Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal

Cite this: DOI: 10.1039/c6ob01644h

A one-pot synthesis of tetrazolones from acid chlorides: understanding functional group compatibility, and application to the late-stage functionalization of marketed drugs†‡

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Received 1st August 2016,
Accepted 31st August 2016

DOI: 10.1039/c6ob01644h

www.rsc.org/obc

A one-pot and scalable synthesis of tetrazolones (tetrazol-5-ones) from acid chlorides using azidotrimethylsilane is presented. The reaction tolerates many functional groups and can furnish aryl-, heteroaryl-, alkenyl-, or alkyl-substituted tetrazolone products in moderate to excellent yield (14–94%). No reduction in yield was observed when the reaction was undertaken on a larger-scale (20–36 g). The method could be used for the late-stage functionalization of pharmaceuticals, to provide tetrazolone congeners of the marketed drugs aspirin, indomethacin, probenecid, telmisartan, bexarotene, niacin (vitamin B3), and the active metabolite of the recently-launched immuno-modulatory agent, BG-12 (Tecfidera®). The ability of a tetrazolone group to serve as a bioisostere of a carboxylic acid, and to improve drug pharmacokinetic profiles is also highlighted.

The tetrazole group is a well-known substructure within medicinal chemistry and is present in a wide-selection of marketed drugs.[1] In many instances, a tetrazole may act as a non-classical bioisostere of a carboxylic acid,[2] but its contribution may also extend beyond isosteric replacement.[3] Relative to their tetrazole counterparts, a tetrazol-5-one group (henceforth, referred to as a tetrazolone), in which oxygen has been added to the 5-position of the tetrazole ring, has been utilized much less frequently by medicinal chemists. For example, a search of approved drugs indicate that only one marketed compound, the analgesic alfentanil **1**, contains a tetrazolone moiety (Fig. 1).[1,4,5] A low occurrence of tetrazolones within medicinal chemistry is unfortunate, as the tetrazolone group has many attractive features. For example, when the nitrogen at the 4-position is unsubstituted, the tetrazolone has a similar pK_a when compared with a tetrazole congener,[6] and can lower the calculated octanol–water partition coefficient (clog P). Therefore, it may be possible that a tetrazolone could also function as a non-classical bioisostere of a carboxylic acid.[7] Additionally, when anionic species are considered, the presence of an oxygen stabilizes the localization of electron-density at the nitrogen 4-position.[8] Thus, the 4-position of a tetrazolone is easy to alkylate,[9] or arylate,[10] to provide 1,4-disubstituted analogues. Studies with such compounds have shown that improvements to drug metabolism and pharamcokinetic properties (DMPK) can be observed. For example, within a series of β3-adrenergic receptor agonists, the tetrazolone L-770,644 **2**, showed improved DMPK in dog, when compared to imidazolidinone, or imidazolone relatives (Fig. 1).[11] Therefore, an expedient synthesis of compounds containing a tetrazolone group would be beneficial for both organic and medicinal chemists, especially if the methodology could be

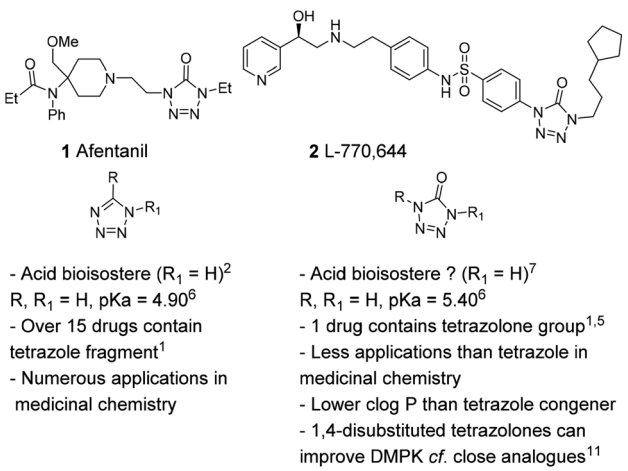

Fig. 1 Alfentanil **1**, L-770,644 **2**, and some characteristics of the tetrazole and tetrazolone groups.[1,2,5–7,11]

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†A separate paper describing the ability of a tetrazolone to act as a bioisostere of a carboxylic acid has been submitted.

‡Electronic supplementary information (ESI) available. See DOI: 10.1039/c6ob01644h

applied to the late-stage functionalization of fully-decorated compounds with pharmacological activity.

