Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 08 Sep 2009.

To cite this article: Helio Gauze Bonacorso, Tatiana Soldati de Moraes, Nilo Zanatta & Marcos Antonio Pinto Martins (2009) Synthesis of New Fluorine-Containing 1,2,3,4-Tetrahydroacridines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:20, 3677-3686, DOI: 10.1080/00397910902803692

To link to this article: http://dx.doi.org/10.1080/00397910902803692

Synthetic Communications®, 39: 3677–3686, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910902803692

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Abstract: A convenient method for the synthesis of a novel series of four 5-trilfluoromethyl-1,2,3,4-tetrahydroacridines, by intramolecular cyclization reactions of 2-trifluoroacetyl-1-(arylamino)-cyclohexene using polyphosphoric acid (PPA), is described. The six new enaminoketone intermediates were obtained by an oxygen–nitrogen exchange reaction from 2-trifluoroacetyl-1-methoxycyclohexene with six 4-substituted anilines.

Keywords: Acridines, cyclohexene, PPA, tetrahydroacridines

INTRODUCTION

It is well documented that acridines have a wide range of biological applications, including antitumor properties,[1] but carcinogenic activity has also been documented. Because of its planar structure, the acridine chromophore moiety sometimes has excellent DNA binding properties. Moreover, a new acridine (tetrahydroacridine) skeleton fused with a six-membered ring yields polycyclic derivatives, which also play an important role against Alzheimer's disease, as for example, the first AChE inhibitor, tetrahydroaminoacridine (Cognex).[2,3] In particular, the chemistry and biological activities of numerous compounds related

Received October 8, 2008.
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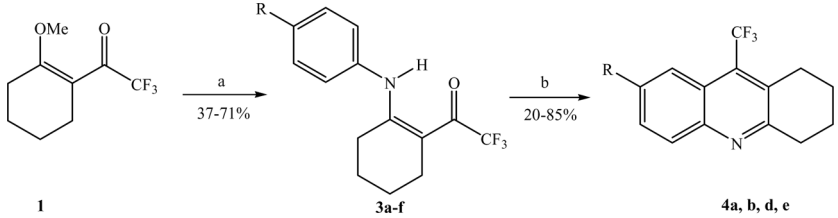
to the benzo[*a*]- and benzo[*b*]acridine families have been widely investigated for the past 50 years, and carcinogenic activities have been detected.[4,5] Acridines have been prepared from improvements of the classical methods developed by Skraup, Conrad–Limpach, Döbner–von Miller, and Friedländer.[6] On the other hand, it has been observed that the introduction of a trifluoromethyl and its higher homologue C_nF_{2n+1} groups into a heterocycle may result in greater activity than that of the parent compound, which is probably a result of the high lipophylicity of perfluoroalkyl substituents.[7,8] Moreover, the inclusion of fluorine atoms in a drug molecule can influence both the disposition of the drug and the interaction of the drug with its pharmacological target.

There are few studies available on the synthesis of trifluoromethylated acridines and derivatives. In one study, De and Gibbs developed a very simple and efficient but very expensive new method to obtain polycyclic acridines by a Friedländer condensation involving 2-aminoarylketones with cyclic ketones in the presence of itrium triflate.[9] Other methods have included the use of microwave (Muscia et al.)[10] and ruthenium catalysis (Cho et al.).[11] Recently, Banwell et al.[12] reported the synthesis of some acridines by an Ullmann coupling mediated by palladium catalysis.

Herein, the present study shows a general method to regiospecifically synthesize β-enaminoketones (**3**) and 5-trifluoromethyl-1,2,3,4-tetrahydroacridines (**4**) from the reaction of a cyclic β-methoxyvinyl trifluoromethyl ketone (**1**) with six substituted anilines (**2**) without use of heavy metals as catalysts (Scheme 1).

Although there are many methods for the synthesis of acridines (**4**) in the literature, none have used the strategy adopted in this study. Our



2-4	a	b	c	d	e	f
R	Me	OMe	NO_2	Cl	Br	I

(a) 4 - $NH_2C_6H_4R$ (**2a-f**), MeCN, reflux, 24 h.
(b) PPA, 90 - 120 °C, 24 h.

