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# A new synthesis of 2-(aminoalkyl)-1,2,4-triazolo[1,5-*a*]pyrimidines

**Mikhail A. Prezent, Elena D. Daeva, Sergey V. Baranin* and Igor V. Zavarzin**

*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: svbar@ioc.ac.ru*

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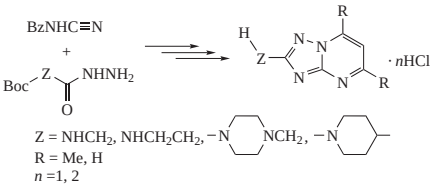
**Nickel(II) acetylacetonate-promoted cycloaddition between Boc-protected amino acid hydrazides and benzoylcyanamide followed by deprotection gives 2-amino-5-aminoalkyl-1,2,4-triazoles, whose reaction with 1,3-dielectrophiles affords the title compounds.**




In the last years, the interest to the chemistry of triazoles has considerably grown, since they possess a wide spectrum of biological activity, in particular antiviral (ribavirin, viramidin),[1,2] antifungal (flukonazol), and soporific (triazolam).[3,4] Recently a new convenient access to the novel type of ionic liquids based on one-pot reaction of 1,2,4-triazole-3-thione and 1-iodopropan-2-one was developed.[5] 5-Alkyl-3-amino-1,2,4-triazoles were found to exhibit a herbicide activity,[6] and showed positive results in the clinic trials for treatment of the Alzheimer disease.[7] Some 3-amino-substituted 1,2,4-triazoles possess anti-inflammatory[8] and analgesic[9] effects in human organisms.

No less interesting are derivatives of 1,2,4-triazolo[1,5-*a*]-pyrimidine. The latter is a privileged structure with a broad range of biological applications. Thus, some 2-(3-alkyl)-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidines demonstrate antitumor activity,[10] 5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines show superior *in vitro* cytotoxicity as compared with the anticancer drug doxorubicin.[11] The organotin(IV) and platinum(II) complexes of 5,7-disubstituted 1,2,4-triazolo[1,5-*a*]pyrimidines exhibit dose-dependent cytotoxic activity in multiple cancer cell lines.[12] Moreover, 5,7-disubstituted 1,2,4-triazolo[1,5-*a*]pyrimidines are inhibitors of the casein kinase 1δ in a potential treatment for neurological disorders.[13] From a high throughput screen, analogues of 1,2,4-triazolo[1,5-*a*]pyrimidine have been identified with neuroactive activities as potential therapeutic agents for neurodegenerative diseases.[14] In addition, 5,7-disubstituted-1,2,4-triazolo[1,5-*a*]pyrimidines have shown promising inhibitory activities for cellular secretion of the hepatitis B virus surface antigen as potential treatment for HBV infection.[15]

In this connection, a search for the new routes of 5,7-disubstituted 1,2,4-triazolo[1,5-*a*]pyrimidines synthesis has received significant attention due to its important practical issue.

In the present work, we suggest a convenient two-step synthesis of 1,2,4-triazolo[1,5-*a*]pyrimidines starting from Boc-protected amino acid hydrazides. It is known that the addition of cyanamides to aliphatic and aromatic acid hydrazides is catalyzed by strong mineral acids.[16–20] Obviously, this method cannot be extended towards obtaining 3-amino-5-(Boc-aminoalkyl)-1,2,4-triazoles **3a**–**d** from hydrazides **2a**–**d** and benzoylcyanamide **1** because of the presence of the Boc-group in the molecules of compounds **2a**–**d** and **3a**–**d**. 3-Amino-5-aminoalkyl-1,2,4-triazoles can also be synthesized by the reaction of the corresponding hydrazide with *S*-methylthiourea sulfate in the presence of an alkali.[21] However, a disadvantage of this method is the liberation of toxic methanethiol.

