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Communications to the Editor

Process Development and Pilot-Scale Synthesis of New Cyclization Conditions of Substituted Phenylacetamides to Tetrahydroisoquinoline-2-ones Using Eaton's Reagent

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Abstract:

Tetrahydroisoquinoline is a ubiquitous structural framework presented in numerous pharmacologically relevant molecules. Although accessible by the Pictet−Spengler cyclization, conditions commonly used for such cyclizations are often difficult to implement on scale. Herein, we report the development of a scaleable approach utilizing Eaton's reagent for the cyclization of substituted phenylacetamide analogues to tetrahydroisoquinoline-2-one. The development, optimization, and safety hazard evaluations, which outline the benefits and ease of workup of this new process, are discussed.

Introduction

Several tetrahydroisoquinoline compounds exemplified in Figure 1[1] have been identified with novel therapeutic benefits and commercialized. These compounds can be readily synthesized by cyclization of the linear amine, with formaldehyde or formaldehyde equivalents, to generate the tetrahydroisoquinoline ring structure. During the course of a process development investigation, several kilogram quantities of one of the key intermediates of the tetrahydroisoquinoline-2-one family (**6a**, Scheme 1) was needed, with the goal of preparing 15−20 kilograms for an eventual GMP campaign. The target compound **6a** was envisioned to be attained via the Pictet−Spengler cyclization,[2] providing a core structural framework with the presence of the carbonyl functionality to lead to other derivatizations. The original synthesis by the medicinal chemistry group utilized polyphosphoric acid (PPA) for the cylization of the phenylacetamide intermediate **5a**. The high-temperature requirement of this reaction coupled with the high viscosity associated with the PPA at 160 °C rendered this condition unattractive on scale. Various conditions to avoid the use of PPA were investigated in hopes of identifying a scaleable process. After numerous investigations, we observed that Eaton's reagent[3]-mediated cyclization provided effective conditions for this transformation. We now report the development, optimization, and safety hazards assessment of this novel reaction condition toward tetrahydroisoquinoline-2-one's.

Results and Discussion

The first step of the synthesis outlined in Scheme 1 came from the original synthesis and was readily scaleable with minor modifications. Acyl chloride formation was previously conducted in 5 equiv of neat thionyl chloride with concentration to dryness and dissolution of the crude product in dichloromethane (DCM)/tetrahydrofuran (THF) with subsequent reaction with aqueous methylamine. Following complete consumption of the acid chloride intermediate, the reaction was quenched with water and extracted with DCM. After the standard drying over sodium sulfate, concentration to dryness afforded the key amide in >95% HPLC purity. In order to streamline the process and to minimize the use of large quantities of thionyl chloride, compound **4a** was suspended in two volumes of toluene and 10 mol % of *N*,*N*-dimethylformamide (DMF) and treated under dose-controlled condition with 1.2 equiv of thionyl chloride. The reaction was then warmed to 40 °C to ensure complete reaction. Complete consumption of **4a** was observed within 30 min, and the resulting solution was cooled to ambient temperature and transferred to an aqueous solution of methylamine at 0 °C. After stirring for several hours, the desired amide **5a** was isolated by filtration, in 88−94% yields and excellent HPLC purity (96.4 to >99%).

Safety assessment of the streamlined process was evaluated via RC1 calorimetry. As expected, the heat output of the amide formation (Figure 2) stayed constant during the addition of the acyl chloride, characteristic of a fast reaction with no potential for latent reaction. Upon completion of the addition, the exotherm subsided, indicating the reaction end point, which was also confirmed by proper analytical testing. The thermal profile indicated that the reaction could be safely performed under proper dose control, and multiple batches were successfully conducted on 3−5 kg scale in our kilo laboratories.

