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PII: S0040-4039(18)30457-X
DOI: https://doi.org/10.1016/j.tetlet.2018.04.014
Reference: TETL 49877

To appear in: *Tetrahedron Letters*

Received Date: 27 February 2018
Revised Date: 27 March 2018
Accepted Date: 9 April 2018

Please cite this article as: Gordon, M.R., Lindell, S.D., Microwave promoted reaction of purin-6-yl magnesium halides with aldehydes in dichloromethane at 100 °C, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.04.014

Tetrahedron Letters
journal homepage: www.elsevier.com

Microwave promoted reaction of purin-6-yl magnesium halides with aldehydes in dichloromethane at 100 °C

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
purin-6-yl magnesium halide
microwave
dichloromethane
nucleobase
Grignard

ABSTRACT

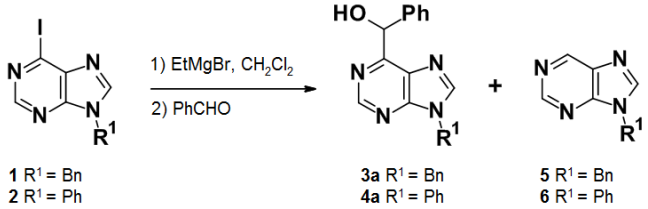
Treatment of a dichloromethane solution of 9-benzyl or 9-phenyl 6-iodopurine with ethereal ethylmagnesium bromide at ambient temperature gives the corresponding purin-6-yl magnesium halides. Addition of an aldehyde followed by heating at 100 °C in a microwave reactor yielded the corresponding carbinols in 52-81% yield.

Introduction

Purines play an essential role in many enzymatic reactions and in the biological regulation of all living organisms. They are integral constituents of DNA and RNA, and are involved in energy regulation as adenylates, signal transduction (GTP and cAMP), metabolism (NAD/NADH) and neurotransmission (purinergic receptors).[1] Purine derivatives containing *C*-substituents at the *C*-6 position show a variety of biological properties of interest within the agrochemical and pharmaceutical industries.[2] For example, certain 6-hydroxymethyl- and 6-aminomethyl-purine nucleosides show interesting levels of cytostatic and/or anti-hepatitis C viral activity.[3] These compounds were synthesised from 6-iodo-9-substituted purines *via* a Negishi cross-coupling reaction with an acyloxymethyzinc iodide.[3] Alternatively, 6-iodo purines can be transformed into 6-lithiated,[4] 6-zincated[5] or 6-magnesiated[6] purines which can then be reacted with various electrophiles to yield purines containing a *C*-6 carbon substituent. However, this approach is hampered by the tendency of these organometallic intermediates to undergo isomerisation to C-8 anions[4] or by low yielding reactions, for example with enolizable aldehydes.[6]

Results and Discussion

We recently reported a method for the generation of stable 6-magnesiopurines by metal halogen exchange of 6-iodopurines **1** or **2** with EtMgBr in CH_2Cl_2 at ambient temperature.[7] These anions reacted with various aromatic and aliphatic aldehydes to give corresponding 6-carbinols in 55-80% yield. However, even



Scheme 1. Metal halogen exchange of 6-iodopurines in CH_2Cl_2

this improved method required an excess of electrophile (3 equiv.), as do all other reported methods describing the reaction of purin-6-yl anions with aldehydes.[4,6] The yield of carbinol **3a** decreased from 79% to 50% and of **4a** from 75% to 47% when the amount of benzaldehyde was reduced from 3 to 1.1 equivalents. The other major products formed in *ca.* equimolar amounts to **3a** and **4a** were the unsubstituted purines **5** and **6** (Scheme 1). Repeating the reaction with the phenyl purine **2**, but quenching after 60 min with D_2O yielded the 6-deutero derivative of **6** in high yield (98%), indicating that the 6-magnesioanion had been formed in near quantitative yield. A second repeat conducted in CD_2Cl_2 followed by quenching with water after 16 h gave a good yield of compound **6** (70%) but showed no deuterium (or chlorine) incorporation, indicating that the anion was stable and that dichloromethane was not participating in the reaction. Finally the reaction was repeated again, this time with addition of benzaldehyde 15 min after anion formation, followed by quenching with D_2O after 16 h. Work-up and chromatographic purification yielded compound **4a** (41%) and

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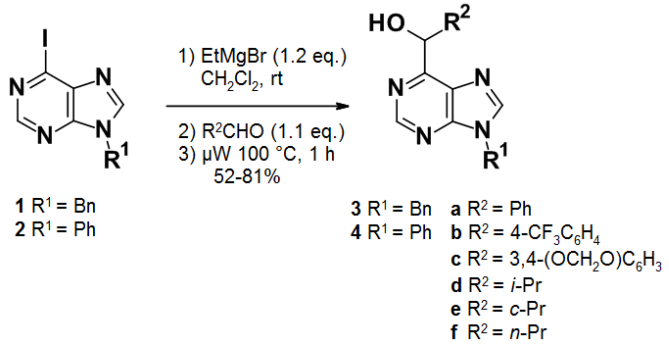
compound **6** showing *ca*. 30% deuterium incorporation at the 6-position (38%). This result was surprising and indicated that the purin-6-yl magnesium halide was present even after 16 h in the presence of benzaldehyde, apparently in a form able to react with D_2O but not with an aldehyde. In an attempt to disrupt postulated organometallic aggregates and thereby increase the reactivity of the 6-magnesio anion, a number of different additives were tested including TMEDA, Et_3N, LiCl, $MgBr_2$ and TMSCl. However, with the exception of TMSCl (3 equiv.) which increased the yield of **4a** from 47% to 64%, no significant effects were observed.