Scheme 1. Route for the synthesis of 1,2,3,4-tetrahydroacridines.

strategy has the following advantages: (i) it is easier to introduce the substituent at position 7 of the acridine ring, and (ii) the reactivity of the β-carbon in **1** and the carbonyl carbon in **3** allows the regiospecific introduction of a wide scope of anilines bearing both electron-donating and electron-withdrawing substituents.

RESULTS AND DISCUSSION

The β-methoxyvinyl trifluoromethyl ketone (**1**) derived from the trifluoroacetylation reaction of cyclohexanonedimethyl acetal was prepared previously.[13–16]

First, a novel series of six 2-trifluoroacetyl-1-(arylamino)-cyclohexenes (**3a**–**f**) was isolated in 37–71% yields by the *O,N*-exchange reaction of 2-trifluoroacetyl-1-methoxycyclohexene with 4-substituted anilines (**2**). The reactions were carried out in acetonitrile under reflux for 24 h, by a methodology similar to that described by Bonacorso et al.[17,18] The best results were obtained when a solution of **2** in anhydrous acetonitrile was added dropwise to **1**, also diluted in the same solvent.

Second, the intramolecular cyclization reactions of 2-trifluoroacetyl-1-(arylamino)-cyclohexene (**3a**–**f**) were carried out in polyphosphoric acid (PPA) in the absence of solvent according to the method described by Bonacorso et al.[17,18] At first, PPA ($P_2O_5 + H_3PO_4$) was prepared at 90°C, and compounds **3a**–**f** were added in small portions to the acid mixture. The cyclization of **3a**–**f** proceeded at only 90–110°C for 24 h to afford the corresponding new series of four 5-trifluoromethyl-1,2,3,4-tetrahydroacridines (**4a**, **4b**, **4d**–**e**) in 20–85% yields. To search for better reaction conditions and results, we tested some Lewis acids and reactions under microwave conditions. Unfortunately, $POCl_3$,[19] P_2O_5/$POCl_3$,[20] and trifluoroacetic acid,[21] as well as microwave conditions, produced no positive results for the synthesis of all acridines, especially for nitro- (**4c**) and iodo- (**4f**) derivatives, which could be not isolated.

An explanation for the wide differences in yields or no isolated products in the presented cyclizations can be found in a comprehensive study of the Combes quinoline synthesis. Roberts and Turner[22] studied the Combes synthesis and observed that anilines substituted in the *meta* position by electron-donating groups readily cyclized, generally leading exclusively to 7-substituted quinolines, whereas *ortho* or *para* electron-donating-group substitutents inhibited or prevented cyclization. Similar results have been observed by Linderman and Kirollos,[23] where the reaction conditions required to obtain a series of trifluoromethyl-substituted quinolines from the respective enamine precursors reflected the activation of the aniline ring.

The unambiguous ^{1}H and ^{13}C NMR chemical shift assignments of compounds **1**, **3a**–**f**, and **4a**, **4b**, **4d**, and **4e** were carried out with the help of HETCORR and COLOQ two-dimensional-NMR experiments and by comparison with NMR data of similar compounds previously reported.[17,18]

CONCLUSION

In conclusion, we have developed a convenient and greener procedure (without heavy metals) to obtain new 5-trifluoromethyl-1,2,3,4-tetrahydroacridines as heteropolycycles derived from cyclohexanone and 4-substituted anilines involving the isolation of 2-trifluoroacetyl-arylamino-cyclohexene intermediates. Furthermore, we have been able to synthesize and use for the first time 1-methoxy-2-trifluoroacetyl-cyclohexenes in the synthesis of acridines. We hope that the new trifluoromethyl-substituted acridines described here contribute to a combinatorial library of acridine derivatives with the aim of determining a more potent drug and its action pathway as an anticancer agent.

