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Facile, diversity-orientated one-pot synthesis of ethyl 1,5-disubstituted-1*H*-1,2,4-triazole-3-carboxylates

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ABSTRACT

Access to the 1,5-disubstituted-1*H*-1,2,4-triazole-3-carboxamide motif is quite laborious and requires forcing conditions to effect the cyclocondensation step. Herein, we report an efficient and mild one-pot protocol to access this substructure in good chemical yields with high regiocontrol.

During a recent programme, the 1-alkylated-5-aryl-1*H*-1,2,4-triazole-3-carboxamide *"Motif 1"* and the 1-arylated-5-alkylated-1*H*-1,2,4-triazole-3-carboxamide *"Motif 2"* presented themselves as interesting focal points for our research (Fig. 1). We were particularly interested in developing flexible methodology that would allow us to vary the two key diversity points at *N*-1 and C-5 and studied multiple routes to the logical building ester blocks **1** and **2** (Schemes 1 and 2).

From our retrosynthetic analysis we generated 3 logical routes (*A, B* and *C*) to the key building block **1**. We quickly excluded *Route A* as we found that access to **3** was going to be quite problematic due to poor selectivity at the alkylation step of **4**.[1] *Route B* and *Route C* are similar disconnections with a change in the order of the reagents. *Route B* allowed us to vary the substitution at *N*-1 easily and with high selectivity as acylation of N-substituted hydrazines (**9**) is well documented at the most substituted nitrogen within reason (i.e., *i*-Pr but not *t*-Bu or Ar) affording **7**.[2] However, cyclisation of **7** with commercially-available ethyl 2-amino-2-thioxoacetate (**5**) has only ever been reported in a two-step manner with unsubstituted primary acyl hydrazides[3] and the final intramolecular cyclisation step involves very harsh conditions (*n*-BuOH,[4] solvent-free,[3,5,8b] DMF/KOH,[6] pyridine and[7] inert high boiling solvents such as *m*-xylene[8] usually at >150 °C) with variable yields. *Route C* involved pre-synthesising the cyclisation precursor (**10**)[6] and carrying out a cyclodehydration reaction with the chosen carboxylic acid (**8**).

Therefore, we decided to focus our efforts on *Routes B* and *C* in order to achieve our goal. For *Route B*, regioselective acylation of methylhydrazine was best achieved using EDCI/ Pfp-OH (pentafluorophenol) with a model substrate, piperonylic acid (**12**), affording a 8/2 mixture of regioisomers that were easily separated by standard chromatographic techniques. As we eluded to earlier in the Letter, application of the cyclisation protocol to substituted acyl hydrazides (i.e., **13**) was very sketchy.[9] After several trials in pyridine, xylene, DMF at 90–160 °C, we found the combination of toluene–AcOH (10:1) at 90–100 °C gave **14** in satisfactory yield. In parallel, we investigated *Route C*. Condensation of **6** with methylhydrazine afforded a 1:1 mixture of **11** and the more lipophilic regioisomer that was easily removed by chromatography. After considerable process development, the amide coupling step with **11** proceeded in good yield using T3P as the coupling agent to afford an unstable intermediate that was immediately cyclised in situ using our mild protocol after concentration of the amide coupling mixture. Unfortunately, although carboxylic acids are readily commercially-available, we were forced to exclude this route as **11** was not found to be sufficiently thermally-stable by DSC testing (Scheme 2).[10]

We tested the scope of *Route B* by preparing a small library of 1,5-disubstituted triazole products (Table 1). Use of the EDCI/Pfp-OH coupling protocol proved advantageous in terms of favouring *N*-1 acylation (entries 1–5, 8–12) compared to previous carbodiimide