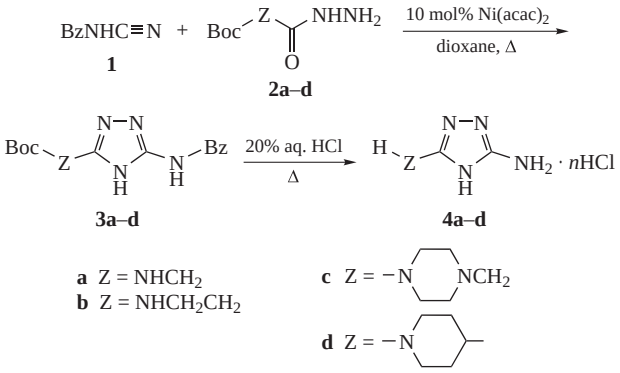
Earlier, we successfully used nickel(II) acetylacetonate as a catalyst in the addition of benzoylcyanamide to methylene active compounds.[22–24] Recently we obtained a number of 3-amino-substituted 1,2,4-triazoles **4b**–**d** by addition of benzoylcyanamide **1** at the amino group of Boc-protected amino acid hydrazides **2** in the presence of nickel(II) acetylacetonate as a catalyst (see the preliminary communication[25]). Note that we for the first time used nickel(II) acetylacetonate as the catalyst for addition of nitrile at amino group and in the absence of $Ni(acac)_2$ the reaction does not proceed.

In continuation of this work, here a new 1,2,4-triazole derivative **3a** was synthesized by heating the mixture of benzoylcyanamide **1** and Boc-protected amino acid hydrazide **2a** in dioxane in the presence of 10 mol% nickel(II) acetylacetonate. Further removal of both Boc-protection and benzoyl groups of triazole **3a** under the action of an aqueous HCl gave the corresponding 3-amino-substituted 1,2,4-triazole hydrochloride **4a** (according to the method developed by us earlier[25]) (Scheme 1).†

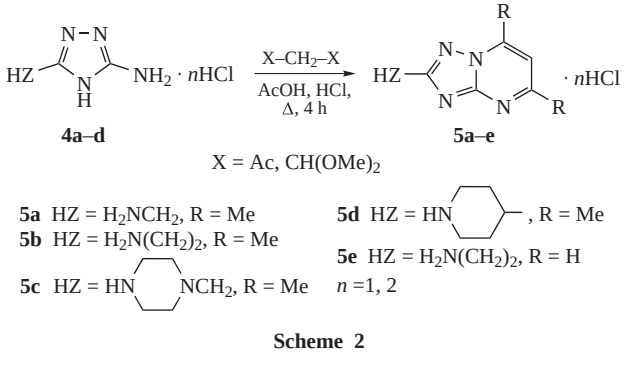
Compound **3a** is a white crystalline powder, poorly soluble in ethanol, dioxane, and benzene, but well soluble in chloroform and DMF. Its IR spectra exhibit absorption bands in the region of 3430–3200 $cm^{-1}$ characteristic of amino groups and in the region of ~1700 $cm^{-1}$ corresponding to the C=O groups of the benzoyl and *tert*-butoxycarbonyl fragments. The mass spectrum of triazole **3a** exhibits a peak of the molecular ion $[M]^+$. In the $^1H$ NMR

† $^1H$ NMR spectra were recorded on a Bruker AM-300 spectrometer (300 MHz) in DMSO-$d_6$, using a residual signal in the deuterated solvent at $\delta$ 2.50 as a reference. IR spectra were recorded on a Specord-M82 instrument in KBr pellets. High resolution mass spectra were measured on a Bruker micrOTOF II instrument using electrospray ionization (ESI). Measurements were performed on both positive and negative ions (capillary voltage 4500 V). The masses were scanned within *m*/*z* 50–300 Da range using both external and internal calibration (Electrospray Calibrant Solution Fluka). Solutions of compounds in methanol or acetonitrile were injected by a syringe, the flow rate was 3 μl $min^{-1}$; the sprayer gas was nitrogen (4 $dm^3$ $min^{-1}$), the interface temperature was 180 °C. Elemental analysis was performed on a Perkin-Elmer Series II CHNS/O 2400 Analyser.

The starting benzoylcyanamide **1**,[27] hydrazides **2a**,**d**,[28] **2b**,**c**[29] and 3-amino-1,2,4-triazoles **4b**–**d**[25] were synthesized according to the described procedures. Commercially available nickel(II) acetylacetonate and dioxane were purchased from Sigma-Aldrich.