EXPERIMENTAL

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. The melting points were determined on a Reichert Thermovar apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were acquired on Bruker DPX 200 (^{1}H at 200.13 MHz) and Bruker DPX 400 (^{1}H at 400.13 MHz and ^{13}C at 100.61 MHz) spectrometers, 5-mm sample tubes, at 298 K, with a digital resolution of ± 0.01 ppm, in $CDCl_3$, and using tetramethylsilane (TMS) as internal reference. Mass spectra were registred in a HP 6890 gas chromatograph (GC) connected to a HP 5973 MSD and interfaced by a Pentium PC. The GC was equipped with a split–splitless injector, autosampler, cross-linked HP-5 capillary column (30 m, 0.32 mm internal diameter), and helium was used as the carrier gas. The CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (São Paulo University, USP, Brazil).

1-(Arylamino)-2-trifluoroacetyl-cyclohexenes (3a–f): General Procedure

A solution of aniline **2a**–**f** (5 mmol) in anhydrous acetonitrile (5 ml) was added dropwise to a magnetically stirred solution of **1** (1.04 g, 5 mmol)

in anhydrous acetonitrile (12 ml) at room temperature. The mixture was stirred under reflux for 24 h. The solvent was evaporated under reduced pressure, and the solid products **3a**–**f** were recrystallized from ethanol (yields 37–71%).

Data

2-Trifluoroacetyl-1-(4-methylphenylamino)-cyclohexene (**3a**)

Yellow solid, yield 37%, mp 87–89°C. ^{1}H NMR ($CDCl_3$): $\delta = 13.2$ (bs, 1H, NH); 7.18 (d, 2H, $J = 7.9$, Ar); 7.01 (d, 2H, $J = 8.2$, Ar); 2.56–2.36 (m, 7H, CH_2 e Me) 1.67–1.62 (m, 4H, CH_2).^{13}C NMR ($CDCl_3$): $\delta = 175.5$ (q, $^2J_{C\text{-}F} = 31.4$, C=O); 167.8 (C1); 136.8; 134.5; 129.7; 125.6 (6C, Ar); 118.2 (q, $^1J_{C\text{-}F} = 289.5$, CF_3); 98.2 (C2); 28.4 (CH_2); 22.3 (CH_2); 22.1(q, $^4J_{C\text{-}F} = 3.3$, C3); 21.0 (CH_2); 20.8 (Me). CG-MS (EI, 70 eV): m/z (%) = 283 (M^+, 43); 214 (100); 199 (3); 186 (17); 172 (5); 91 (21); 69 (6). Anal. calcd. for $C_{15}H_{16}F_3NO$ (283.12): C, 63.60; H, 5.69; N, 4.94%. Found: C, 63.42; H, 5.52; N, 4.81%.

2-Trifluoroacetyl-1-(4-methoxyphenylamino)-cyclohexene (**3b**)

Brown solid, yield 51%, mp 83–85°C. ^{1}H NMR ($CDCl_3$): $\delta = 13.14$ (bs, 1H, NH); 7.07 (d, 2H, $J = 8.7$, Ar); 6.90 (d, 2H, $J = 9.0$, Ar); 3.82 (s, 3H, OMe); 2.56–2.35 (m, 4H, CH_2); 1.66–1.63 (m, 4H, CH_2). ^{13}C NMR ($CDCl_3$): $\delta = 175.5$ (q, $^2J_{C\text{-}F} = 31.4$, C=O); 168.3 (C1); 158.4; 130.0; 127.2; 114.3 (6C, Ar); 118.3 (q, $^1J_{C\text{-}F} = 289.5$, CF_3); 98.1 (C2); 55.3 (OMe); 28.5 (CH_2); 22.4 (CH_2); 22.1 (q, $^4J_{C\text{-}F} = 2.5$, C3); 21.1 (CH_2). CG-MS (EI, 70 eV): m/z (%) = 299 (M^+, 99); 230 (100); 202 (32); 107 (13); 77 (19); 69 (7). Anal. calcd. for $C_{15}H_{16}F_3NO_2$ (299.11): C, 60.20; H, 5.39; N, 4.68%. Found: C, 60.19; H, 5.33; N, 4.72%.