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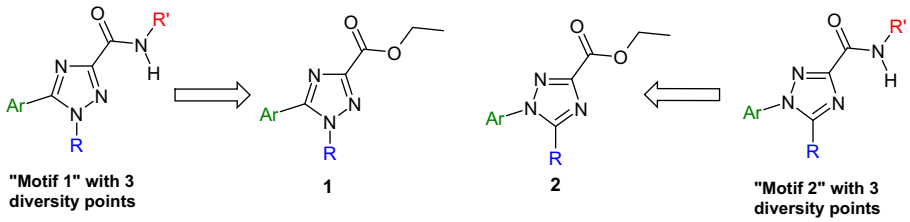
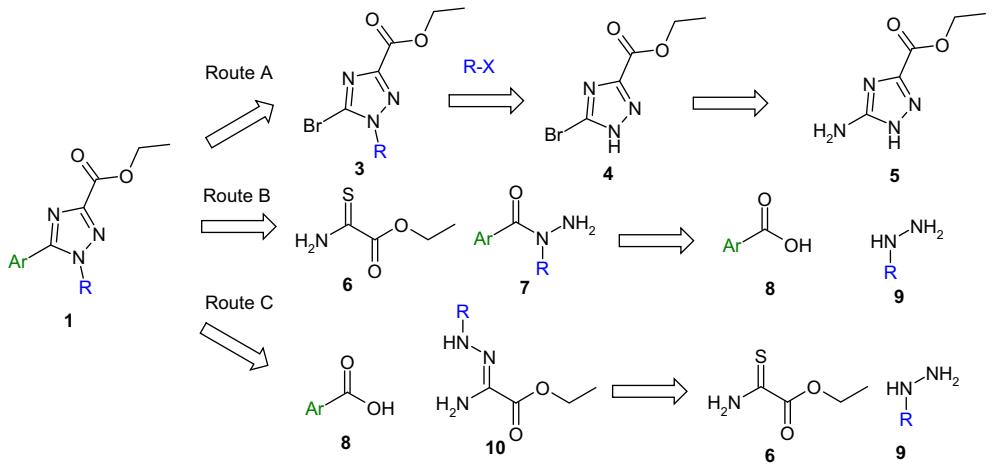
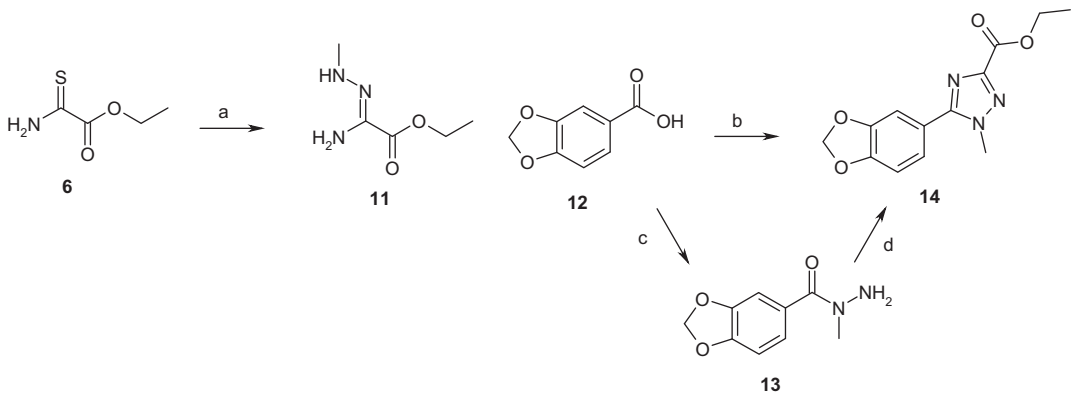


Figure 1. Key target motifs for our research.



Scheme 1. Retrosynthetic analysis of first target synthon **1**.