**Scheme 1**




**Scheme 2**

spectra of compound **3a**, the signals at ~13.00 and 12.00 ppm, corresponding to the triazole NH protons and the benzoylamino group, are observed. The signal for the proton of the Boc-protected NH group in compound **3a** was found at 6.90 ppm. Hydrochloride **4a** is a white crystalline compound, poorly soluble in dioxane, acetone, and chloroform, but soluble in water, methanol, and ethanol. Its mass spectrum exhibits the $[M - 2HCl]^+$ ion peak. The signals at 4.10 ppm of the $CH_2$ group protons and in the region of 7.30–8.60 and 8.90 ppm of the $[NH_3]^+$ groups protons characterize the $^1$H NMR spectra of compound **4a**.

Further, we successfully used 3-aminotriazoles **4a–d** as convenient building blocks for the construction of 1,2,4-triazolo-[1,5-*a*]pyrimidines. In fact, triazole hydrochlorides **4a–d** undergo condensation with 1,3-dielectrophilic reagents, such as acetylacetone or 1,1,3,3-tetramethoxypropane, in boiling acetic acid in the presence of HCl providing high yields of 2-aminoalkyl-1,2,4-triazolo[1,5-*a*]pyrimidine hydrochlorides **5a–e**, respectively (Scheme 2).‡

Salts **5** are white crystalline substances, soluble in water, methanol, DMF, and DMSO, and poorly soluble in other organic solvents. In their IR spectra the absorption bands in the region 3500–2400 cm$^{-1}$, characteristic of the amino groups, and 1620 cm$^{-1}$ attributed to C=N bond, were observed. Their mass spectra contain the molecular ion $[M]^+$ peaks. The $^1$H NMR spectra of compounds **5a–d** indicated the presence of methyl and pyrimidine protons. The location of C(2) atom signal in the $^{13}$C NMR spectra is in the region 154–156 ppm, and thus completely confirms the structure of **5a–e**.[26]

In conclusion, a convenient synthesis of 2-aminoalkyl-1,2,4-triazolo[1,5-*a*]pyrimidines from available reagents has been developed. The resulting compounds **5** are the promising biologically active substances with versatile properties.

## References

1 A. R. Glanville, A. I. Scot, J. M. Morton, C. L. Aboyoun, M. L. Plit, I. W. Carter and M. A. Malouf, *J. Heart Lung Transplant*., 2005, **24**, 2114.
2 M. V. Chudinov, A. V. Matveev, A. N. Prutkov, I. D. Konstantinova, I. V. Fateev, V. S. Prasolov, O. A. Smirnova, A. V. Ivanov, G. A. Galegov and P. G. Deryabin, *Mendeleev Commun*., 2016, **26**, 214.
3 R. Cha and J. D. Sobel, *Expert Rev. Anti Infect. Ther*., 2004, **2**, 357.
4 N. P. Bel'skaya, M. A. Demina, S. G. Sapognikova, Z.-J. Fan, H.-K. Zhang, W. Dehaen and V. A. Bakulev, *ARKIVOC*, 2008, **xvi**, 9.

*3-Benzoylamino-5-[(2*-tert-*butoxycarbonylamino)methyl]-1,2,4-triazole* **3a**. A mixture of hydrazide **2a** (11.5 mmol), benzoylcyanamide **1** (10 mmol), and nickel(II) acetylacetonate (1 mmol) in anhydrous dioxane (10 ml) was refluxed with stirring for 12 h under dry nitrogen. The mixture was triturated, a white powder precipitate of compound **3a** was filtered and dried *in vacuo*, yield 62%, mp 245–247 °C. IR (KBr, $\nu$/cm$^{-1}$): 3430 and 3200 (NH), 3004 (CH), 1721 and 1680 (C=O). $^1$H NMR, $\delta$: 1.45 (s, 9 H, 3 Me), 4.10 (d, 2 H, $CH_2$, *J* 5 Hz), 6.90 s (1H, NH), 7.40–7.60 (m, 3 $H_{Ar}$, *J* 7 Hz), 8.05 (d, 2 $H_{Ar}$, *J* 7 Hz), 12.00 (br. s, 1H, NH), 13.00 (br. s, 1H, NH). Found (%): C, 56.45; H, 5.82; N, 22.35. Calc. for $C_{15}H_{19}N_5O_3$ (%): C, 56.78; H, 5.99; N, 22.08.