2-Trifluoroacetyl-1-(4-nitrophenylamino)-cyclohexene (**3c**)

Yellow solid, yield 40%, mp 115–117°C. ^{1}H NMR ($CDCl_3$): $\delta = 13.35$ (bs, 1H, NH); 8.25 (d, 2H, $J = 9.0$, Ar); 7.27 (d, 2H, $J = 9.0$, Ar); 2.59 (m, 4H, CH_2); 1.73–1.70 (m, 4H, CH_2). ^{13}C NMR ($CDCl_3$): $\delta = 177.8$ (q, $^2J_{C\text{-}F} = 32.3$, C=O); 165.3 (C1); 143.7; 126.3; 125.0; 113.3 (6C, Ar); 117.7 (q, $^1J_{C\text{-}F} = 289.6$, CF_3); 101.1 (C2); 29.1 (CH_2); 22.3 (CH_2); 22.2

(q, $^4J_{C\text{-}F} = 3.7$, C3); (CH_2); 21.1 (CH_2). CG-MS (EI, 70 eV): m/z (%) = 314 (M^+, 97); 245 (87); 217 (31); 199 (100); 170 (30); 69 (85). Anal. calcd. for $C_{14}H_{13}F_3N_2O_3$ (314.09): C, 53.51; H, 4.17, N, 8.91%. Found: C, 53.45; H, 3.88; N, 8.67%.

1-(4-Chlorophenylamino)-2-trifluoroacetyl-cyclohexene (**3d**)

Yellow solid, yield 43%, mp 96–97°C. ^{1}H NMR ($CDCl_3$): δ = 13.18 (bs, 1H, NH); 7.35 (d, 2H, $J = 8.5$, Ar); 7.08 (d, 2H, $J = 8.7$, Ar); 2.56–2.38 (m, 4H, CH_2); 1.75–1.64 (m, 4H, CH_2).^{13}C NMR ($CDCl_3$): δ = 176.4 (q, $^2J_{C\text{-}F} = 31.7$, C=O); 167.1 (C1); 135.9; 132.5; 129.3; 127.0 (6C, Ar); 118.1 (q, $^1J_{C\text{-}F} = 289.6$, CF_3); 99.0 (C2); 28.5 (CH_2); 22.2 (CH_2); 22.1 (q, $^4J_{C\text{-}F} = 3.7$, C3); 21.0 (CH_2). CG-MS (EI, 70 eV): m/z (%) = 303 (M^+, 50); 234 (100); 206 (16); 111 (13); 75 (11); 69 (4). Anal. calcd. for $C_{14}H_{13}ClF_3NO$ (303.06): C, 55.37; H, 4.31; N, 4.61%. Found: C, 55.14; H, 4.10; N, 4.56%.

1-(4-Bromophenylamino)-2-trifluoroacetyl-cyclohexene (**3e**)

Yellow solid, yield 71%, mp 127–128°C. ^{1}H NMR ($CDCl_3$): δ = 13.17 (bs, 1H, NH); 7.50 (d, 2H, $J = 8.5$, Ar); 7.02 (d, 2H, $J = 8.5$, Ar); 2.56–2.38 (m, 4H, CH_2); 1.67–1.64 (m, 4H, CH_2).^{13}C NMR ($CDCl_3$): δ = 176.4 (q, $^2J_{C\text{-}F} = 33.0$, C=O); 166.9 (C1); 136.5; 132.3; 127.3; 120.3 (6C, Ar); 118.1 (q, $^1J_{C\text{-}F} = 288.9$, CF_3); 99.0 (C2); 28.5 (CH_2); 22.2 (CH_2); 22.1 (q, $^4J_{C\text{-}F} = 3.7$, C3); 21.0 (CH_2). CG-MS (EI, 70 eV): m/z (%) = 347 (M^+, 81); 278 (88); 250 (16); 199 (100); 171(22); 76 (22); 69 (9). Anal. calcd. for $C_{14}H_{13}BrF_3NO$ (347.01): C, 48.03; H, 3.76; N, 4.02%. Found: C, 48.23; H, 3.74; N, 3.82%.