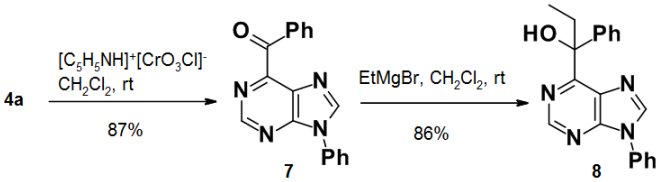
Scheme 2. Metal halogen exchange of 6-iodopurines in CH_2Cl_2 followed by anion quenching with aldehydes at 100 °C

Table 1. Reaction of purin-6-yl magnesium halides with aldehydes in CH_2Cl_2 at 100°C in a microwave reactor

Entry	Compd No	R^1	R^2	Isolated yield
1	**3a**	Bn	Ph	78%
2	**3b**	Bn	4-$CF_3C_6H_4$	81%
3	**3c**	Bn	3,4-$(OCH_2O)C_6H_3$	55%
4	**3d**	Bn	*i*-Pr	63%
5	**3e**	Bn	*c*-Pr	74%
6	**3f**	Bn	*n*-Pr	58%
7	**4a**	Ph	Ph	75%
8	**4b**	Ph	4-$CF_3C_6H_4$	75%
9	**4c**	Ph	3,4-$(OCH_2O)C_6H_3$	52%
10	**4d**	Ph	*i*-Pr	65%
11	**4e**	Ph	*c*-Pr	81%
12	**4f**	Ph	*n*-Pr	52%

Our next attempt to increase the reactivity of the purin-6-yl magnesium halides was by increasing the reaction temperature. The metal halogen exchange was performed on iodopurines **1** or **2** with EtMgBr in CH_2Cl_2 at ambient temperature as before, then after 15 min 1.2 equivalents of benzaldehyde were added and immediately thereafter heating was started. Due to the low boiling point of CH_2Cl_2 the reactions were conducted in a sealed vessel in a microwave reactor. Pleasingly these experiments showed a significant temperature effect and by increasing the temperature to 100 °C for 60 min immediately after addition of benzaldehyde, the yields of carbinols **3a** and **4a** could be increased to 77% and 75%, respectively. The reaction was general for a variety of aryl and alkyl aldehydes to give the corresponding carbinols in 52-81% yield as shown in Scheme 2 and Table 1. The best yields were obtained with the more electron deficient aromatic aldehydes (Entries 1, 2, 7 and 8) or with cyclopropyl carboxaldehyde (Entries 5 and 11) (74-81%). Lower but still very acceptable yields were obtained with electron rich aromatic aldehydes (Entries 3 and 9) or with enolizable aliphatic aldehydes (Entries 4, 6, 10 and 12) (52-65%). The stability of the purin-6-yl magnesium halides at 100°C in CH_2Cl_2 seems quite remarkable when compared to the extensive decomposition seen even at rt in THF, where only low yields of impure carbinols are obtained (<15%).[7]

Standard reaction conditions were as follows: A 3M solution of EtMgBr (1.2 mmol) in diethyl ether was added over 30 sec. to a 0.1M solution of the 6-iodopurine **1** or **2** (1 mmol) in dry CH_2Cl_2 at ambient temperature and under an inert gas atmosphere. The resulting mixture was stirred at r.t. for 15 min. and then neat aldehyde (1.1 mmol) was added to the mixture over 30 sec. The reaction mixture was then heated for 1 h at 100 °C in a Biotage Initiator microwave reactor.[8] Following work-up and purification by column chromatography the carbinols **3a-f** and **4a-f** were isolated in 52-81% yield (Table 1).[9]



Scheme 3. Synthesis of keto and tertiary carbinol derivatives

The product yields obtained in the current work are comparable to those obtained in our previous room temperature studies.[7] However, the current method has the advantage of a much shorter reaction time (1 h *vs*. 16 h) and the use of only a single equivalent of electrophile as opposed to the three equivalents previously required. Attempts to extend the present or previously reported[7] methodology to other electrophiles such as acid chlorides, acid anhydrides, nitriles or ketones failed or gave only low yields. However, the keto and tertiary alcohol products expected from these reactions can be readily synthesised starting from the carbinols **3** and **4**. For example, oxidation of **4a** with pyridinium chlorochromate yielded ketone **7** in 87% yield, which reacted with ethylmagnesium bromide to give the tertiary alcohol **8** in 86% yield (Scheme 3).[9]