With the preparation of compound **5a** streamlined, our focus shifted to the cyclization reaction. Initially, this reaction was conducted in polyphosphoric acid at 160 °C with paraformaldehyde. Upon completion, the reaction was quenched with water, extracted with ethyl acetate, dried over magnesium sulfate, and concentrated to dryness to afford an oil. Investiga-

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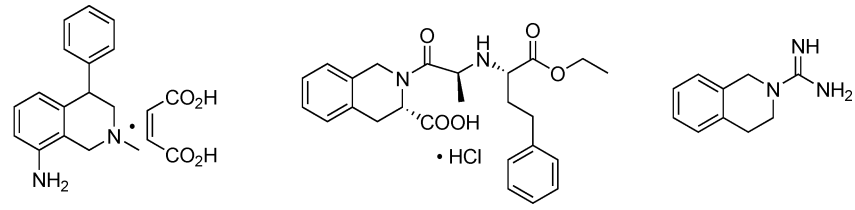
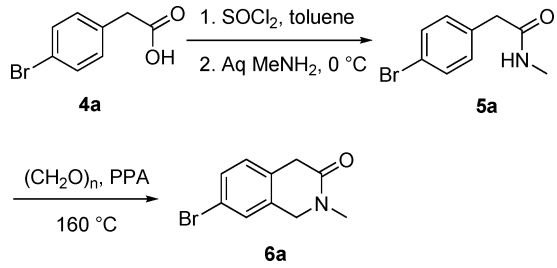


Merital-Nomifensine (1) **Quinapril Hydrochloride (2)** **Debrisoquin (3)**

Figure 1. **Examples of commercial APIs with tetrahydroisoquinoline cores.**

Scheme 1. **Original Cyclization Using PPA**



tion of various alternative conditions was pursued to allow multikilogram preparations. Neither the use of paraformaldehyde (with either phosphoric acid, PPA, or sulfuric acid in acetic acid) or the use of *p*-toluenesulfonic acid in refluxing toluene in the presence of *s*-trioxane was successful. However, when **5a** was treated with paraformaldehyde and Eaton's reagent (P_2O_5 in methanesulfonic acid, a reagent with properties similar to those of PPA,[4]) at 60−80 °C, the desired product was isolated in 92% yield and >94% HPLC purity after neutralization. The handling of neat PPA at high temperatures is a safety hazard that becomes further accentuated since the resultant mixtures are quite viscous. The safety concerns are minimized with the use of Eaton's reagent since the resultant mixtures are more mobile solutions with temperature requirements much lower than that of PPA. To our surprise, we found no precedence in the literature for the use of Eaton's reagent-mediated cyclization of phenylacetamide derivatives with formaldehyde, although the use of Eaton's reagent as a dehydrating agent in various reactions is well documented.[5−13] The novel use of this reagent in the cyclization of phenylacetamides was broadened to understand the scope and limitation of the process.

Table 1 lists the scope of the reaction with various functional groups. In all cases, the desired cyclized products were isolated

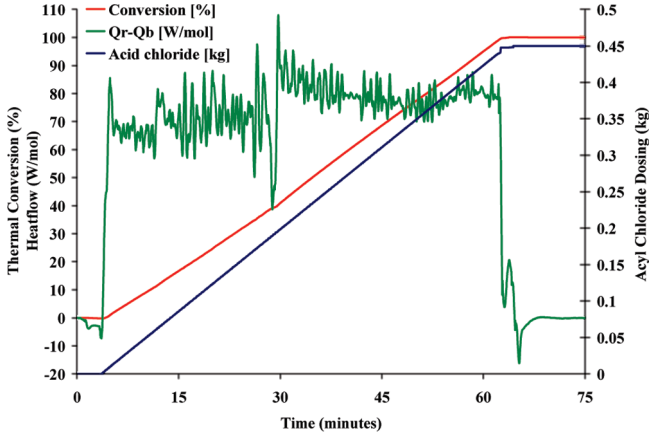


Figure 2. **RC1 calorimetry of acylation showing proportional heat output to dose-controlled addition of acyl chloride.**

in excellent yield by neutralization of the reaction to pH 8.0 with sodium hydroxide, followed by extraction of the product with isopropyl acetate (IPAc) and isolation by concentration. We anticipate this will be a useful addition to synthetic methodology, particularly for applications at large scale.