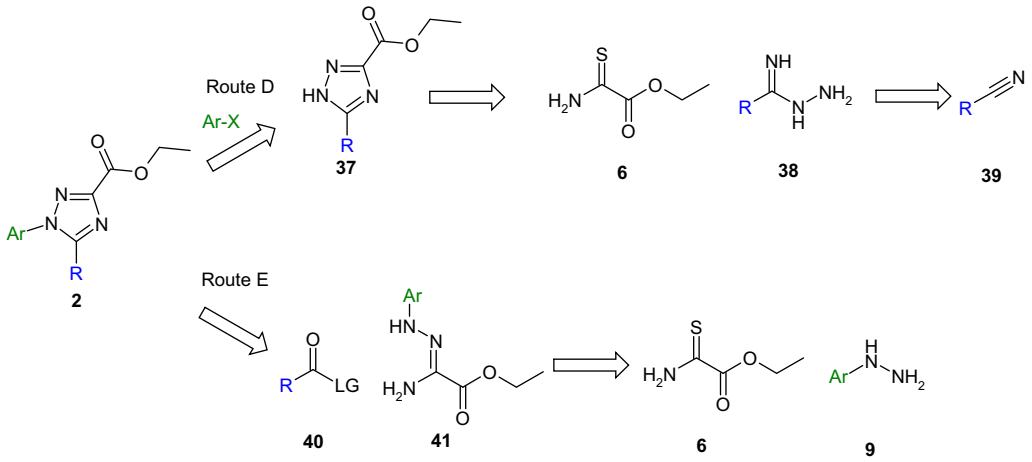


Scheme 2. Preparation of ethyl 3-(benzo[d][1,3]dioxol-5-yl)-1-methyl-1*H*-1,2,4-triazole-5-carboxylate (**14**). Reagents and conditions: (a) methylhydrazine sulfate, K_2CO_3, EtOH, 0 °C to r.t., 20 h, 37%; (b) T3P (50% w/w in EtOAc), 3 equiv DIPEA, 1,4-dioxane, r.t. 1 h then concentrate and dissolve in AcOH/1,4-dioxane (1:1), 100 °C, 1 h, 64%; (c) EDCI, Pfp-OH, DCM, r.t., 2 h then add methylhydrazine, 74%; (d) ethyl 2-amino-2-thioxoacetate (**6**), toluene/AcOH (10:1), 100 °C, 16 h, 64%.

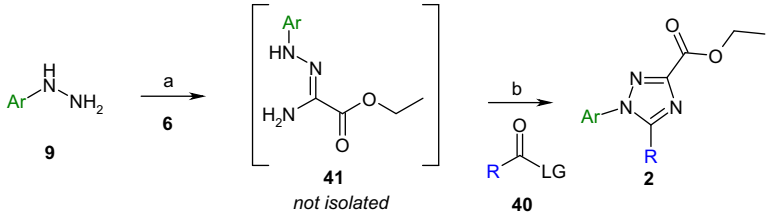
reported methodology.[2b] As expected, acylation was entirely regioselective at *N*-2 in the case of *t*-butylhydrazine and *p*-methoxyphenylhydrazine driven by the steric and electronic factors, respectively. Application of our mild cyclisation protocol proceeded with good overall isolated yields when cyclising the N-1 substituted acyl hydrazides (entries 1–5, 8–12) perhaps with a notable exception of entry 5 where there was some evidence of degradation during cyclisation. However, cyclisation of *N*-2 alkylated acyl hydrazides afforded very poor isolated yields of cyclised product that can be attributed to steric hindrance (entry 6) and the poor nucleophilicity of the terminal substituted nitrogen atom (entry 7).

After having accessed *"Motif 1"*, we turned our attention to *"Motif 2"* that required us to vary the aryl group at *N*-1, therefore, targeting building block **2**. Based on the few existing references in the literature[11,12] *Route D* (like *Route A*) was viewed as very ambitious as it relied on attaining good chemical and regiochemical yields (*N*-1 v *N*-2) at the arylation step on **37**. The synthesis of **37** could be envisaged from substituted carboximidohydrazides (**38**) readily attained from nucleophilic addition of hydrazine directly on the cyano precursors (**39**)[13] or passing via an intermediate imidate.[14] *Route E* (like *Route C* in Scheme 1) had several advantages as the regiochemistry is fixed at the first step and there is high convergence with *Routes B* and *C*, all using commercially-available **6** (Scheme 3).

Consequently, we employed *Route E* (Scheme 3) and were delighted to observe that the entire process from the aryl hydrazine[15] reactant could be carried out in a one-pot manner. Firstly, condensation of the aryl hydrazine (**9**) with **6** proceeded efficiently at room temperature in toluene-AcOH (10:1) to afford the intermediate **41** that was simply treated with a threefold excess of the final

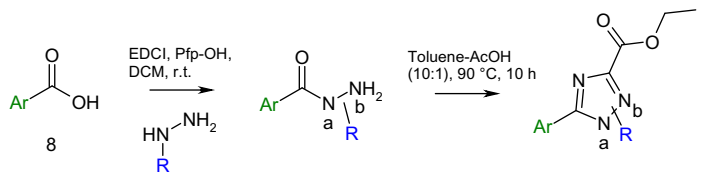


Scheme 3. Retrosynthetic analysis of second target synthon **2**.