Acknowledgments

We thank the European Commission for a Marie Curie Fellowship for M. Gordon (FP7-PEOPLE-2012-ITN, Project: ECHONET "Expanding Capability in Heterocyclic Organic Synthesis," No. 316379)

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9. **General experimental procedure for the microwave promoted reaction of purin-6-yl magnesium halides with aldehydes in dichloromethane**: Dry dichloromethane (10 mL) was added to the iodopurine **1** or **2** (1.0 mmol)[7] under an inert atmosphere of dry argon and the mixture was stirred at r.t. until the purine was completely dissolved. A solution of EtMgBr (3M in Et_2O, 0.4 mL, 1.2 mmol) was then added to the solution over a period of 30 sec. The resulting mixture was stirred at r.t. for 15 min., then neat aldehyde (1.1 mmol) was added to the mixture over 30 sec and the reaction mixture was heated to 100 °C in a sealed thick-walled microwave reaction vial using a Biotage Initiator microwave reactor.[8] The temperature was maintained at 100 °C for 60 minutes and then allowed to cool to r.t. before the reaction mixture was quenched by the addition of 1M aqueous NH_4Cl (5 mL) and then diluted with sat. aq. $NaHCO_3$ (15 mL). The organic phase was separated and the aqueous phase extracted with dichloromethane (3 x 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo* at 40 °C. The crude product was purified by column chromatography to afford pure carbinols **3a-f** and **4a-f** (see Table 1 for yields).
The ^1H and ^{13}C NMR spectra for compounds **3a-d** were identical to those reported previously by Tobrman and Dvořák[6] and for compounds **3e-f** and **4a-f** to those reported by Gordon *et al*.[7]
Phenyl(9-phenyl-9*H*-purin-6-yl)methanone (7): Phenyl(9-phenyl-9*H*-purin-6-yl)methanol (**4a**) (363 mg, 1.2 mmol), pyridinium chlorochromate (517 mg, 2.4 mmol) and Celite (5g) were stirred in CH_2Cl_2 (10 mL) at rt until TLC showed full conversion. The mixture was filtered through Celite and chromatographed to give pure phenyl(9-phenyl-9*H*-purin-6-yl)methanone (**7**) (314 mg, 1.1 mmol, 87%): ^1H and ^{13}C NMR spectra were identical to those reported previously by Miyashita and co-workers.[10]
1-Phenyl-1-(9-phenyl-9*H*-purin-6-yl)propan-1-ol (8): A solution of EtMgBr (3M in Et_2O, 0.4 mL, 1.2 mmol) was added over 30 sec to a stirred solution of phenyl(9-phenyl-9*H*-purin-6-yl)methanone (**7**) (300 mg, 1.0 mmol) in dry CH_2Cl_2 (10 mL) at rt under an atmosphere of dry argon. After 4 h, a sat. aq. solution of $NaHCO_3$ (15 mL) was added. The organic phase was separated and the aqueous phase extracted with dichloromethane (3 x 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography yielded pure 1-phenyl-1-(9-phenyl-9*H*-purin-6-yl)propan-1-ol (**8**) as a colourless solid (285mg, 0.86mmol, 86%). ^1H NMR (600 MHz, $CDCl_3$): δ 0.94 (t, *J* = 6 Hz, 3H), 2.68 (m, 1H), 2.91 (m, 1H), 6.22 (bs, 1H), 7.19 (t, *J* = 6 Hz, 1H), 7.32 (t, *J* = 6 Hz, 2H), 7.48 (t, *J* = 6 Hz, 1H), 7.58 (t, *J* = 6 Hz, 2H), 7.66 (d, *J* = 6 Hz, 4H), 7.86 (d, *J* = 6 Hz, 2H), 8.32 (s, 1H), 8.98 (s, 1H) ppm. ^{13}C NMR (150 MHz, CDCl3): δ 8.2, 33.1, 78.9, 123.7, 126.0, 127.0, 128.1, 128.7, 130.0, 130.7, 134.1, 142.8, 145.5, 151.7, 151.9, 163.9 ppm. (IR, solid): υ_m 3434, 3056, 2970, 1583, 1508, 1333, 1266, 1230, 910 cm-1. HRMS (ESI/QTOF) m/z: [MH]+ Calcd for $C_{20}H_{19}N_4O$ 331.1559; Found 331.1559.
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Graphical Abstract

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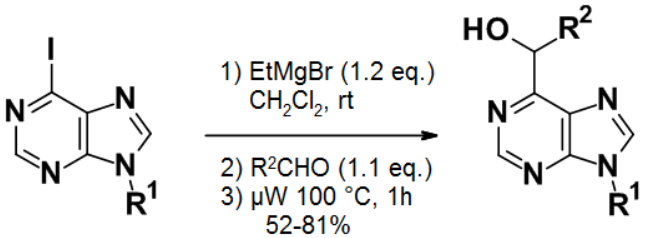

R^1 = Bn, Ph

R^2 = Alkyl, Aryl

Highlights

Generation of purin-6-yl magnesium halides in dichloromethane
Microwave assisted reaction with aldehydes at 100 °C
Preparation of purin-6-yl carbinol and keto derivatives