Most methods for preparing tetrazolones rely on a reaction of an isocyanate with an azide (Fig. 2). For example, reaction of phenylisocyanate with $NaN_3/AlCl_3$ gives *N*-phenyltetrazolone in a 76% yield.[12] The same reaction can proceed in quantitative yield if azidotrimethylsilane is used as the source of azide.[13] The isocyanate can also be prepared *in situ*, *via* a Curtius rearrangement, and this has led to syntheses starting from acid chlorides, progressing through an acyl azide to isocyanate to tetrazolone in one pot. For example, $NaN_3/AlCl_3$,[12] or $NaN_3/SiCl_4$ have been used for this transformation.[14] One paper has described the use of azidotrimethylsilane in carbon tetrachloride for the synthesis of thienyltetrazolones from thenoyl chlorides.[15,16] However, only three examples were described, and an acylated tetrazolone by-product could also be formed, if the stoichiometry of azidotrimethylsilane was low. Our own research group has an interest in compounds containing a tetrazolone, and we have previously disclosed uses within a series of kinase inhibitors.[17] As part of our efforts to broaden the use of tetrazolones within medicinal chemistry,[18] we wished to examine their preparation in further detail. In this paper we report an expedient synthesis of tetrazolones from acid chlorides using azidotrimethylsilane, which is used as both a co-reactant and solvent. Such a protocol can minimize the formation of by-products, and provide tetrazolone products in moderate to excellent yield. The facile nature of the process was demonstrated by conducting reactions up to 36 g in scale, and by utilizing the methodology for the late-stage functionalization of marketed drugs.[19]

Our synthesis of tetrazolones began by examining the reaction of 2-bromo-4-fluorobenzoyl chloride **3** with azidotrimethylsilane (TMS-N_3) at 100 °C (Table 1). Reacting **3** (1.5 g) with 6.0 equiv. of TMS-N_3 afforded the desired tetrazolone **4** in 82% isolated yield (entry 1). Reducing the stoichiometry of TMS-N_3 led to significant formation of a symmetrical urea by-product, and a lower isolated yield of desired tetrazolone **4**. For example, the use of 4.5 equivalents of TMS-N_3 gave a 76% yield of tetrazolone **4** (entry 2), while the use of 3.0 equivalents of TMS-N_3 gave a 37% yield of tetrazolone **4** (entry 3), together with large quantities of a symmetrical urea, 1,3-bis-(2-bromo-4-fluorophenyl)urea.[4] Significantly, it was found that the desired tetrazolone **4** was easily obtained from all the above reaction mixtures by cooling, evaporation of the excess TMS-N_3 and use of a base/acidification extraction process to give product of high purity (>96%). The reaction could also be scaled-up without any loss in yield. For instance, undertaking reactions with 20–36 g of acid chloride **3** and 4.0–6.0 equivalents of TMS-N_3 resulted in a 80–94% isolated yields of tetrazolone **4** (entry 4). These yields were similar to that obtained when commercially-available 2-bromo-4-fluoro-isocyanatobenzene was reacted with TMS-N_3 under similar conditions, indicating that acylazide formation and subsequent Curtius rearrangement progressed uneventfully.[4]

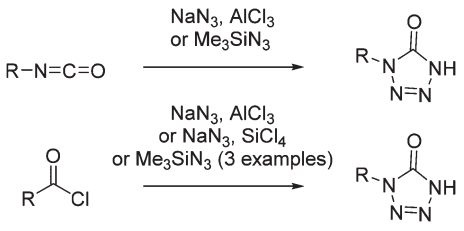
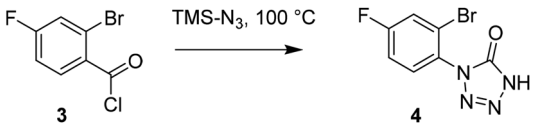


Fig. 2 Representative synthesis of tetrazolones.[11–16]

