Pergamon

Tetrahedron Letters 42 (2001) 7353–7355

TETRAHEDRON LETTERS

Radical alkylation of *N*-alkyl 1,2,4-triazoles

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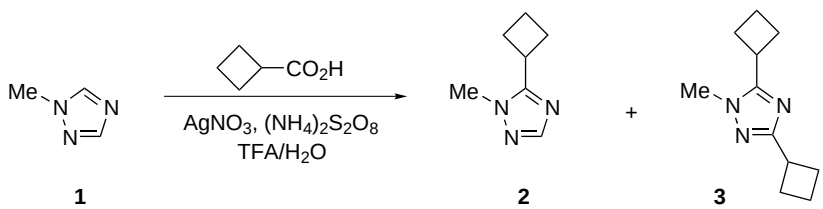
Received 1 June 2001; accepted 19 July 2001

Abstract—Reaction of 1-*N*-alkyl triazoles with an alkyl radical generated from the corresponding carboxylic acid, affords the triazole ring alkylated selectively in the 5 position. Secondary radicals perform best in the intermolecular reaction, while primary radicals alkylate the triazole in an intramolecular fashion.

We recently wished to prepare alkylated derivatives of 1-*N*-methyl triazole **1** as part of our research efforts (Scheme 1). *N*-Alkyl triazoles are typically alkylated by deprotonation of the triazole ring, followed by reaction with electrophiles such as ketones, amides or primary iodides.[1] A complementary approach to formation of the carbon–triazole bond would be the addition of alkyl radicals directly to the triazole ring. Carbon radicals generated from carboxylic acids via silver catalysis have been shown to alkylate many six-membered nitrogen-containing ring systems under aqueous acidic conditions,[2] however, there are fewer reports of the alkylation of five-membered nitrogen heterocycles using this method.[3] Herein we report the extension of this methodology to the alkylation of 1-*N*-alkyl 1,2,4-triazoles.

In order to assess the feasibility of this strategy, we subjected **1**[4] to conditions we had developed for the alkylation of 3,6-dichloropyridazine, which were modified from those originally reported by Samartoni.[5] Treatment of a trifluoroacetic acid (TFA)/water solution of methyltriazole, 1.1 equiv. cyclobutanecarboxylic acid and 10 mol% $AgNO_3$ at 70°C with an aqueous solution of 1.5 equiv. $(NH_4)_2S_2O_8$ resulted after workup in the isolation of a mixture of 5-cyclobutyl triazole **2**, unreacted starting material and a small amount of dicyclobutyl triazole **3** (Scheme 1). The HPLC assay yield of **2** was 33% and no triazole monoalkylated in the 3 position was isolated from the reaction. Increasing the amount of oxidant and carboxylic acid in the reaction did not significantly enhance the conversion of the methyl triazole substrate. However, by controlling the addition rate of the carboxylic acid by dissolving it as its sodium salt in the oxidant solution and slowly adding this mixture to the reaction, the yield of **2** was raised to 62% with 10–15% of **3** as the major by-product along with unreacted **1**.

The scope of the reaction was explored by examining other alkyl carboxylic acids under the conditions outlined above. The results are summarized in Table 1.[6] The desired products could be separated from dialkylated material by vacuum distillation of the crude reaction mixture. However, they were generally isolated as a mixture with dialkylated triazole (>90:10 ratio of monoalkylated to dialkylated by ^{1}H NMR) after removing unreacted starting material by elution through a plug of silica gel. Secondary carboxylic acids,



1 **2** **3**

Scheme 1.

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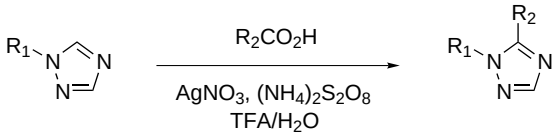
0040-4039/01/$ - see front matter
PII: S0040-4039(01)01518-0

Table 1.



1 R_1 = Me
4 R_1 = Et

5 R_1 = Me
6 R_1 = Et

Entry	Substrate	R_2	Product[d]	HPLC yield (%)	Isolated yield (%)
1	**1**	Octyl		<5	–
2	**1**	Cyclopropyl[c]	**5a**	62	60
3	**1**	Cyclobutyl	**2**	62	54[a]
4	**1**	Cyclopentyl	**5b**	36	35
5	**1**	Cyclohexyl	**5c**	53	54[b]
6	**1**	Isopropyl	**5d**	69	53[b]
7	**4**	Isopropyl	**6**	55	–
8	**1**	*tert*-Butyl		<5	–

[a] Purified by vacuum distillation.
[b] Isolated as a mixture of mono and dialkylated triazole after removal of starting material via elution of crude reaction mixture through a plug of SiO_2 with 1:1 EtOAc:hexanes.
[c] 3 equiv. of carboxylic acid were used in this reaction.
[d] For ^{1}H NMR data, see Ref. 7.

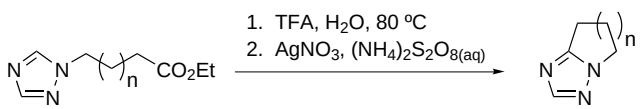
both cyclic and acyclic, performed best in the reaction (entries 2–7) with yields in the 50–60% range. Pivalic acid and octanoic acid (entries 1 and 8) were poor substrates for the alkylation and gave little or no desired products. Replacement of the methyl group on the nitrogen with an ethyl group afforded the corresponding *N*-ethyl derivative **6** (entry 7).