*3-Amino-5-aminomethyl-1,2,4-triazole dihydrochloride* **4a**. A solution of compound **3a** (10 mmol) in 20% aq. HCl (20 ml) was refluxed with stirring for 4 h. A white precipitate formed was filtered, washed with acetone, and dried *in vacuo*, yield 83%, mp > 350 °C. IR (KBr, $\nu$/cm$^{-1}$): 3470, 3400 and 3200–2970 ($NH_2$ and NH), 1670 (C=N). $^1$H NMR, $\delta$: 4.10 (s, 2 H, $CH_2$), 7.30–8.60 (br. s, 3 H, $NH_3^+$), 8.90 (s, 3 H, $NH_3^+$). Found (%): C, 18.98; H, 4.52; N, 37.35; Cl, 38.45. Calc. for $C_3H_9N_5Cl_2$ (%): C, 19.35; H, 4.84; N, 37.63; Cl, 38.17.

‡ *Compounds* **5a–e** *(general procedure)*. A mixture of triazole (**4a–d**) (10 mmol), acetylacetone or 1,1,3,3-tetramethoxypropane (11 mmol) and 1 ml of concentrated HCl in 30 ml of acetic acid was refluxed with stirring for 4 h. The volatiles were removed, the residue was crystallized from EtOH, washed with acetone and dried *in vacuo*.

*2-Aminomethyl-5,7-dimethyl[1,2,4]triazolo[1,5*-a*]pyrimidine hydrochloride* **5a**. White powder, yield 85%, mp > 350 °C. IR (KBr, $\nu$/cm$^{-1}$): 3430 and 3200–2970 ($NH_2$ and CH=), 1610 (C=N). $^1$H NMR, $\delta$: 2.65 (s, 3 H, Me), 2.80 (s, 3 H, Me), 4.30 (s, 2 H, $CH_2$), 7.25 (s, 1H, CH), 8.90 (s, 3 H, $NH_3^+$). Found (%): C, 44.68; H, 5.52; N, 32.35; Cl, 16.45. Calc. for $C_8H_{12}N_5Cl$ (%): C, 44.96; H, 5.62; N, 32.79; Cl, 16.63.

*2-(2-Aminoethyl)-5,7-dimethyl[1,2,4]triazolo[1,5*-a*]pyrimidine hydrochloride* **5b**. White powder, yield 84%, mp > 350 °C. IR (KBr, $\nu$/cm$^{-1}$): 3430 and 3250–2960 ($NH_2$ and CH=), 1644 (C=N). $^1$H NMR, $\delta$: 2.55 (s, 3 H, Me), 2.70 (s, 3 H, Me), 3.25 (s, 2 H, $CH_2$), 7.22 (s, 1H, CH), 8.45 (s, 3 H, $NH_3^+$). $^{13}$C NMR, $\delta$: 16.62 ($CH_2$), 24.85 (Me), 26.20 (Me), 38.60 ($NCH_2$), 112.33 ($C^6$), 148.10 ($C^{8a}$), 153.60 ($C^2$), 162.18 and 166.65 ($C^5$ and $C^7$). Found (%): C, 47.20; H, 6.02; N, 30.35; Cl, 15.95. Calc. for $C_9H_{14}N_5Cl$ (%): C, 47.47; H, 6.15; N, 30.77; Cl, 15.60.

*2-(Piperazin-4-ylmethyl)-5,7-dimethyl[1,2,4]triazolo[1,5*-a*]pyrimidine dihydrochloride* **5c**. White powder, yield 80%, mp > 350 °C. IR (KBr, $\nu$/cm$^{-1}$): 3430 and 3420 ($NH_2$), 3220–2360 (CH=), 1633 (C=N). $^1$H NMR, $\delta$: 2.55 (s, 3 H, Me), 2.75 (s, 3 H, Me), 3.40 (t, 4 H, 2 $CH_2$, *J* 4 Hz), 3.60 (t, 4 H, 2 $CH_2$, *J* 4 Hz), 4.70 (s, 2 H, $NCH_2$), 7.30 (s, 1H, CH), 10.00 (s, 3 H, $NH_2^+$ and $NH^+$). $^{13}$C NMR, $\delta$: 25.02 (2 Me), 39.78 (2 $NHCH_2$), 48.59 (2 $CH_2N$), 53.07 ($CH_2N$), 112.45 ($C^6$), 148.10 ($C^{8a}$), 155.42 ($C^2$), 158.00 and 166.65 ($C^5$ and $C^7$). HRMS (ESI), *m*/*z*: 247.1672 $[M+H]^+$ (calc. for $C_{12}H_{18}N_6$, *m*/*z*: 247.1666). Found (%): C, 44.90; H, 6.02; N, 26.01; Cl, 22.65. Calc. for $C_{12}H_{20}N_6Cl_2$ (%): C, 45.14; H, 6.27; N, 26.33; Cl, 22.26.