2-Trifluoroacetyl-1-(4-iodophenylamino)-cyclohexene (**3f**)

Orange solid, yield 43%, mp 152–153°C. ^{1}H NMR ($CDCl_3$): δ = 13.18 (bs, 1H, NH); 7.69 (d, 2H, $J = 8.7$, Ar); 6.88 (d, 2H, $J = 8.2$, Ar); 2.56–2.39 (m, 4H, CH_2); 1.68–1.64 (m, 4H, CH_2).^{13}C NMR ($CDCl_3$): δ = 176.4 (q, $^2J_{C\text{-}F} = 31.8$, C=O); 166.9 (C1); 138.3; 137.1; 127.5; 91.4 (6C, Ar); 118.1 (q, $^1J_{C\text{-}F} = 289.5$, CF_3); 99.1 (C2); 28.6 (CH_2); 22.2 (CH_2); 22.0 (q, $^4J_{C\text{-}F} = 3.5$, C3); 21.0 (CH_2). CG-MS (EI, 70 eV): m/z (%) = 395 (M^+, 96); 326 (36); 298 (14); 199 (100); 170 (28); 76 (39); 69 (15). Anal. calcd. for $C_{14}H_{13}F_3INO$ (395): C, 42.55; H, 3.32; N, 3.54%. Found: C, 42.30; H, 3.24; N, 3.52%.

5-Trifluoromethyl-1,2,3,4-tetrahydroacridines (**4a**, **4b**, **4d**–**e**): General Procedure

To a magnetically stirred solution of H_3PO_4 (2 ml) and P_2O_5 (3 g) (PPA) at 90°C, **3a**–**f** (5 mmol) were added at room temperature. The mixture was stirred for 24 h at 110°C. Distilled water (10 ml) and chloroform (10 ml) were added to the mixture at room temperature. The solution was then extracted with chloroform (three times, 10 ml). The combined organic layers were washed with aq. 10% solution of NaOH (three times, 10 ml) and distilled water (three times, 10 ml) and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting solid products were recrystallized from ethanol (yields 20–85%).

Data

9-Trifluoromethyl-7-methyl-1,2,3,4-tetrahydroacridine (**4a**)

Yellow solid, yield 85%, mp 63–65°C. ^{1}H NMR ($CDCl_3$): $\delta = 7.91$–7.89 (m, 2H, Ar); 7.50 (m, 1H, Ar); 3.18–3.15 (m, 4H, CH_2); 2.54 (s, 3H, Me); 2.0–1.87 (m, 4H, CH_2).^{13}C NMR ($CDCl_3$): $\delta = 158.2$ (C4a); 145.2 (C10a); 136.8 (C7); 131.1 (C5); 130.4 (q, $^2J_{C\text{-}F} = 28.9$, C9); 130.3 (q, $^3J_{C\text{-}F} = 1.8$, C8); 125.2 (q, $^1J_{C\text{-}F} = 278.8$, CF_3); 126.6 (C6); 122.9 (q, $^3J_{C\text{-}F} = 4.9$, C8a); 122.7 (q, $^4J_{C\text{-}F} = 1.4$, C9a); 34.3 (CH_2); 27.1 (q, $^4J_{C\text{-}F} = 4.9$, C1); 22.6 (CH_2) 22.1 (CH_2); 21.9 (Me). CG-MS (EI, 70 eV): m/z (%) = 265 (M^+, 100); 250 (19); 196 (36); 181 (15); 90 (4); 77(4); 69 (5). Anal. calcd. for $C_{15}H_{14}F_3N$ (265.11): C, 67.91; H, 5.32; N, 5.28%. Found: C, 67.52; H, 5.02; N, 5.20%.