Once generated, alkyl radicals can either attack the electrophilic, protonated triazole in a productive fashion to afford **5**[2a] or react with other species in solution to afford alkane by-products.[8] This paradigm explains why highly electron-deficient heterocycles such as dichloropyridizine are alkylated in high yields using this procedure.[2b] The lower yields observed for the alkylation of *N*-alkyl triazoles **1** and **4** may be due to it being less electrophilic than the dichloropyridizine ring system. The poor performance of octanoic and pivalic acid in the reaction can also be explained using this rationale. Highly reactive primary radicals may react with other species in solution rather than the desired heterocycle, while a tertiary radical may not be nucleophilic enough to their react with protonated triazole.

In the case of primary radicals, covalently attaching the carboxylic acid precursor to the heterocycle should promote reactivity between the two species. To test this hypothesis, we synthesized triazoles **7a**–**c** with a primary ester moiety tethered to the triazole nitrogen through an alkyl chain. The esters groups of **7a**–**c** were hydrolyzed by heating in TFA/water at 70°C. Upon complete hydrolysis of the ethyl ester, the reaction was then charged with 20 mol% $AgNO_3$ followed by slow addition of an aqueous solution of ammonium persulfate (2 equiv.). Table 2 summarizes the results of these experiments. In the case of the butane tether **7b**, the 6–5 fused system **8b** was observed as the only product of the reaction after workup. When the chain was extended one methylene, the 7–5 system **8c** was isolated, albeit in lower yield. Shortening the chain by one methylene resulted in none of the 5–5 cyclized product **8a** being formed, most likely due to strain of the ring system. Thus, primary radicals can alkylate the triazole ring system when held in close proximity to the triazole ring.

We have demonstrated the alkylation of a triazole heterocycle with alkyl radicals generated from carboxylic acids. While triazoles are not as reactive under these conditions as other heterocyclic substrates reported in the literature, 1,5-dialkyl triazoles with secondary alkyl substituents in the 5 position can be isolated in synthetically useful yields using this method. While secondary radicals work best in the intermolecular sense, primary radicals alkylate triazoles in an intramolecular fashion to form bicyclic ring systems.

Table 2.



7 **8**

Substrate	*n*	Product[a]	Yield%
7a	1	**8a**	0
7b	2	**8b**	84
7c	3	**8c**	63

[a] For ^{1}H NMR data, see Ref. 9.

Acknowledgements

We thank Dr. Peter Dormer for aid in structure determination.

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6. General procedure: A flask equipped with an addition funnel and mechanical stirrer was charged with **1** (10.0 g, 0.12 mol), water (10 mL) and trifluoroacetic acid (27.8 mL, 0.36 mol). The solution was heated to 70°C. A homogeneous solution of $NH_4S_2O_8$ (68.66 g, 0.30 mol), water (69 mL), carboxylic acid (0.24 mol) and 5N NaOH (48 mL, 0.24 mol) was prepared and charged to the addition funnel. A solution of $AgNO_3$, prepared by dissolving $AgNO_3$ (2.0 g, 0.012 mol) in water (6 mL), was charged to the reaction flask. The drop-wise addition of the $NH_4S_2O_8$/carboxylic acid solution was initiated and within 5–10% of the addition the temperature began to rise rapidly and gas evolution was observed. The temperature was maintained between 80–90°C by controlling the rate of addition. Once the addition was complete, the reaction was aged for 1 h as it cooled to room temperature. The temperature was then lowered to 0°C and concentrated NH_4OH was slowly added, keeping the temperature below 20°C, until the pH was adjusted to approximately 12. The mixture was then transferred to a separatory funnel and extracted with ethyl acetate (2×400 mL). The organic layers were combined, washed with brine (200 mL), dried with $MgSO_4$ and filtered. The solution was then concentrated under reduced pressure to afford a yellow oil. Purification of the product was performed by either vacuum distillation of the crude concentrate or elution through a plug of silica gel with 1:1 ethyl acetate/hexanes.
7. Compound **5a**: ^{1}H NMR ($CDCl_3$) δ 7.61 (s, 1H), 3.82, (s, 3H), 1.78 (quint., $J=6.7$ Hz, 1H), 1.00 (d, $J=6.7$ Hz, 4H). Compound **2**: ^{1}H NMR ($CDCl_3$) δ 7.72 (s, 1H), 3.69 (s, 3H), 3.54 (m, 1H), 2.39 (m, 4H), 2.07 (m, 1H), 1.97 (m, 1H). Compound **5b**: ^{1}H NMR ($CDCl_3$) δ 7.70 (s, 1H), 3.78 (s, 3H), 3.09 (m, 1H), 2.00 (m, 2H), 1.82 (m, 4H), 1.64 (m, 2H). Compound **5c**: ^{1}H NMR ($CDCl_3$) δ 7.77 (s, 1H), 3.83 (s, 3H), 2.72 (m, 1H), 1.89 (m, 4H), 1.70 (m, 3H), 1.35 (m, 3H). Compound **5d**: ^{1}H NMR ($CDCl_3$) δ 7.69 (s, 1H), 3.76 (s, 3H), 3.02 (sept., $J=6.7$ Hz, 1H), 1.26 (d, $J=6.7$ Hz, 6H). Compound **6**: ^{1}H NMR ($CDCl_3$) δ 7.77 (s, 1H), 4.10 (q, $J=7.3$ Hz, 2H), 3.05 (sept., $J=6.8$ Hz 1H), 1.44 (t, $J=7.3$ Hz, 3H), 1.33 (d, $J=6.8$ Hz, 6H).
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9. Compound **8b**: ^{1}H NMR ($CDCl_3$) δ 7.76 (s, 1H), 4.09 (m, 2H), 2.85 (m, 2H), 2.02 (m, 2H), 1.93 (m, 2H). Compound **8c**: ^{1}H NMR ($CDCl_3$) δ 7.69 (s, 1H), 4.29 (m, 2H), 2.96 (m, 2H), 1.95 (m, 2H), 1.81 (m, 2H), 1.71 (m, 2H).