*2-(Piperidin-4-yl)-5,7-dimethyl[1,2,4]triazolo[1,5*-a*]pyrimidine hydrochloride* **5d**. White powder, yield 78%, mp > 350 °C. IR (KBr, $\nu$/cm$^{-1}$): 3520 and 3420 (NH), 3120–2360 (CH=), 1629 (C=N). $^1$H NMR, $\delta$: 2.00–2.25 (m, 4 H, 2 $CH_2$), 2.55 (s, 3 H, Me), 2.75 (s, 3 H, Me), 3.10 (m, 2 H, $CH_2$), 3.30 (m, 3 H, $CH_2$ and CH), 7.15 (s, 1H, CH), 9.20 (s, 1H, $NH^+$), 9.40 (s, 1H, $NH^+$). $^{13}$C NMR, $\delta$: 16.80 ($C^{4'}$), 25.02 (Me), 27.03 (Me), 33.18 ($C^{3'}$ and $C^{5'}$), 42.34 ($C^{2'}$ and $C^{6'}$), 112.78 ($C^6$), 148.60 ($C^{8a}$), 153.72 ($C^2$), 158.00 and 167.24 ($C^5$ and $C^7$). HRMS (ESI), *m*/*z*: 232.1565 $[M+H]^+$ (calc. for $C_{12}H_{17}N_5$, *m*/*z*: 232.1557). Found (%): C, 53.40; H, 6.42; N, 26.01; Cl, 13.62. Calc. for $C_{12}H_{18}N_5Cl$ (%): C, 53.83; H, 6.73; N, 26.17; Cl, 13.27.

*2-(2-Aminoethyl)[1,2,4]triazolo[1,5*-a*]pyrimidine hydrochloride* **5e**. White powder, yield 81%, mp > 350 °C. IR (KBr, $\nu$/cm$^{-1}$): 3420 and 3250–2980 ($NH_2$ and CH=), 1614 (C=N). $^1$H NMR, $\delta$: 3.25 (t, 2 H, $CH_2$, *J* 5 Hz), 3.55 (t, 2 H, $CH_2N$, *J* 5 Hz), 7.30 (t, 1H, $H^6$, *J* 7 Hz), 8.25 (s, 3 H, $NH_3^+$), 8.85–9.30 (dd, 2 H, $H^5$ and $H^7$, *J* 7 Hz). Found (%): C, 42.48; H, 5.32; N, 35.35; Cl, 17.45. Calc. for $C_7H_{10}N_5Cl$ (%): C, 42.11; H, 5.01; N, 35.09; Cl, 17.79.