9-Trifluoromethyl-7-methoxy-1,2,3,4-tetrahydroacridine (**4b**)

White solid, yield 20%, mp 147–149°C. ^{1}H NMR ($CDCl_3$): $\delta = 8.04$ (d, 1H, $J = 9.2$, Ar); 7.35 (dd, 1H, $J = 2.5$, $J = 2.5$, Ar); 7.15 (d, 1H, $J = 2.5$, Ar) 3.9 (s, 3H, OMe); 3.14–3.01 (m, 4H, CH_2); 2.0–1.87 (m, 4H, CH_2).^{13}C NMR ($CDCl_3$): $\delta = 159.0$ (C7); 143.6 (q, $^2J_{C\text{-}F} = 31.4$, C9); 142.6 (C4a); 139.7 (C10a); 131.8 (C9a); 129.4 (C8a); 127.5 (C5); 122.4 (q, $^1J_{C\text{-}F} = 276.0$, CF_3); 121.3 (C6); 100.4 (C8); 55.3 (OMe); 25,8 (CH_2); 24.8 (q, $^4J_{C\text{-}F} = 3.0$, C1); 21.8 (CH_2); 21.6 (CH_2). CG-MS (EI, 70 eV): m/z (%) = 281 (M^+, 100); 250 (7); 212 (17); 181 (6); 77 (8); 69 (23). Anal. calcd. for $C_{15}H_{14}F_3NO$ (281.1): C, 64.05; H, 5.02; N, 4.98%. Found: C, 64.12; H, 4.74; N, 4.67%.

7-Chloro-9-trifluoromethyl-1,2,3,4-tetrahydroacridine (**4d**)

Brown solid, yield 40%, mp 131–133°C. ^{1}H NMR ($CDCl_3$): $\delta = 8.06$ (d, 1H, $J = 8.7$, Ar); 7.93 (d, 1H, $J = 2.0$, Ar); 7.63 (dd, 1H, $J = 2.0$, $J = 2.3$, Ar); 3.15–3.03 (m, 4H, CH_2); 1.99–1.90 (m, 4H, CH_2). ^{13}C NMR ($CDCl_3$): $\delta = 146.4$ (q, $^2J_{C\text{-}F} = 32.0$, C9); 143.8 (C4a); 142.3 (10a); 134.4 (C7); 132.1 (C6); 129.9 (C5); 129.1 (9a); 128.4 (C8a); 122.0 (q, $^1J_{C\text{-}F} = 276.9$, CF_3); 121.7 (C8); 30.8 (CH_2); 25.8 (CH_2); 24.8 (q, $^4J_{C\text{-}F} = 3.1$, C1); 21.7 (CH_2). CG-MS (EI, 70 eV): m/z (%) = 285 (M^+, 100); 250 (37); 216 (16); 181 (10); 69 (7). Anal. calcd. for $C_{14}H_{11}ClF_3N$ (285.05): C, 58.86; H, 3.88; N, 4.90%. Found: C, 58.57; H, 3.72, N, 4.83%.

7-Bromo-9-trifluoromethyl-1,2,3,4-tetrahydroacridine (**4e**)

Beige solid, yield 52%, mp 133–134°C. ^{1}H NMR ($CDCl_3$): $\delta = 8.11$ (d, 1H, $J = 2.0$, Ar); 7.98 (d, 1H, $J = 8.7$, Ar); 7.76 (dd, 1H, $J = 2.0$, $J = 2.0$, Ar); 3.15–3.04 (m, 4H, CH_2); 1.99–1.85 (m, 4H, CH_2). ^{13}C NMR ($CDCl_3$): $\delta = 146.5$ (q, $^2J_{C\text{-}F} = 32.0$, C9); 143.7 (C4a); 142.5 (C10a); 132.5 (C6); 132.1 (C5); 129.4 (C9a); 128.4 (C8a); 125.0 (C8); 122.0 (q, $^1J_{C\text{-}F} = 276.9$, CF_3); 122.8 (C7); 25.8 (CH_2); 24.8 (q, $^4J_{C\text{-}F} = 3.0$, C1); 21.7 (CH_2); 21.4 (CH_2). CG-MS (EI, 70 eV): m/z (%) = 329 (M^+, 100); 260 (7); 250 (36); 181 (14); 152 (20); 69 (5); 75 (7). Anal. calcd. for $C_{14}H_{11}BrF_3N$ (329): C, 50.93; H, 3.36; N, 4.24%. Found: C, 50.92; H, 3.17; N, 4.17%.

ACKNOWLEDGMENTS

The authors thank Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for financial support. Fellowships from the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) (T. S. M.) and Fundação de Apoio a Tecnologia e Ciência (FATEC) are also acknowledged.

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