Safety assessment of the cyclization was evaluated by RC1 calorimetry and demonstrated that the reaction could safely be operated on scale. Figure 3 shows the representative heat output of the reaction. A mild thermal event took place upon addition of the phenylacetamide ($\Delta H = -35$ kJ/mol, $\Delta T_{ad} = 14$ K) which rapidly subsided. Addition of paraformaldehyde was marked by an initial endothermic event devoid of any significant thermal activity until the system was heated. The thermal profile observed during heating resulted in a net output of −120 kJ/mol ($\Delta T_{ad} = 43$ K). Upon completion of the heat cycle, a decaying heat flow was observed which ended within an hour, indicating that no rapid temperature spike or uncontrollable heat accumulation occurred. Typically, the reaction was stirred for an additional half hour before proceeding to the workup. The rapid conversion was also substantiated by analysis of the mixture by HPLC which confirmed the reaction kinetics. Multiple batches were successfully executed in our kilo laboratories on 2−3 kg scale and afforded the desired product in >90% yield and >92% HPLC purity.[14] A mild exotherm of 12 °C was observed on 2.3 kg scale during the addition of phenylacetamide, which quickly subsided upon the completion of the addition. Thermal events associated with the addition of paraformaldehyde and the subsequent heating of the reaction were mild, and at no point did the system become self-heating.

Conclusions

A new Eaton's reagent-mediated condition for the cyclization of phenylacetamide derivatives with formaldehyde to generate

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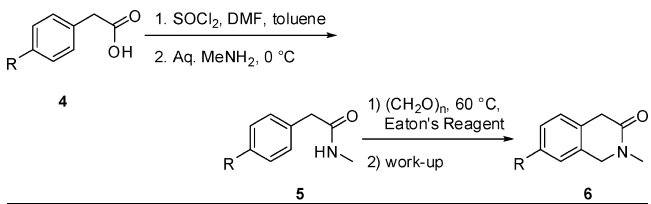
(14) This purity was sufficient for the downstream chemistry; thus, further upgrade of product purity was not attempted.

Table 1. **Scope of cyclization using Eaton's reagent**



4 5 6

Entry	Starting Material	Isolated Yield (%)	Crude Purity (% AUC)	Product
1	**5a**	95	93.1	**6a**
2	**5b**	98	95.2	**6b**
3	**5c**	89	86.2	**6c**
4	**5d**	96	85.0	**6d**
5	**5e**	98	>99	**6e**

tetrahydroisoquinoline-2-one's has been identified. The reaction was conducted at 60−80 °C, a much lower temperature than for the original PPA-mediated reaction which required a temperature around 160 °C. The commercial availability and the ease of handling Eaton's reagent has made it ideal for this cyclization. The ease of workup of the reaction mixture allowed the large-scale production of this key intermediate. Further detail on the scope of this cyclization and functional group tolerability is also provided.

Experimental Section

General Methods. Reaction progress and chemical purity were evaluated by HPLC analysis using a Waters Sunfire C18 column (150 mm × 4.6 mm) with mobile phases A (water + 0.05% TFA) and B (acetonitrile + 0.05% TFA) and detection at 220 nm; flow: 1.0 mL/min; temp. 25 °C; and gradient: 0 min: A = 95%, B = 5%; 10 min: A = 5%, B = 95%; 20 min: A = 5%, B = 95%; and 22 min: A = 95%, B = 5%.

Large-Scale Preparation of Eaton's Reagent. Commercial Eaton's reagent available from Aldrich (7.7 wt % of P_2O_5 in MsOH) was used initially for the investigation. On scale up, Eaton's reagent was prepared in-house at a concentration of 7.5 wt % using the following procedure. Eaton's reagent was routinely prepared by adding P_2O_5 (1.2 kg) to methanesulfonic acid (10 L) at <25 °C. A slight exotherm occurred which was easily controlled by the rate of P_2O_5 addition. Once the addition was complete, the solution was stirred at ambient temperature for 18 h and then stored in airtight containers.

General Procedure for the Preparation of Analogues of 5. Phenylacetic acid (55 mmol) in toluene (25 mL) was treated with thionyl chloride (66 mmol, 1.2 equiv) and anhydrous *N,N'*-dimethylformamide (63 mmol, 1.14 equiv) under nitrogen. A slight exotherm was noted, and the clear solution was heated at 40 °C for 30 min. TLC analysis (10% methanol/dichloromethane, reaction mixture quenched into methanol or methylamine solution) was used to monitor the reaction. The resulting acid chloride solution was added into a cooled (0−5 °C) methylamine solution (275 mmol, 5.0 equiv) through an addition funnel over approximately 30 min, while maintaining the internal temperature at ≤20 °C. Cooling was removed, and the reaction was stirred for 30 min, at which point HPLC analysis showed the reaction was complete. The suspension was diluted with water (50 mL) and extracted with EtOAc (50 mL). The organic layer was washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL) and concentrated to give the desired product as a white solid.