5 L. G. Shagun, I. A. Dorofeev, L. V. Zhilitskaya, L. I. Larina and N. O. Yarosh, *Mendeleev Commun*., 2015, **25**, 334.
6 F. Calo, M. Kordes, H. Kraus, T. Mietzner, T. Seitz, K. Kreuz, M. Pasternak, T. W. Newton and D. Massa, *Patent WO 007564 A1*, 2015.
7 K. Baumann, A. Floh, E. Goetschi, H. Jacobsen, S. Jolidon and T. Luebbers, *Patent US 20090215759 A1*, 2009.
8 K. Bell, M. Sunose, K. Ellard, A. Cansfield, J. Taylor, W. Miller, N. Ramsden, G. Bergamini and G. Neubauer, *Bioorg. Med. Chem. Lett*., 2012, **22**, 5257.
9 T. F. Gregory, J. L. Wright, L. D. Wise, L. T. Meltzer, K. A. Serpa, C. S. Konkoy, E. R. Whittemore and R. M. Woodward, *Bioorg. Med. Chem. Lett*., 2000, **10**, 527.
10 X.-L. Zhao, Y.-F. Zhao, S.-C. Guo, H.-S. Song, D. Wang and P. Gong, *Molecules*, 2007, **12**, 1136.
11 L. Q. Wu, C. Zhang and W. L. Li, *Bioorg. Med. Chem. Lett*., 2013, **23**, 5002.
12 (*a*) M. A. Girasolo, L. Canfora, P. Sabatino, D. Schillaci, E. Foresti, S. Rubino, G. Ruisi and G. Stocco, *Inorg. Biochem*., 2012, **106**, 156; (*b*) I. Łakomska, M. Fandzloch, B. Popławska and J. Sitkowski, *Spectrochim. Acta, Part A*, 2012, **91**, 126.
13 J. M. H. Sheridan, J. R. Heal, W. D. O. Hamilton and I. Pike, *Patent WO 2012080729 A2*, 2012.
14 D. Kokel, J. Bryan, C. Laggner, R. White, C. Y. J. Cheung, R. Mateus, D. Healey, S. Kim, A. A. Werdich, S. J. Haggarty, C. A. MacRae, B. Shoichet and R. T. Peterson, *Nat. Chem. Biol*., 2010, **6**, 231.
15 W. Yu, C. Goddard, E. Clearfield, C. Mills, T. Xiao, H. Guo, J. D. Morrey, N. E. Motter, K. Zhao, T. M. Block, A. Cuconati and X. Xu, *J. Med. Chem.*, 2011, **54**, 5660.
16 V. Pandeya and R. Singh, *J. Indian Chem. Soc*., 1980, **57**, 1247.
17 A. V. Dolzhenko, G. Pastorin, A. V. Dolzhenko and W. K. Chui, *Tetrahedron Lett*., 2008, **49**, 7180.
18 F. Liu, F. Li, A. Ma, E. Dobrovetsky, A. Dong, C. Gao, I. Korboukh, J. Liu, D. Smil, P. J. Brown, S. V. Frye, C. H. Arrowsmith, M. Schapira, M. Vedadi and J. Jin, *J. Med. Chem.*, 2013, **56**, 2110.
19 H. G. Bonacorso, G. P. Bortolotto, J. Navarini, L. M. F. Porte, C. W. Wiethan, N. Zanatta, M. A. P. Martins and A. F. C. Flores, *J. Fluorine Chem*., 2010, **131**, 1297.
20 P. Mamalis, *J. Chem. Soc.*, 1960, 229.
21 G. Mitchell, *Patent WO 144234 A1*, 2013.
22 V. A. Dorokhov, M. F. Gordeev, Z. K. Dem'yanets, M. N. Bochkareva and V. S. Bogdanov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 1654 (*Izv. Akad. Nauk SSSR, Ser. Khim*., 1989, 1806).
23 V. A. Dorokhov and M. F. Gordeev, *Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1988, **37**, 1265 (*Izv. Akad. Nauk SSSR, Ser. Khim.*, 1988, 941).
24 V. A. Dorokhov, M. F. Gordeev, E. M. Shashkova, A. V. Komkov and V. S. Bogdanov, *Bull. Acad. Sci. USSR, Div. Chem. Sci*., 1991, **40**, 2274 (*Izv. Akad. Nauk SSSR, Ser. Khim*., 1991, 2600).
25 M. A. Prezent, E. D. Daeva, S. V. Baranin and V. A. Dorokhov, *Russ. Chem. Bull., Int. Ed*., 2015, **64**, 1089 (*Izv. Akad. Nauk, Ser. Khim*., 2015, 1089).
26 A. Salgado, C. Varela, A. M. Garcia Collazo and P. Pevarello, *Magn. Reson. Chem*., 2010, **48**, 614.
27 A. F. Crowther, F. H. S. Curd and F. L. Rose, *J. Chem. Soc*., 1948, 586.
28 S. Poojari, P. P. Naik and G. Krishnamurthy, *Tetrahedron Lett*., 2014, **55**, 305.
29 D. Kumar, G. Patel, A. K. Chavers, K.-H. Chang and K. Shah, *Eur. J. Med. Chem*., 2011, **46**, 3085.

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