; N, 19.19.

Compound 5e

Yield: 87%; solid; mp 310–312 °C.

IR (KBr): 1685, 1735 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 9.3 Hz, 1 H), 7.56–7.61 (m, 3 H), 7.29–7.36 (m, 4 H), 6.14 (d, *J* = 9.9 Hz, 1 H), 5.56 (d, *J* = 14.6 Hz, 1 H), 4.66 (d, *J* = 14.5 Hz, 1 H), 3.46 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 37.2, 52.1, 116.0, 117.8, 118.5, 120.1, 125.7, 125.8, 126.7, 126.9, 129.2, 129.5, 137.8, 140.6, 145.5, 152.5, 158.9, 166.0.

MS: *m*/*z* = 358 $[M^+]$.

Anal. Calcd for $C_{20}H_{14}N_4O_3$: C, 67.03; H, 3.94; N, 15.63. Found: C, 67.21; H, 4.01; N, 15.88.

Compound 5f

Yield: 89%; solid; mp 298–300 °C.

IR (KBr): 1686, 1732 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 9.1 Hz, 1 H), 7.51–7.58 (m, 3 H), 7.28–7.34 (m, 4 H), 6.10 (d, *J* = 9.9 Hz, 1 H), 5.45 (d, *J* = 14.3 Hz, 1 H), 4.58 (d, *J* = 14.2 Hz, 1 H), 4.33–4.42 (m, 1 H), 3.62–3.69 (m, 1 H), 1.06 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.0, 43.9, 52.4, 116.1, 117.8, 120.1, 120.5, 125.6, 126.8, 127.8, 129.2, 129.3, 129.6, 136.2, 140.5, 145.6, 152.7, 158.9, 165.0.

MS: *m*/*z* = 372 $[M^+]$.

Anal. Calcd for $C_{21}H_{16}N_4O_3$: C, 67.73; H, 4.33; N, 15.05. Found: C, 67.98; H, 4.41; N, 15.26.

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