Scheme 4. Preparation of ethyl 1-arylated-5-substituted-1*H*-1,2,4-triazole-3-carboxamides. Reagents and conditions: (a) ethyl 2-amino-2-thioxoacetate (**6**), toluene-AcOH (10:1), r.t., 1 h, assumed quant.; (b) acylating reagent (3 equiv), 100 °C, 1 h, 27–71%.

Table 1
Selected results obtained after acylation of *N*-alkylhydrazines followed by cyclisation to the 1,2,4-triazole-3-carboxylic acid ethyl esters



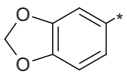
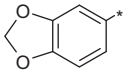
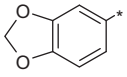
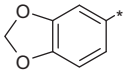
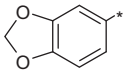
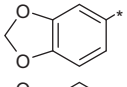
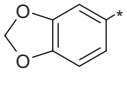
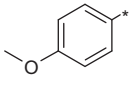
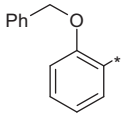
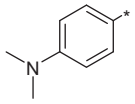
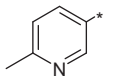
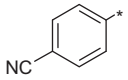
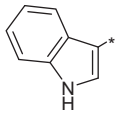
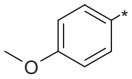
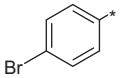
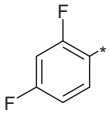
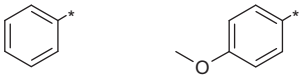
Entry	Compound	Ar	R	Acylation % yield[a] N1/N2	Compound	Cyclisation % yield[a] N1/N2
1	**13a/b**		CH_3	70/18	**14a/b**	64/12
2	**15a**		Et	70/traces	**26a**	70/NA
3	**16a**		*i*-Pr	58/traces	**27a**	60/NA
4	**17a**			65/traces	**28a**	57/0
5	**18a**			49/16	**29a**	35/NA
6	**19b**		*t*-Bu	traces/57[a]	**30b**	NA/traces
7	**20b**			traces/49[a]	**31b**	NA/14

Table 1 (*continued*)

Entry	Compound	Ar	R	Acylation % yield[a] N1/N2	Compound	Cyclisation % yield[a] N1/N2
8	**21a**		CH_3	71/traces	**32a**	68/NA
9	**22a**		CH_3	62/traces	**33a**	53/NA
10	**23a**		CH_3	69/traces	**34a**	55/NA
11	**24a**		CH_3	48/traces	**35a**	64/NA
12	**25a**		CH_3	59/traces	**36a**	70/NA

NA = not applicable as the reaction was not carried out as only traces of the *N*-2 or *N*-1 isomer were isolated after the first step.
[a] Isolated yields.

Table 2
Selected results obtained for the one-pot synthesis of 1-aryl-5-substituted-1*H*-1,2,4-triazole-3-carboxylic acid ethyl esters (**2**)

Entry	Compound	Ar	R	% Yield
1	**42**		CH_3	61
2	**42**		CH_3	41[a]
3	**43**		CH_3	71
4	**44**		CH_3	62
5	**45**		CH_3	53
6	**46**		CH_3	44
7	**47**			35
8	**48**			27[a]
9	**49**		*t*-Bu	Traces

[a] The corresponding acid chloride was used in the last step.

acylating component and heated to effect cyclodehydration to the 1,2,4-triazole ring (**2**) (Scheme 4). During our experimentation, we found that anhydrides were superior to acid chlorides (Table 2, entry 1 v 2) and with sterically-hindered acylating agents such as pivalic anhydride (entry 9), only trace amounts of desired product were observed. However, the yields were acceptable for a one-pot method with just one single purification and no work-up.

In conclusion and to the best of our knowledge, we have developed an efficient, rapid and diversity-orientated one-pot synthesis to access the 1-5-disubstituted-1*H*-1,2,4-triazole-3-carboxylic acid ethyl ester motif under mild conditions.

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Supplementary data

Supplementary data (Full experimental procedures and supporting LCMS and ^1H, ^{13}C NMR and HRMS characterisation data are available at noextra charge via the on-line version.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.130.

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