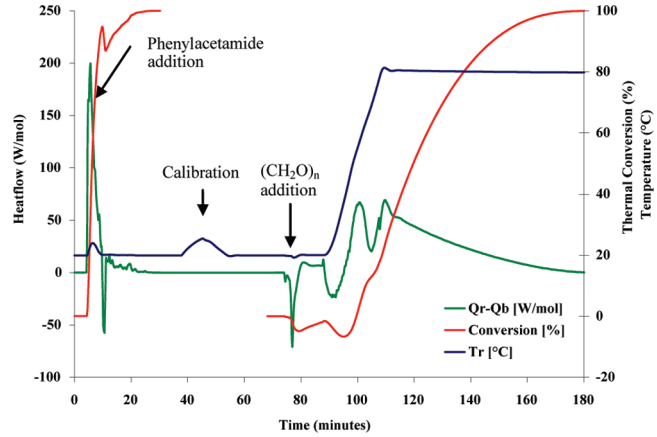


Figure 3. **RC1 calorimetry of cyclization reaction using Eaton's reagent.**

***N*-Methyl 4-bromophenylacetamide (5a):**[15] white solid; yield: 91%; HPLC >99%. Spectral data were consistent with those reported in the literature.

***N*-Methyl 4-chlorophenylacetamide (5b):**[16] white solid; yield: 77%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, 2 H, J = 8.4 Hz), 7.20 (d, 2 H, J = 8.4 Hz), 5.45 (bs, 1 H), 3.53 (s, 2 H), 2.76 (d, 3 H, J = 4.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 133.8, 133.7, 131.2, 129.5, 43.3, 26.9; MS *m/z* 184.1 $[M + H]^+$; HPLC >99%.

***N*-Methyl 4-fluorophenylacetamide (5c):**[17] white solid; yield: 62%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (m, 2 H), 7.06 (m, 2 H), 5.35 (bs, 1 H), 3.55 (s, 2 H), 2.78 (d, 3 H, J = 4.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 164.1, 160.8, 131.4, 131.3, 131.1, 131.0, 116.4, 116.1, 43.1, 26.9; MS *m/z* 168.1 $[M + H]^+$; HPLC 97.9%.

***N*-Methyl phenylacetamide (5d):**[18] white solid; yield: 56%; HPLC 97.4%. Spectral data were consistent with those reported in the literature.

***N*-Methyl 4-nitrophenylacetamide (5e):**[19] white solid; yield: 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, 2 H, J = 8.6 Hz), 7.48 (d, 2 H, J = 8.6 Hz), 5.60 (bs, 1 H), 3.66 (s, 2 H), 2.81 (d, 3 H, J = 4.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ

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170.1, 147.6, 142.8, 130.6, 124.3, 43.6, 27.0; MS *m/z* 184.1 $[M + H]^+$; HPLC >99%.

Large-Scale Preparation of 5a. To a stirred suspension of 4-bromophenylacetic acid (**4a**) (3.31 kg, 15.39 mol) in toluene (6.6 L) was added DMF (0.11 kg, 1.54 mol). The suspension was heated to 38 °C, at which point $SOCl_2$ (2.2 kg, 18.47 mol) was added over 1.5 h while maintaining the temperature at 35−40 °C. The reaction was stirred at 40 °C for 30 min, at which point HPLC analysis indicated that the reaction was complete.[20] The reaction was cooled to ambient temperature and added to a solution of methylamine (40 wt %, 5.98 kg, 76.96 mol) in water (6.6 kg) over 3 h at 0−25 °C. The reaction was stirred at ambient temperature for 16 h, and the resulting suspension was filtered. The filter cake was rinsed with water (2 × 6.0 L) and dried under vacuum at 40 °C for 64 h to afford 3.31 kg of the desired product as a white solid [94% yield, >99% purity (t_R = 8.1 min)].