Table 1 Reaction of 2-bromo-3-fluorobenzoyl chloride with azidotrimethylsilane

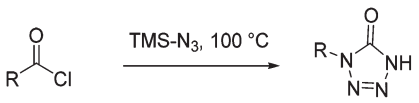


3 **4**

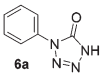
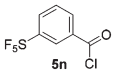
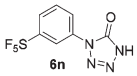
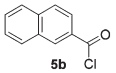
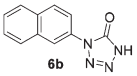
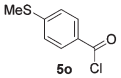
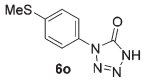
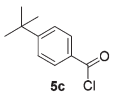
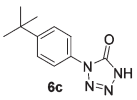
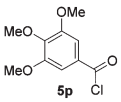
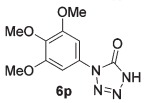
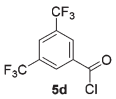
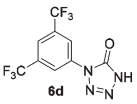
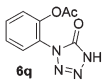
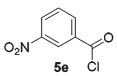
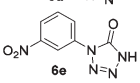
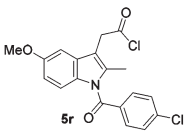
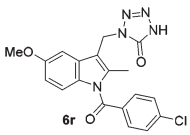
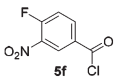
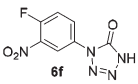
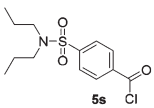
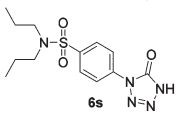
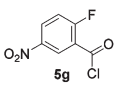
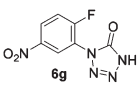
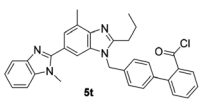
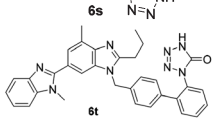
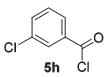
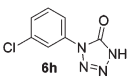
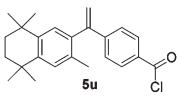
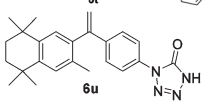
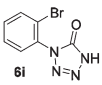
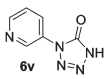
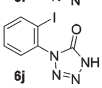
Entry	TMS-N_3 (equiv.)	Yield of **4** (%)
1	6.0	82
2	4.5	76
3	3.0	37
4	4.0–6.0 (20–36 g scale)	80–94

Next, we examined the application of the optimal reaction conditions identified above (at least 6.0 equivalents of neat TMS-N_3) with a diverse range of acid chloride substrate. In order to demonstrate that tetrazolone formation could be undertaken in a parallel manner, we performed some reactions in sealed vials employing a pressure-release cap, usually undertaking multiple reactions in a single heating block. After completion of the reaction, the mixture was worked-up by evaporating the excess TMS-N_3, extracting using a base/acid protocol, and purifying further with silica gel chromatography if required. The results of our experiments are shown in Table 2. As can be seen, the reaction tolerates a diverse-range of functionality on the acid chloride. For example, alkyl, trifluoromethyl, aryl, heteroaryl, alkenyl, nitro, fluoro, chloro, bromo, iodo, ketone, nitrile, pentafluorosulfanyl, ether, thioether, ester, amide and sulfonamide groups all remain intact under the reaction conditions (entries 1–21). Additionally, reactions of acid chlorides directly attached to heteroaryl, alkenyl, or alkyl-moieties were also successful (entries 22–26). A number of reactions in Table 2 deserve further comment. For instance, reactions of acid chlorides containing trifluoromethyl- or fluoro-groups were notable, as fluorine is a valuable substituent within medicinal chemistry (entries 4, 6 and 7).[20] It was also significant to observe that groups prone to nucleophilic aromatic displacement, such as activated halides, remain intact under the reaction conditions (entries 6, 7, 9 and 10). Additionally, the efficiency of the reaction seemed to be unaffected by the presence of large *ortho*-substituents (entries 9–11). In this respect, the formation of a tetrazolone analog of the commercial herbicide 2,4-D was particularly rewarding (entry 11). The reaction of an acid chloride containing a ketone group is also noteworthy, as no evidence for concomitant Schmidt reaction was observed (entry 12). Similarly,

Table 2 Tetrazolone formation with acid chlorides and azidotrimethylsilane



5a-5z 6a-6z

Entry	Starting material	Product	Yield (%)	Entry	Starting material	Product	Yield (%)
1	 5a	 6a	76	14	 5n	 6n	65[a]
2	 5b	 6b	66	15	 5o	 6o	73[a]
3	 5c	 6c	61	16	 5p	 6p	20
4	 5d	 6d	56	17	 5q	 6q	56
5	 5e	 6e	90	18	 5r	 6r	82[a]
6	 5f	 6f	70	19	 5s	 6s	68[a]
7	 5g	 6g	86	20	 5t	 6t	33[a]
8	 5h	 6h	60	21	 5u	 6u	89[a]
9	 5i	 6i	76	22	 5v	 6v	65
10	 5j	 6j	66	23	 5w	6w	30
11	5k	6k	43[a]	24	5x	6x	86
12	5l	6l	59[a]	25	5y	6y	62[a]
13	5m	6m	90	26	5z	6z	14

[a] Acid chloride prepared from acid prior to reaction with azidotrimethylsilane – reported yield is from acid to tetrazolone (see ESI).