General Procedure for the Preparation of 6 Analogues. *N*-Methyl phenylacetamide (10 mmol) in Eaton's reagent (10 mL) was treated with paraformaldehyde (12 mmol, 1.2 equiv) and heated at 80 °C for 1 h. The solution was allowed to cool to room temperature, diluted with water (10 mL), and basified with 50% NaOH solution (8 mL) to pH = 8. The resulting solution was extracted with EtOAc (2 × 20 mL), and the organic layer was dried over Na_2SO_4, filtered, and concentrated to give the desired product as a yellow solid.

7-Bromo-2-methyl-1,4-dihydro-2 H-isoquinolin-3-one (6a):[21] yellow solid; yield: 95%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (dd, 1 H, J_1 = 1.7 Hz, J_2 = 8.1 Hz), 7.33 (s, 1 H), 7.05 (d, 1 H, J = 8.2 Hz), 4.46 (s, 2 H), 3.55 (s, 2 H), 3.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 133.4, 131.7, 131.0, 129.4, 128.5, 120.6, 52.7, 36.8, 34.8; MS *m/z* 241.9 $[M + H]^+$; HPLC 93.1%.

7-Chloro-2-methyl-1,4-dihydro-2 H-isoquinolin-3-one (6b):[21] yellow solid; yield: 98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, 1 H, J = 8.1 Hz), 7.15 (s, 1 H), 7.07 (d, 1 H, J = 8.1 Hz), 4.47 (s, 2 H), 3.56 (s, 2 H), 3.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 133.0, 132.6, 131.1, 129.1, 128.1, 125.6, 52.8, 36.7, 34.7; MS *m/z* 196.0 $[M + H]^+$; HPLC 95.2%.

7-Fluoro-2-methyl-1,4-dihydro-2 H-isoquinolin-3-one (6c): yellow solid; yield: 89%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (dd, 1 H, J_1 = 5.4 Hz, J_2 = 8.5 Hz), 6.98 (dt, 1 H, J_1 = 2.7 Hz, J_2 = 8.7 Hz), 6.87 (dd, 1 H, J_1 = 2.4 Hz, J_2 = 8.8 Hz), 4.48 (s, 2 H), 3.58 (s, 2 H), 3.12 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 163.4, 160.2, 132.8, 132.7, 129.5, 129.3, 127.9, 127.8, 115.2, 115.2, 112.4, 112.1, 53.0, 36.2, 34.7; MS *m/z* 180.1 $[M + H]^+$; HPLC 86.2%.

2-Methyl-1,4-dihydro-2 H-isoquinolin-3-one (6d):[22] yellow solid; yield: 96%; HPLC 85.0%. Spectral data were consistent with those reported in the literature.

7-Nitro-2-methyl-1,4-dihydro-2 H-isoquinolin-3-one (6e): yellow solid; yield: 98%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, 1 H, J = 8.5 Hz), 8.07 (s, 1 H), 7.35 (d, 1 H, J = 8.5 Hz), 4.58 (s, 2 H), 3.75 (s, 2 H), 3.15 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 147.2, 140.2, 132.9, 128.8, 123.2, 120.9, 52.8, 37.5, 34.9; MS *m/z* 207.0 $[M + H]^+$; HPLC >99%.

Large-Scale Preparation of 6a. To a stirred solution of Eaton's reagent (11.5 L) was added *N*-methyl-4-bromophenylacetamide (**5a**) (2.30 kg, 10.08 mol) portionwise, causing a mild exotherm from 19 to 31 °C. Paraformaldehyde (0.36 kg, 12.1 mol) was added, and the resulting reaction mixture was heated to 80 °C over 30 min and stirred at 80 °C for 75 min, at which point HPLC analysis indicated that the reaction was complete. The reaction was cooled to 60 °C and quenched into water (11.5 L) over 2 h at <50 °C. IPAc (9.2 L) was added, followed by 50 wt % NaOH to adjust the pH to 8.0−8.5. The layers were heated to 30−40 °C and separated, and the aqueous layer was extracted with IPAc (9.2 L). The combined organic layers were washed with brine (9.2 L), concentrated to a thick suspension, and filtered. The solid was dried at 25 °C under vacuum to afford 2.54 kg of the desired product as a yellow solid [100% yield, 94.1% purity (t_R = 8.7 min)].

Acknowledgment

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Note Added after ASAP: This paper was published on the Web on November 17, 2009, with errors in the description of Eaton's reagent and in the title of Scheme 1. The corrected version was reposted on December 31, 2009.

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