azidotrimethylsilane did not react with a substrate containing a nitrile group (entry 13). The successful reaction of an acid chloride containing a pentafluorosulfanyl substituent was also gratifying, since there has been intense interest in the pentafluorosulfanyl group as a "super trifluoromethyl" equivalent within medicinal chemistry (entry 14).[21] The successful outcome of this reaction also provides another illustration as to the robust nature of this substituent. Of particular significance, were reactions that provided tetrazolone congeners of marketed drugs. Our aim with this work was to demonstrate

an ability to form a tetrazolone in a final-step, from fully-functionalized substrates commonly encountered by medicinal chemists, and to evaluate the ability of a tetrazolone group to serve as a carboxylic acid bioisostere (see accompanying paper). Toward this end, a small set of readily-available marketed drugs were chosen for reaction. We started, by preparing a tetrazolone congener of aspirin. The reaction proceeded uneventfully, and gave a 56% isolated yield of tetrazolone product (entry 17). We then proceeded to prepare tetrazolone analogs of the marketed drugs indomethacin, probenecid, telmisartan and bexarotene, which are approved for inflammation, gout, blood-pressure modulation and cancer, respectively (entries 18–21).[22] Isolated yields were good (33–89%). In particular, the preparation of a tetrazolone of telmisartan (**6t**; entry 20) was pleasing, as related marketed 'sartans' (*e.g.* candesartan, irbesartan, losartan, olmesartan, valsartan), contain a tetrazole group. Thus, it will be possible to compare the biological activity of tetrazolone **6t** to both a marketed acid congener (Telmisartan), and a tetrazole relative (see accompanying paper). Also of significance, was the reaction with hetroaroyl chlorides. Both electron-deficient six-membered heterocycles (entry 22), and electron-rich five-membered heterocycles (entries 23 and 24) formed tetrazolone products under the reaction conditions. It should be noted, that compound **6v** (entry 22) is a direct tetrazolone analog of the marketed drug niacin. To complete our examination of the tetrazolone-forming reaction, we looked at the reaction of acid chlorides attached to an olefin, or alkane (entries 25 and 26). The reaction of hemi-fumarate **5y**, progressed smoothly to give a 62% yield of tetrazolone **6y** (entry 25). This is an interesting example, as compound **6y** is related to monomethyl fumarate, the active metabolite of the recently-launched immuno-modulatory drug, BG-12 (Tecfidera®). The reaction with an acid chloride attached to an alkane progressed less-well. For instance, propionyl chloride **5z** afforded ethyl-tetrazolone **6z**, a building block for alfentanil synthesis,[5] in a modest 14% yield under our reaction conditions (entry 26; compare also with entries 11 and 18).

In summary, this paper describes a facile synthesis of tetrazolones from acid chlorides, using azidotrimethylsilane as a co-reactant and solvent. The reaction tolerates functional groups commonly encountered within medicinal chemistry, and has shown a particular aptitude for preparing tetrazolone analogues of commercial drugs. The methodology disclosed in this paper will be of interest to medicinal chemists, where the late-stage functionalization of agents with pharmacological activity, and use of novel bioisosteres of carboxylic acids, is highly soughtafter.[23,24]

Acknowledgements

We thank Mark Irving, Van Ybarra and Duayne Tokushige of Rigel, Inc. analytical chemistry for high-resolution mass spectrometry.

Notes and references

1 R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845–5859.
2 (*a*) A. J. Zych and R. J. Herr, *PharmaChem*, 2007, **6**, 21–24; (*b*) R. J. Herr, *Bioorg. Med. Chem.*, 2002, **10**, 3379–3393; (*c*) H. Singh, A. S. Chawla, V. S. Kapoor, D. Paul and R. K. Malhortra, *Prog. Med. Chem.*, 1980, **17**, 151–183.
3 L. V. Myznikov, A. Hrabalek and G. I. Koldobskii, *Chem. Heterocycl. Compd.*, 2007, **43**, 1–9.
4 See ESI‡ for details.
5 F. Janssens, J. Torremans and P. A. Janssen, *J. Med. Chem.*, 1986, **29**, 2290–2297.
6 L. D. Hansen, E. J. Baca and P. Scheiner, *J. Heterocycl. Chem.*, 1970, **7**, 991–996.
7 For an example wherein tetrazolone was not an effective bioisostere see: K. L. Kees, T. J. Caggiano, K. E. Steiner, J. J. Fitzgerald, M. J. Kates, T. E. Christos, J. M. Kulishoff, R. D. Moore and M. L. McCaleb, *J. Med. Chem.*, 1995, **38**, 617–628.
8 X. Chen and H. Xiao, *Propellants, Explos., Pyrotech.*, 1999, **24**, 319–324.
9 H. Quast and L. Bieber, *Chem. Ber.*, 1981, **114**, 3253–3272.
10 A. S. Gundugola, K. L. Chandra, E. M. Perchellet, A. M. Waters, J. P. H. Perchellet and S. Rayat, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 3920–3924.
11 T. L. Shih, M. R. Candelore, M. A. Cascieri, C. L. Shuet-Hing, L. F. Colwell, L. Deng, W. P. Feeney, M. J. Forrest, M. J. Horn, D. E. MacIntyre, R. R. Miller, R. A. Stearns, C. D. Strader, L. Tota, M. J. Wyvratt, M. H. Fisher and A. E. Weber, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1251–1254.
12 J. P. Horwitz, B. E. Fisher and A. J. Tomasewski, *J. Am. Chem. Soc.*, 1959, **81**, 3076–3079.
13 O. Tsuge, S. Urano and K. Oe, *J. Org. Chem.*, 1980, **45**, 5130–5136.
14 T. A. Salama, S. S. Elmorsy, A. G. M. Khalil and M. A. Ismail, *Chem. Lett.*, 2011, **40**, 1149–1151.
15 M. Toselli and P. Zanirato, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1101–1104.
16 In an attempt to prepare an isocyanate, one other paper has noted the formation of a tetrazolone by-product from reaction of an acid chloride with azidotrimethylsilane. See: K. Burger, E. Windeisen and R. Pires, *J. Org. Chem.*, 1995, **60**, 7641–7645.
17 (*a*) R. Singh, K. Tso, J. Zhang, M. Duncton, S. Alvarez, R. Kolluri, J. Ramphal and S. Holland, *US Patent*, 0130415, 2011; *Chem. Abstr.*, 2011, **155**, 40991; (*b*) M. Duncton and R. Singh, *WO* 075316, 2012; *Chem Abstr.*, 2012, **157**, 76933; (*c*) M. Duncton and R. Singh, *Org. Lett.*, 2013, **15**, 4284–4287; (*d*) R. Singh, M. Duncton, J. Zhang, S. Alvarez, K. Tso, S. Holland, R. Yen, R. Kolluri, T. Heckrodt, Y. Chen, E. Masuda, H. Li, D. G. Payan and R. Kelley, *WO* 152198, 2013; *Chem. Abstr.*, 2013, **159**, 608680; (*e*) M. Duncton and M. D. Burke, *US Patent*, 0331583, 2013; *Chem. Abstr.*, 2013, **160**, 63411; (*f*) D. McMurtrie, R. Kolluri, E. Masuda, K. Tso, S. Alvarez, T. Heckrodt, S. Holland, R. Kelley, M. Duncton and R. Singh, *WO* 089112, 2014; *Chem. Abstr.*, 2014, **161**, 99264.

18 (*a*) M. Duncton and R. Singh, *US Patent*, 0213648, 2016; *Chem. Abstr.*, 2016, **165**, 236086; (*b*) M. Duncton, R. B. Murray, G. Park and R. Singh, Late-stage functionalization of marketed drugs: synthesis and use of tetrazolones as a carboxylic acid bioisostere, presented at *252nd ACS National Meeting and Exposition*, Philadelphia, PA, United States, August 21–25, 2016, MEDI-238.

19 M. A. J. Duncton, M. A. Estiarte, R. J. Johnson, M. Cox, D. J. R. O'Mahony, W. T. Edwards and M. G. Kelly, *J. Org. Chem.*, 2009, **74**, 6354–6357.

20 (*a*) J. T. Welch, *Tetrahedron*, 1987, **43**, 3123–3197; (*b*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320–330.

21 (*a*) S. Altomonte and M. Zanda, *J. Fluorine Chem.*, 2012, **143**, 57–93; (*b*) P. R. Savoie and J. T. Welch, *Chem. Rev.*, 2015, **115**, 1130–1190.

22 For potential of bexarotene in Alzheimer's disease see: P. E. Cramer, J. R. Cirrito, D. W. Wesson, D. C. Y. Lee, J. C. Karlo, A. E. Zinn, B. T. Casali, J. L. Restivo, W. D. Goebel, M. J. James, K. R. Brunden, D. A. Wilson and G. E. Landreth, *Science*, 2012, **335**, 1503–1506.

23 The suitability of this reaction for continuous synthesis using flow chemistry is under evaluation.

24 For an accompanying paper describing the use of a tetrazolone group as a bioisostere of a carboxylic acid see, M. A. J. Duncton, R. B. Murray, G. Park and R. Singh, *Org. Biomol. Chem.*, DOI: 10.1039/c6ob01646d.